Genetic correlates of prostate cancer visibility (and invisibility) on mpMRI: It's time to take stock

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Article type: Comment.
Conflicts of interest: None to declare.
Word count: 1000 words

Keywords: Epigenetics, genetics, genomics, multiparametric MRI, prostate cancer, transcriptomics.
Ethics: Not required.
Funding: Joseph M. Norris is funded by the Medical Research Council (MRC) on an MRC Clinical Research Training Fellowship (MRC Grant Ref: MR/S00680X/1). Benjamin S. Simpson is funded by the Rosetrees Trust.

Abbreviations: ERG, ETS-related gene; CENPF, centromere protein F; cm, centimetre; DWI, diffusion weighted imaging; mpMRI, multiparametric magnetic resonance imaging; PECAM1, platelet and endothelial cell adhesion molecule; PI-RADS, Prostate Imaging Reporting and Data System; SCHLAP1, second chromosome locus associated with prostate-1; SPOP, speckle-type POZ protein; SWI/SNF, switch/sucrose non-fermentable.

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Article type : Comment

Multiparametric magnetic resonance imaging (mpMRI) has enhanced risk stratification for men at risk of prostate cancer, through accurate pre-biopsy detection of high-risk disease [1]. However, it has become apparent that not all clinically significant prostate cancer is detected by mpMRI. Approximately 10-20% of significant disease is invisible to mpMRI, depending on the threshold set for significance, and on the quality of mpMRI acquisition and interpretation. The threshold for significance has recently been challenged by the 29-year follow-up of the SPCG-4 study, in which men with overall Gleason score 3 + 4 did not suffer prostate-cancer-related death [2], whilst those with overall Gleason score 4 + 3 did suffer prostate-cancer related death (adjusted relative risk 5.73; 95% CI 1.59–20.67) potentially suggesting a new threshold for clinically significant disease. This finding is important, given that in PROMIS, no men with overall Gleason score 4 + 3 had negative pre-biopsy mpMRI [1], indicating that actually mpMRI may identify all truly significant cancer (if SPCG-4 is used to guide our threshold). Nonetheless, over the past two years, there has been increasing drive to better understand the nature of mpMRI-inconspicuous disease, particularly at the molecular level.

Purysko and colleagues recently sought to address this challenge by correlating the Decipher Genomic Classifier with mpMRI phenotypes for men undergoing radical prostatectomy (n = 72) [3]. Lesions were classified as either mpMRI-visible (PI-RADSv2 scores 3-5) or mpMRI-invisible (PI-RADSv2 scores 1-2) and were microdissected from radical prostatectomy specimens and profiled with the Decipher gene panel. Decipher scores were significantly higher in mpMRI-visible lesions (mean difference 0.22; 95% CI 0.13, 0.32; $p < 0.0001$) indicating an enrichment of genes associated with high-risk prostate cancer (in this case, elevated risk of early metastatic spread) in mpMRI-conspicuous disease; however, in this study, they did not control for the dominant effect that tumour grade and size has on mpMRI conspicuity. Similar findings were confirmed by Houlahan and colleagues [4] who took a cohort of men who underwent radical prostatectomy (n = 40), defining tumours as mpMRI-visible (PI-RADSv2 score 5) or mpMRI-invisible (PI-RADSv2 score 1-2). Unlike Purysko, they stipulated inclusion of only ‘clinically significant’ cancer (using their definition of Gleason score 3 + 4 with a minimum tumour diameter of 1.5 cm). They performed genomic and transcriptomic profiling of these tumours, and in parallel with Purysko, demonstrated that mpMRI-visible tumours were enriched for aggressive molecular and microenvironmental features, potentially ratifying the prognostic benefit afforded by mpMRI.

Some authors have taken this even further. Li and colleagues recently used an extensive approach [5] where they firstly macrodissected mpMRI-visible (PI-RADS score 4-5) and mpMRI-invisible (PI-RADS score 1) tumours from radical prostatectomy specimens (n = 16) and then performed RNAseq, to identify differentially expressed genes between the two groups. They then cross-referenced these with publicly available gene databases and

created murine prostate cancer xenografts in which genes with potential roles in mpMRI conspicuity were knocked down. Through this staged approach, they reiterated that tumour visibility on mpMRI was associated with genes typically related to prognostic significance. Interestingly, they were one of the few research groups to postulate a cause-effect relationship between gene expression, histopathological changes, and visibility on the diffusion weighted imaging sequence (DWI) of mpMRI, which estimates movement of extracellular water (reflecting tumour perfusion). They found that by knocking out Centromere Protein F (CENPF; responsible for tumour cell growth, migration and invasion), tumours seemingly had lower levels of perfusion and DWI-visibility, suggesting the key role that CENPF may play in tumour mpMRI-conspicuity. This was confirmed histologically as reduced cellular proliferation and density, when CENPF was supressed (albeit indirectly, using an inducible miRNA system). Of note, they also found that CENPF correlated weakly with tumour volume, suggesting CENPF contributes to cancer visibility beyond simply influencing tumour size.

The aforementioned studies all showed correlation between mpMRI-visibility of prostate cancer and the expression of genes associated with poor clinical prognosis, however, not all authors agree that tumour mpMRI-invisibility is necessarily reassuring. Parry and colleagues recently took radical prostatectomy specimens (n = 6) and obtained clock-face punch biopsies from the mid-gland level [6]. After retrospectively assigning each punch biopsy as mpMRI-visible (PI-RADSv2 score 3-5) or mpMRI-invisible (PI-RADSv2 score 1-2) they compared them using low-pass whole genome sequencing, methylation arrays and RNAseq, to gain detailed molecular profiles. There was a high intra-patient molecular heterogeneity, but they found that three of six cores obtained from mpMRI-invisible tumours harboured genetic alterations observed in metastatic castration-resistant prostate cancer. Whilst this is potentially concerning, we should be cautious when drawing conclusions given the low sample size, and the recognised challenge of coregistration of radical prostatectomy with mpMRI. The concern of potentially missing significant cancer was also partly supported Purysko, as three patients in their study who had mpMRI-invisible cancer were found to have elevated Decipher scores [3], although this risk was only classed as intermediate.

Despite progress that has been made so far, it is unlikely that this is the end of the story. Whilst the studies highlighted here have suggested potential candidate genes (table 1) that may account, or be associated with, conspicuity or inconspicuity of prostate cancer on mpMRI, there are several unanswered questions. The most important outstanding question is likely to be that of prognostication, and the related issue of true clinical significance of mpMRI-inconspicuous disease. mpMRI-visible tumours may be enriched with mutations in differentially expressed/methylated genes linked to poor prognosis, but this does not confirm that men with visible tumours will have worse clinical outcomes. The answer to this question will potentially only come from long-term clinical studies with longitudinal mpMRI data, which are understandably difficult to conduct. The next important challenge is to elucidate whether there are factors that account for tumour conspicuity on mpMRI beyond the well-appreciated characteristics of cancer grade and size. Finally, the conundrum of how to improve detection of seemingly mpMRI-invisible prostate cancer will need to be addressed, especially if deemed to be truly clinically significant. This may require refinement of mpMRI sequences, or identification of peripheral biomarkers, specifically designed to identify significant, inconspicuous tumours.

Conflicts of Interest

None declared.

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Table 1. Potential genetic candidates related to conspicuity of prostate cancer on mpMRI.

Gene (or panel)	Reference	Function	Relevance for mpMRI
Decipher	Purysko, 2019 [3]	Panel of genes involved in the early metastatic spread of prostate cancer	mpMRI-visible tumours highly express the Decipher gene panel, potentially suggesting that visibility on mpMRI may have prognostic significance.
SCHLAP1	Houlahan, 2019 [4]	Gain-of-function of this non-coding RNA (involving the SWI/SNF complex) results in increased invasiveness and metastasis of prostate cancer	SCHLAP1 is more highly expressed in mpMRI-visible tumours, which may confer poor prognosis.
CENPF	Li, 2018 [5]	Controls tumour cell growth, migration and invasion.	Tumour visibility on DWI appears to be, in part, influenced by expression of CENPF, through increased cell growth.
PECAM1	Li, 2018 [5]	Encodes proteins in the immunoglobulin superfamily, that likely have key roles in angiogenesis.	PECAM1 potentially influences prostate cancer visibility on mpMRI by increasing levels of tumour angiogenesis.
SPOP	Parry, 2018 [6]	Potential regulator of the transcription factor ERG. Mutations in SPOP may cause ERG overexpression.	Some mpMRI-invisible tumours were found to express SPOP1, which may imply that mpMRI-invisibility does not necessarily confer improved clinical prognosis.

ERG, ETS-related gene; CENPF, centromere protein F; mpMRI, multiparametric magnetic resonance imaging; PECAM1, platelet and endothelial cell adhesion molecule; SCHLAP1, second chromosome locus associated with prostate-1; SPOP, speckle-type POZ protein; SWI/SNF, switch/sucrose non-fermentable.