To see or not to see – what set of attributes render prostate cancer visible?

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The one thing we have learnt during the past 30 years about prostate cancer risk stratification is that using PSA and trans-rectal ultrasound (TRUS) biopsy in tandem - as a diagnostic intervention - has failed to identify men that are at risk of a premature prostate cancer-related death (1). There are two main reasons for this. The first relates to the high degree of imprecision of the combined tests. The second is linked to the high rate of missed diagnoses and over-diagnosis (detection of cancers that were not destined to result in a prostate cancer related death) that results when these two tests are combined. Taken in combination this means that the outputs of PSA and TRUS biopsy are only weakly associated with the known principal risk factors of tumour; grade, stage and volume.

The introduction of magnetic resonance imaging (MRI) into the prostate cancer diagnostic pathway has provided us with an opportunity to identify men that are at true risk of premature death as MRI positivity is positively associated with tumour grade, stage and volume (2,3). The challenge that remains is where to place the threshold of disease severity - at the level of the individual - that discriminates between those men that are at high risk from those that are not. That prostate cancer grade and stage (and presumably volume, as it is so closely correlated) are closely associated with premature prostate cancer-related death has been shown in the latest update of the SPCG-4 study that reports the 29-year follow-up (4). Well-characterised (by radical prostatectomy) Gleason 3 plus 4 disease was not associated with a prostate cancer related death. Gleason 4 plus 3 or worse was, as was extra-prostatic extension. In PROMIS, the most accurately phenotyped cohort that we will ever have, there were no Gleason 4 plus 3 or worse tumours associated with a 'normal' MRI (2). This means that within the new image-guided pathway there should be few, if any, critical misses.

Whilst most reassuring for future patients in terms of appropriate and effective risk-stratification the question does remain as to what it is that we are seeing (or not seeing) when we scrutinize an MRI of the prostate and use this as our principal risk-stratification tool.

The recent paper by Houlahan and colleagues helps considerably in this regard (5). By a process of selection and rejection of cases teams from UCLA and University of Toronto managed to curate a cohort of 40 men who had tumours described as Gleason 3 plus 4 in their resected prostate that met or exceeded 1.5cm in maximum diameter. In half the men the tumour was declared non-visible as a consequence of

a PIRADS 1-2 score. In the other half it was declared 'very' visible as a consequence of a PIRADS 5 score. Despite the contingencies of the case selection process the men with visible PIRADS 5 lesions were more likely to have greater tumour volume, higher pathological stage, a greater proportion of Gleason pattern 4, and were more likely to have cribriform architecture than their PIRADS 1-2 counterparts.

Was, therefore, the intriguing observation by Houlihan and colleagues that MRI conspicuity - as determined by PIRADS 5 lesions versus PIRADS 1-2 lesions - was associated with molecular changes that we would normally associate with a greater propensity for progression attributable to the MRI-derived phenotype itself or was it merely that these cancers were bigger, of higher grade proportionally and more invasive compared to those that were not seen?

What makes a tumour visible in the prostate? Ultimately, it is the degree to which tumour related attributes (the signal) that are specifically interrogated by the imaging sequence differ significantly from the background prostate (the noise) so that the naked eye (and in future, the software) might be able to detect a boundary between the two. There are many reasons to think that tumours that we 'see' might be more aggressive compared to those we cannot – over and above issues relating to tumour volume (a proxy for the number of tumour cells present). The observation that a given tumour can exhibit a strong signal on the dynamic contrast enhanced (DCE) T1-gadolinium sequence implies the establishment of an abnormal, tumour-mediated blood supply that may well be a condition for further proliferation (6). The presence of a low apparent diffusion coefficient (ADC) tends to be associated with greater cell density – a status that is conferred by a tendency towards anaplasia and invasion resulting in a re-modelling of tissue microstructure. Novel sequences are in development that interrogate other tissue attributes such as the T2 quantification of luminal water which, again, may give us insights into specific cancer sub-types (7).

The paper by Houlihan and colleagues did not seek to classify which transcriptomic signal was associated with which MRI-derived endotype (+ve T2 versus -ve T2; +ve DCE versus –ve DCE; high ADC versus low ADC) and it is indeed possible that this may have provided the greatest yield and insight into the upstream drivers of tissue microstructure. Instead, they used the PIRADS (version 2) scoring system - a rule-based process that was designed to reduce between observer variability in the reporting of prostate MRI. PIRADS scores are derived though a Boullian process that treats anatomically distinct parts of the prostate differently, places weight on some sequences over others, and explicitly incorporates a volume threshold. For these and other reasons it may not be the best reference standard to use when seeking to understand the dominant signalling that is associated with the range of phenotypic expression that we see when we look at a man's prostate cancer, as expressed by the standard MRI sequences.

The observation that cancers that we can 'see' are worse (in terms of propensity to invade and metastasize) than those we cannot 'see' should be self-evident as it

seems to hold true for all other solid cancers. In no solid organ, other than prostate, do we seek to procure and interrogate tissue in the presence of a normal imaging.

Perhaps the next step is to better understand the determinants and fate of the rich spectrum of endotypes that MRI of prostate provides us with so that we might gain insights into the cancer that we are seeing and, in so doing, be better able to classify it (possibly without recourse to biopsy) and, in time, predict its fate (8).

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