Dropping the GAD – just a fad?

The case for a simpler, quicker, safer and cheaper prostate MRI

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It is not without irony that - at the very moment that the UK's National Institute for Health and Care Excellence (NICE) are poised to ratify the recommendation that multi-parametric MRI (mp-MRI) be introduced into the prostate cancer diagnostic pathway - we are seeking to significantly modify the very intervention on which they are about to provide judgement on (1).

The modification proposed is both compelling and plausible as it renders the process of imaging the prostate in order to detect and localise clinically significant prostate cancer; simpler, quicker, safer and cheaper. It entails dropping the most complex and time-consuming component of the three multi-parametric sequences – the dynamic (time-dependent) T1 weighted gadolinium enhanced sequence. This was a sequence that was imbued to have biological significance because it was capable of exploiting the differences in the micro-vascular architecture and function that we have tended to associate with cancer and non-cancer in order to discriminate between the two - or so we thought (2).

The systematic review in this issue of the BJUI by Alabousi and colleagues explores, via the process of systematic review, whether the omission of the T1-gadolinium sequence results in any clinically important reduction in test performance when compared the full sequence scan comprising traditional T2, diffusion and T1-gadolinium sequences (3). It did not.

By any stretch this is a tough analysis to pull-off as T1-gadolinium sequences are not standardised in terms of acquisition or reporting. As such they tend to suffer from quality control issues, possibly to a greater extent than the T2 and diffusion sequences. The verification of the signal by biopsy strategy and sampling intensity will have varied across studies as will the threshold of the definition of clinically significant prostate cancer. These inherent methodological problems are all familiar to readers and issues that are pertinent to any imaging study in the detection of prostate cancer. There are, however, two issues that make any current assessment of gadolinium versus no gadolinium really problematic. The first is the almost exclusive reliance on single-centre retrospective data. In the few studies that claim a prospective design no comparative data were available. Studies of this type are typical in the early phase of exploring a clinical question and will, in time, be corrected. The other, largely hidden, hardly discussed and truly problematic issue relates to the manner by which we synthesize an overall risk score from the MRI sequences that we derive.   The near ubiquitous use of the PIRADS scoring system introduces a systematic bias by the way in which it uses a Boolean form of logic to the importance it confers on different sequences. According to the manner by which PIRADS is applied it tends to render the T1-gadolinium sequence subordinate (only relevant in a minority of cases), contingent (to T2 / diffusion) and disparate (dependent on prostate zone) in the way it is invoked (4). This result is, that within the majority framework, the T1-gadolinium sequence is destined to play a relatively small role in driving the overall summary score of risk. It might, therefore, not be too surprising if removing it made little difference to the overall detection of clinically significant prostate cancer.

So what are the next steps? Clearly this is a very important issue and a simpler, quicker, safer and cheaper MRI would be desirable from multiple perspectives. It would render what is currently a complex intervention - that comprises an invasive component - into a totally passive image acquisition in which no medically trained health professional need be present. It is almost certainly a pre-requisite for adoption in resource poor jurisdictions and for entertaining the role of MRI as a primary population-based screening test.

It took a large number of randomised trials to get mp-MRI accepted into the prostate cancer diagnostic pathway. What is the minimum amount of evidence required to disinvest in one of its key components? In other words how many clinically significant cancers would we tolerate missing in order to offer the less complex test?

A head to head non-inferiority randomised comparative study would, following some of our own recent calculations, require over 3,000 men to participate which might just prove a little too challenging. An alternative approach is a study in which men would have lesions declared using a Likert score -thereby making no prior assumptions on the role and utility of any single sequence - by traditional mp-MRI (standard) but also by a T2-diffusion MRI (experimental) with appropriate blinding. Some lesions would be private to either standard or experimental imaging but most, it is likely, would be shared. All would require sampling. The yield, the misses, the test accuracy for each approach could be calculated with necessary adjustments for the inevitable incorporation and verification biases.

It is interesting to observe that in many parts of the world mp-MRI was introduced by clinicians before a large body of evidence was accumulated because they felt it was the right thing to do (5). It may well be the case that 'dropping the GAD' will be subject to the same decision making process and precede any definitive judgement based on reliable on evidence. Recent activity on PUBMED would suggest that this might already have happened (6).

Acknowledgements

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