An end to the phenomenon of 'up-grading' in early prostate cancer?

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The phenomenon of 'up-grading' in early prostate cancer is one of those unusual events that is both useful to us on the one hand and at the same time undesirable on the other. Useful - because the phenomenon gifts us a direct measure of the precision of our risk stratification methods for men recently diagnosed. Undesirable - because the perfect pathway should, ideally, be free of any 'up-grading'.

The phenomenon of 'up-grading' occurs in a number of settings. We see it at play to some degree when an unreliable test is re-applied on the same subject. The REDUCE study showed us that just under one fifth of men will convert from a status of 'cancer-free' to one of 'cancer-present' as a result of a second exposure the same test – transrectal ultrasound (TRUS) guided biopsy (1). We see it in full play when an unreliable test is followed by a more accurate test. Shaw and colleagues – as have a number of others - reminded us once again of our limited ability to risk stratify patients with early prostate cancer. They reported a 50% upgrading when they compared the results of TRUS biopsy against the final pathology at radical prostatectomy. In other words, half the patients went on to their definitive therapy with an incorrect grade attribution (2).

It would be a great pity if, in the modern era, the only route available to patients who wanted to be sure of their risk status was to agree to surgical removal of the prostate. Surely, the value of accurate risk stratification is derived from using it to allocate appropriate and effective care. Risk stratification needs to be linked to or closely follow diagnosis if it is to be put to work for patients.

Nowhere is this need greater than in men whose treatment preference is tissue preservation. The study, in this issue, by Pessoa and colleagues adds to our knowledge on the subject and equips us with a strategy to mitigate some of the errors that are inherent to the standard diagnostic pathway (3).

In this study, the authors evaluated the role of a single exposure to MRI (and the opportunity that resulted to undertake a targeted biopsy to an MRI-derived abnormality as well as systematic sampling) to 105 men who had been attributed a diagnosis of low risk prostate cancer – and, as a result, were deemed to be suitable for active surveillance. The authors used the PIRADS system to interpret and communicate MRI-risk. In summary, men attributed a low PIRADS score (PIRADS 1-3) had a low probability of being re-classified to a higher risk. In contrast, men attributed PIRADS 4 or 5 had between a 70-100% of being re-classified. The authors calculated a sensitivity of 93% for MRI to predict 're-classification'. This equates to a 93% sensitivity to predict the presence of clinically significant disease as re-classification occurred when there was a transition from low risk to higher risk disease.

These results concur with those of others that are working in this area (4) and are in line with current recommendations (5). One observation that is worth highlighting – because it is a current controversy in the field - relates to the utility of the systematic (or semi-random) biopsies as a component of the confirmatory biopsy. Whilst targeted biopsy was superior to systematic biopsy at identifying clinically significant disease, omission of the systematic biopsies would have resulted in 5 significant cancers being overlooked. The less perfect the targeted biopsy, the greater the reliance on the systematic. In this study, the lesion-generation and the targeting may have been compromised by one or two issues. Using TRUS biopsy as the authors did (as opposed to trans-perineal biopsy) to access all areas of the prostate is always going to be a challenge. To do so without image-registration makes it even harder. To use PIRADS – as opposed to a Likert scale - as a method of interpreting and communicating MRI outputs will, very likely, lead to an under-reporting of the smaller, high-grade lesions (6). This is because PIRADS 2.0 is triggered by a volume

threshold towards the upper end of the scale. Such lesions might be more prevalent in an apparently 'low-risk' population such as the one under scrutiny. If this is the case, they will not be identified as 'targets' by virtue of a high PIRADS score. As a consequence they cannot be identified by targeting but might be picked up by the random fall of the needles.

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