Title page

Can a negative prostate MRI give us the reassurance we need to avoid standard biopsy? An evidence based practical approach

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I congratulate Panebianco and colleagues on the publication of 'Negative multi-parametric magnetic resonance imaging for prostate cancer – what next?[1]', in this months' European Urology. They report 1255 men with 48 month biopsy and MRI follow up after a negative prostate MRI. This addresses the question of how to manage men with a negative MRI, made particularly topical by the publication of PRECISION - the first randomised controlled study to assess a pathway where men who tested negative on MRI were not offered a protocol biopsy[2].

Panebianco reports 659 MRI-negative men with no prior biopsy, of whom 395 underwent standard biopsy immediately after the MRI, revealing only 12 clinically significant cancers. A further 264 men in this group had a deferred biopsy within 48 months, and this revealed a further 24 cases of clinically significant cancer, giving rise to 95% freedom from clinically significant disease by 48 months. This confirms other reports that suggest a negative predictive value of MRI for Gleason 7 disease, of 98%[3].

We should be mindful of the fact that the MRIs in Panebianco's report were considered 'truly negative' – ie PIRADS 1-2, in an expert centre with almost 5000 MRI's done in the 5 year study period. PRECISION data shows a truly negative MRI in 28% of men presenting for the first time with a clinical suspicion of prostate cancer based on a raised PSA or abnormal digital rectal examination (DRE).

A further 20-30% of men in a first referral cohort would be expected to have an equivocal MRI, according to PRECISON and PROMIS[4] data. The 5mm template mapping biopsy approach in PROMIS found that 20% of men with an equivocal MRI (Likert 3) have significant cancer according to the primary PROMIS definition of any Gleason 4 + 3 or 6mm any cancer. This increased risk of an equivocal rather than a negative MRI should be remembered when considering biopsy strategies.

The UK NICE guidelines on prostate cancer[5] are the first to specifically recommend no additional biopsies in men with a prior negative standard biopsy and a negative MRI. It is reasonable to ask whether a negative standard biopsy prior to negative MRI gives additional reassurance that clinically significant prostate cancer has not been missed. In Panebianco's cohort freedom from clinically significant cancer at 48 months after negative MRI was 96% in men with prior negative biopsy and 95% in men who were biopsy naïve, suggesting that any additional reassurance is small. Formal assessment showed that negative prior biopsy did not independently predict clinically significant disease on multi-variate analysis.

So, can we omit routine standard biopsy in all men with a negative MRI? It certainly seems that no immediate harm will be done, as none of the men in the study progressed or died of prostate cancer during 4 years of follow up. And 95% freedom from clinically significant disease at 48 months would be acceptable to many, in order to avoid the known risks associated with biopsy. These risks increase with the sampling density of the biopsy approach, with a 5mm template biopsy approach associated with a 23% urinary retention rate and 20% de novo erectile dysfunction, albeit usually temporary[6].

However, we can apply additional risk stratification in MRI-negative or MRI-equivocal men. Panebianco shows that PSA density shows a hazard ratio of over 7 for the diagnosis of clinically significant prostate cancer in the setting of an MRI classified as negative – a very strong indicator that MRI-negative men with a high PSA density ($\geq$ 0.15ng/ml) should be offered a biopsy. This use of PSA density in conjunction with MRI findings has been shown in other series to increase the negative predictive value of MRI to close to 100%[7].

What do we know about MRI-negative cancers? Panebianco analyses the missed cancers seen on subsequent radical prostatectomy, and shows that one third of the 36 men who had MRI-negative cancers and subsequent radical prostatectomy had small tumours in the anterior horn – an issue that may in part be addressed by additional training. Eight of the 36 had cribriform pattern cancer, and 1 had mucinous cancer – both a more worrisome finding, although rare when looked at the cohort of 1255 men as a whole. Work from New York University suggests that there are distinct histological differences between MR-visible and MR-non visible prostate cancers[8], and postulates that MRI-negativity may independently confer a more favourable prognosis.

Panebianco's work, along with PROMIS and PRECISION data, challenges us to incorporate MRI as a standard part of the assessment of all men at risk of prostate cancer. Men with an equivocal or negative MRI should have risk assessment including PSA density, and biopsy be discussed, taking into account the possible short terms harms of biopsy and the small likelihood of missing clinically significant disease.

We must acknowledge the presence of a learning curve in the adoption of an MRI and targeted biopsy pathway. At one UK centre the negative predictive value of MRI improved from 67% in the first cohort to 89% in the final cohort of a series of 340 men[9]. Pinto reports a 1003 man cohort, where 62 men had significant disease detected on standard biopsy not detected with fusion biopsy. They report that the causes of a false negative biopsy can include MRI-reader error, and missing the target by the biopsy operator, as well as true MR-invisibility[10]. Whilst centres develop an MRI programme, including training in MRI acquisition and reporting, and targeted biopsy, it is likely that more men will be offered some form of systematic sampling, at least until the negative predictive value of MRI at that centre is known.

In some countries, such as the UK and Australia, there is widespread use of pre-biopsy MRI across different settings. In light of Panebianco's work on the mid term outcome of men with a negative regarding the significance of a negative MRI, in conjunction with PROMIS and PRECISION, the time has come for urologists to strive to make pre-biopsy MRI available to all men being assessed for prostate cancer.

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