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Minimizing the over-diagnosis and over-treatment of localized prostate cancer is a huge challenge for both patients and health care systems. Evidence now supports the role of pre-biopsy multi-parametric MRI (mp-MRI) as a triage tool.

The ProtecT and PIVOT studies [1, 2] demonstrate that up front active treatment of low risk prostate cancer has no impact on 10 year overall survival, and in the current era active surveillance is recommended for those with low risk disease and selected men with intermediate risk localized prostate cancer.

Unlike other diagnostic pathways where imaging identifies tumor which is then biopsied, the converse has been standard in prostate cancer. Most commonly men present with an elevated PSA and/or abnormal digital rectal examination. The diagnostic pathway then utilizes trans-rectal ultrasound-guided biopsy (TRUS biopsy) but is relatively blind to the location of the cancer. A post TRUS biopsy MRI then provides local staging but interpretation can be hampered by haemorrhage.

Mp-MRI consists of multiple imaging sequences providing different but complimentary information to guide intra-prostatic tumor identification. Generally T2, diffusion weighted (DW) and dynamic contrast enhanced (DCE) sequences are acquired. Once a likely tumour is demonstrated, biopsies can be targeted using either visual registration (cognitive fusion) or software assisted MRI-US fusion techniques. Reporting consensus guidelines, the Prostate Imaging-Reporting and Data System (PIRADS), have been developed and are updated regularly aiding widespread implementation of pre-biopsy mp-MRI [3-6].

The following multi-centre clinical trials in biopsy naïve men have evaluated the role of pre-biopsy mp-MRI.

Ahmed et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a pairing validating confirmatory study. Lancet 2017 [7].

Summary: This paired cohort study tested the diagnostic accuracy of mp-MRI and TRUS-biopsy against a reference test (template prostate mapping biopsy [TPM-

biopsy]). All participants were assigned to undergo mp-MRI followed by both TRUS-biopsy and TPM-biopsy. TPM-biopsy samples the entire prostate with an estimated 95% sensitivity for clinically significant prostate cancer. Clinically significant cancer was defined as ≥ISUP Grade Group 3 (Gleason 4+3) or maximum core length ≥ 6mm. 740 men were recruited, with 576 undergoing mp-MRI followed by MRI targeted TRUS-biopsy and non-targeted TPM-biopsy. On TPM-biopsy (the reference test) 408 (71%) had cancer and 230 of these (40%) were considered clinically significant. For clinically significant cancer, mp-MRI was more sensitive (93%, 95% CI 88-96%) than TRUS-biopsy (48%, 42-55%; p<0.0001) and less specific (41%, 36-46% for mp-MRI vs. 96%, 94-98% for TRUS-biopsy). The negative predictive value of mp-MRI was 89% for clinically significant prostate cancer.

The authors conclude that using mp-MRI upfront to triage men may allow 27% of patients to avoid biopsy. If mp-MRI findings directed biopsy, 18% more cases of clinically significant prostate cancer could be detected.

Comments: The design of the PROMIS study provides estimates of mp-MRI test sensitivity and negative predictive values, at 93% and 89% respectively. With high sensitivity and negative predictive value it provides Level 1 evidence for mp-MRI as an initial diagnostic test.

However, mp-MRI does have a low specificity as it cannot correctly identify all those without clinically significant prostate cancer, with up to 60% of true negatives told biopsy is needed. An ideal diagnostic test would have both high sensitivity and specificity, but the alternative of a high sensitivity and low specificity imaging test, followed by biopsy (which has a high specificity) means that nearly all false positives will be identified as not having prostate cancer on subsequent biopsy.

Kasivisvanathan et al. MRI-targeted or Standard biopsy for Prostate-Cancer Diagnosis. NEJM 2018 [8].

Summary: Investigators in the PRECISION (Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not?) non-inferiority study randomized 500 men to mp-MRI triage or standard TRUS-biopsy. In those

undergoing mp-MRI, no biopsy was undertaken if the MRI was not suggestive of prostate cancer and if MRI was suggestive of prostate cancer, then biopsy of the abnormal area only was undertaken.

252 men were assigned to the mp-MRI group, with 240 undergoing intervention. 71 of 252 men (28%) had mp-MRI not suggestive of prostate cancer and avoided biopsy. Clinically significant cancer, defined as any ≥ISUP Grade Group 2 cancer (Gleason score 3+4), was detected in 95 men (38%) in the MRI-targeted biopsy group, as compared with 64 of 248 (26%) with standard biopsy. Fewer men received a diagnosis of clinically insignificant cancer in the MRI-targeted biopsy group than the standard-biopsy group (23 men [9%] vs. 55 [22%].

Patient reported complications at 30-days were less frequent in the MRI triage group, although this includes those who did not proceed to biopsy.

Comments: The proportion of men with negative pre-biopsy MR and thereby avoiding biopsy in PRECISION are similar to those in the PROMIS study (28% and 27% respectively) suggesting this is a consistent finding in this population. The definition of clinically significant is more conservative than PROMIS. The study design was pragmatic demonstrating its applicability to a general setting. Fewer biopsy cores were obtained in the MRI-targeted group and this may result in reduced acute toxicity.

Rouviere O, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naïve patients (MRI-FIRST): a prospective, multi-centre, paired diagnostic study. Lancet Oncology 2019 [9].

Summary: In this paired diagnostic study participants underwent mp-MRI followed by TRUS-guided 12 core systematic biopsies and up to 2 cores targeting TRUS lesions with the operator blind to mp-MRI findings. In the same patient, a second operator undertook mp-MRI targeted biopsy of up to 2 lesions. Clinically significant prostate cancer was defined as any ≥ISUP Grade Group 2 (Gleason 3+4) cancer and was detected in 94 of 251 patients (37%). 13 (14%) by systematic biopsy only, 19 (20%) by mp-MRI targeted biopsy only and 62 (66%) by both techniques.

Clinically significant prostate cancer would have been missed in 5.2% (95% CI 2.8-8.7) had systematic biopsies not been done.

Comments: In contrast to the previous study, all patients underwent standard systematic biopsy and acted as their own control regardless mp-MRI findings. This design provides estimation of sensitivity of standard systematic versus mp-MRI targeted biopsies and the combination of the two. Combining both systematic and mp-MRI targeted biopsies provides the highest sensitivity in detecting ISUP grade Group 2 and above disease. The added value of standard systematic biopsy was marginal in detecting ISUP grade group 3 and above. It also allows calculation of the likely percentage of men with a false negative diagnosis in the absence of MR visible lesions (5.2%).

Discussion

These trials demonstrate that mp-MRI can be used as a triage test for the detection of ≥ISUP grade group 2 prostate cancer with biopsy omitted in those with negative mp-MRI. In mp-MRI positive patients combining both standard systematic and mp-MRI targeted biopsies provides the highest sensitivity in detecting clinically significant prostate cancer. Using mp-MRI triage may mean that a small proportion of clinically significant prostate cancer is missed highlighting the need for shared decision making between patient and clinician and on-going follow-up in those with negative mp-MRI who don't undergo biopsy.

The EAU Guidelines now recommend that mp-MRI should be performed before biopsy and reported according to PI-RADS [10]. In those with PIRADS≥3 lesions, targeted and standard systematic biopsy are advised. In men with PI-RADS ≤ 2 and low clinical suspicion of prostate cancer, prostate biopsy can be omitted based on shared decision making with the patient. NICE has made similar recommendations [11].

For the radiation oncology community the implementation of pre-biopsy MR will reduce the diagnosis of low and intermediate risk localized prostate cancer. This may add to the decline of brachytherapy [12] and may impact on SABR referrals. In those patients with MR visible tumour, the availability of pre-biopsy MR will facilitate

the recruitment of patients into clinical trials investigating the impact of dose escalation via integrated boost to visible tumour.

The NCCN clinical practice guidelines extensively review the molecular biomarkers that can be used for risk stratification but make no mention of the role of pre-biopsy mp-MR [13]. The incorporation of pre-biopsy MRI information into clinical nomograms can improve risk stratification and guide treatment decisions [14]. How both imaging and genomics may be combined to guide biopsy and treatment decisions is uncertain. Another challenge is that currently percentage positive cores are incorporated but there is no information on the impact on outcomes when MR targeted biopsies are used to diagnose prostate cancer.

Is there future potential for MR in population screening? It is minimally invasive, has few side effects, and most importantly identifies clinically significant prostate cancer. Fast MRI utilising bi-parametric MR (T2 and DW) can reduce scan times and costs and is being investigated in the RE-IMAGINE study [15].

Using mp-MRI before biopsy has been a divisive topic amongst urologists [16] but with an increasingly solid evidence base and incorporation into guidelines its use is likely to become standard of care across nations. Challenges of MRI capacity and clinician training in image interpretation need to be overcome. For men at risk of prostate cancer pre-biopsy MRI offers a reliable and accurate diagnosis and for a proportion may avoid harm.

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