TITLE: The 'Is MRI Enough' or IMRIE study: a multicentre evaluation of pre-biopsy multi-parametric MRI compared to biopsy

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Abstract

Background

Multiparametric magnetic resonance imaging (mpMRI) is now recommended pre-biopsy in numerous healthcare regions based on the findings of high-quality studies from expert centres. Concern remains about reproducibility of mpMRI to rule-out clinically significant prostate cancer (csPCa) in real-world settings.

Objective

To assess the diagnostic performance of mpMRI for csPCa in a real-world setting.

Design, Setting, and Participants

A multicentre, retrospective cohort study including men referred with a raised PSA or abnormal digital rectal exam who had undergone mpMRI followed by transrectal or transperineal biopsy. Patients could be biopsy naïve or have had previous negative biopsies.

Outcome Measurements and Statistical Analysis

The primary definition for csPCa was defined as ISUP Grade Group 2 or higher (any Gleason >/=7); the accuracy for other definitions was also evaluated.

Results and Limitations

Across 10 sites 2642 men were included (January/2011-November/2018). Mean age and PSA were 65.3 years (SD 7.8 years) and 7.5ng/ml (SD 3.3ng/ml). 35.9% had a 'negative' MRI' (score 1-2). 51.9% underwent transrectal biopsy and 48.1% had transperineal biopsy; with 43.4% diagnosed with csPCa overall. The sensitivity and negative predictive value (NPV) for

ISUP GG >/=2 were 87.3% and 87.5%, respectively. The NPV was 87.4% and 88.1% for men undergoing transrectal and transperineal biopsy, respectively. Specificity and positive predictive value of MRI were 49.8% and 49.2%, respectively. The sensitivity and NPV increased to 96.6% and 90.6% when a PSA-density threshold 0.15ng/ml/ml was used in MRI scores 1-2; these metrics increased to 97.5% and 91.2%, respectively, for PSA density 0.12ng/ml/ml. ISUP GG >/=3 (Gleason >/=4+3) was found in 2.4% (15/617) of men with MRI score 1-2. They key limitation of this study is the heterogeneity and retrospective nature of the data.

Conclusions

mpMRI when used in real-world settings is able to accurately rule-out csPCa suggesting that about one-third of men might avoid an immediate biopsy. Men should be counselled about the risk of missing some significant cancers.

Patient Summary

mpMRI is a useful tool for ruling out prostate cancer, especially when combined with PSA density. Previous results published from specialist centres can be reproduced at smaller institutions. However, patients and their clinicians must be aware that an early diagnosis of clinically significant prostate cancer could be missed in nearly 10% of patients by relying on MRI and PSAD alone.

Introduction

Prostate cancer diagnosis using pre-biopsy MRI is now supported by multiple high quality publications [1–4] . Recently, UK NICE and EAU guidance have recommended adoption of pre-biopsy MRI [5,6]. In 2017 the PROMIS study showed that mpMRI not only outperforms conventional transrectal ultrasound guided systematic (TRUS) biopsy at cancer detection but may also allow a quarter of men to avoid an immediate prostate biopsy [4]. Subsequently, the PRECISION RCT went on to confirm that an MRI-targeted biopsy pathway was superior to TRUS-biopsy in terms of clinically significant cancer detection with 28% of men avoiding an immediate biopsy [1]. PRECISION did not include systematic sampling in the intervention group.

A recent Cochrane systematic review has shown a reported sensitivity and negative predictive value (NPV) for clinically significant cancer (csPCa) (any ISUP Grade Group 2 or higher) of 91% and 91%, respectively[7]. However, this performance is predominantly based on data from high volume expert centres with an arguable paucity of real-world data. Many have therefore questioned the view that men with a non-suspicious mpMRI can avoid a biopsy.

The aim of our current study was to analyse the ability of mpMRI to rule-out csPCa and permit men to avoid an immediate biopsy, namely sensitivity and NPV, in a real-world multi-centre setting.

Materials and Methods

Is mp**MRI** **E**nough (IMRIE) was a retrospective, multi-centre cohort study which included consecutive patients undergoing mpMRI for a clinical suspicion of prostate cancer at 10 sites who were approached by the lead and senior authors to participate from a total of 18 invited sites (January/2011- November/2018). Five of the involved centres would be classified as expert centres that have published their data or centres involved in the PROMIS trial. The study was registered as a service evaluation at each centre and local institutional ethical exemption was granted at each site. Inclusion criteria were men referred with a raised age-specific PSA level, abnormal digital rectal examination (DRE) or both who also underwent mpMRI and either a TRUS biopsy or transperineal systematic biopsy with sampling every 5-10mm. mpMRI was reported prospectively prior to biopsy. As this is real-world clinical data biopsy operators were not blinded to the mpMRI result and biopsy type and number of cores were at the discretion of each centre, including incorporated targeting either within the existing cores or separately identified. Patients were either biopsy-naïve or evaluated following one or more previous negative biopsies. Those with known prostate cancer (on active surveillance) or a PSA level >15ng/ml were excluded for consistency with the PROMIS trial entry criteria[4].

Outcome Measure

The primary objective was to demonstrate the ability of mpMRI to rule-out clinically significant prostate cancer (csPCa), namely sensitivity and NPV. We defined csPCa as ISUP Grade Group >/=2 (i.e., any Gleason >/=3+4). Different definitions were tested as per the methodology from the PROMIS trial including UCL/Ahmed 1 (any Gleason >/=4+3 or

maximum cancer core length [MCCL] >/=6mm of any grade) and UCL/Ahmed 2 (any Gleason >/=3+4 or MCCL >/=4mm of any grade). Gleason score was based on the most frequent two patterns seen, not on the highest grade detected on histological analysis. Secondary outcomes included testing variation in NPV with differing PSAD thresholds and describing inter-site variability. Specificity and positive predictive value (PPV) were also reported.

MRI

The MRI devices and reporter experience at each centre are shown in **Table 1**. Multiparametric MRI was used in all centres including T2-weighted, diffusion weighting (multi b-value for deriving apparent diffusion coefficient [ADC] maps with additional high *b*-value (*b*=1500 or 2000) sequences with dynamic gadolinium contrast enhancement. Images were given an MRI score from 1 to 5 (PI-RADS or LIKERT scoring systems); these were used interchangeably in this study and have been shown to have similar results [8,9]. The highest MRI score was recorded for the gland as a whole.

<Table 1>

Statistics

All data were collected retrospectively in each centre for consecutive cases. Diagnostic performance metrics (sensitivity, specificity, NPV and PPV) were calculated primarily when using a score threshold of 3 or greater to denote a suspicious mpMRI and MRI score 1-2 as non-suspicious and histology at the whole-gland level. These metrics were also calculated for each MRI score group using the final biopsy result at a whole-gland level as the reference test. NPV was calculated both as a whole for the cohort and for individual hospitals, except for two (centres 6 and 8) who did not provide sufficient data on non-suspicious mpMRIs as they were no longer routinely biopsying patients with a negative mpMRI during the study period. The primary analysis of diagnostic performance metrics were calculated with these two sites excluded, however a secondary analysis with them included was added for comparison. Other than centre 3, all other sites were still routinely biopsying patients with raised PSA and negative mpMRI's. In addition, diagnostic performance metrics were calculated when incorporating PSA density (PSAD) as this had previously been shown by a number of other studies to have predictive value for csPCa alongside MRI scores. Area Under the Receiver-operating characteristics (AUROC) curves were calculated for PSA level, PSAD, MRI score and a combination of PSAD and MRI score. Statistics were performed with a 5% significance level using the Statistical Package for the Social Sciences (SPSS, version 23; SPSS Inc., IMB Corp., Armonk, NY, USA) and R Core Team 2017 (R: A language and environment for statistical computing, version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Across 10 sites 2642 men were included (January/2011-September/2018). The mean age and PSA were 65.3 years (SD 7.8 years) and 7.5ng/ml (SD 3.3ng/ml) respectively (Table 2).

<Table 2>

<Figure 1>

Overall any cancer was detected in 64.0% (1691/2642) and csPCa according to the primary definition (ISUP >/=GG2) was found in 43.5% (1149/2642). This included 29.2% (771/2642) with ISUP Grade Group 2, 8.3% (218/2642) ISUP Grade Group 3, 2.8% (74/2642) ISUP Grade Group 4 and 3.3% (86/2642) ISUP Grade Group 5.

1371 (51.9%) patients underwent TRUS biopsy with a mean (SD) of 14.6 (4.3) cores and 1271 (48.1%) underwent transperineal biopsy with a mean 43.4 (19.4) cores taken. GG2 or greater prostate cancer was found in 37.7% (517/1371) of TRUS-biopsy and 49.7% (632/1271) of transperineal biopsy.

Table 3 shows the diagnostic results for sensitivity, specificity, PPV and NPV for mpMRI for each definition of clinically significant cancer. The sensitivity of mpMRI for the primary definition of clinically significant cancer (Grade Group >/=2) was 87.3% (95% CI 84.7-90.0%) and NPV 87.5% (95% CI 84.9-90.1%). Specificity of mpMRI was 49.8% (95% CI 46.8-52.8%) and PPV 49.2% (95% CI 46.2-52.3%). Table 4 shows these diagnostic metrics with the addition of Centres 6 and 8 that submitted no data for negative mpMRI's.

<Table 3>

<Table 4>

Table 5 shows the diagnostic results for the primary definition of csPCa (GG >/=2) according to biopsy type used. mpMRI had a sensitivity and NPV of 88.2% and 87.4%, respectively, in patients undergoing TRUS-biopsy, with an underlying 37.7% prevalence of csPCa. In patients

who underwent a transperineal biopsy sensitivity and NPV were 97.5% and 88.1%, respectively, with an underlying csPCa prevalence of 49.7%.

<Table 5>

Figure 2 shows the proportion of insignificant and significant cancer for each MRI score. 35.9% (606/1687) men had a non-suspicious MRI (MRI scores 1-2), in centres that submitted data for both positive and negative MRI scans. The detailed histology outcomes in those with ISUP GG >/=2 cancer in the men who still harboured csPCa in non-suspicious mpMRIs are shown in **Table 6.**

<Figure 2>

24% (635/2642) men had an MRI score 3, of whom 25.4% (161/635) had ISUP GG >/=2 on biopsy, the individual histology for these is shown in **Table 6**. 1390 had an MRI score of 4 or 5, of whom 65.5% (911/1390) had GG >/=2 (56.5% in MRI score 4; 76.6% in MRI score 5).

<Table 6>

The NPV varied between 82.9-91.3% across the different sites, although once the outlier of 82.9% was excluded the range was 87.7-91.3% (**Table 7)**. NPV could not be calculated for Centre 6 and Centre 8 due to insufficient data on negative mpMRI scans.

<Table 7>

PSA Density

<Table 8>

<Figure 3>

In patients with PSAD available (n=2360), the NPV increased from 88.1% to 90.6% for MRI scores 1-2 and from 81.5% to 86.3% for an MRI score of 1-3 when PSAD was <0.15ng/ml used (**Table 8)**. This could be further improved to 91.2% and 87.5%, respectively, with a more conservative PSAD threshold of 0.12ng/ml/ml. The respective AUROCs are shown in **Figure 3,** with MRI score alone AUROC 0.80 compared with MRI score and PSAD in combination 0.82 ($p<0.0001$).

Discussion

In summary, to our knowledge, IMRIE represents the largest 'real-world' multicentre evaluation of mpMRI in prostate cancer diagnosis. The high NPV of 87.5% and sensitivity of 87.3% suggest that men with a non-suspicious mpMRI (MRI score 1-2) have a low probability of harbouring csPCa. Indeed, this high detection rate also appears to be remarkably consistent across sites with NPV variation between 87.7-91.3%, with the exclusion of one outlier (82.9%). In men with a negative mpMRI and PSAD < 0.15ng/ml/ml the NPV improved to 90.6%. If a non-suspicious mpMRI is defined as MRI score 1,2 or 3 the NPV is 81.5%, rising to 86% if a PSAD cut-off of 0.15ng/ml/ml is used.

The NPV in our paper is consistent with previous prospective and retrospective studies (approximately 90%) [10–12]. The PROMIS study found a NPV of 75% and sensitivity of 88% for any Gleason 7 [4]. The improved NPV of 87.5% found in our study is to be expected given the more rigorous 5mm sampling performed in the PROMIS study [13]. The conclusion from many recent studies has been, that given such reassuring sensitivity and NPV, patients with a negative mpMRI could consider avoiding a prostate biopsy. Our findings support such a conclusion. Nonetheless, we have also shown that some clinically high-risk cancers can be missed with 10 ISUP GG3 cancers, 4 GG4 and 1 GG5; equivalent to 1 in every 50 patients with a negative mpMRI (2.4%). Whether a 12.5% risk of missing, or at least delaying the diagnosis of, any GG >/=2 or a 2.4% risk of missing a GG >/=3 cancer is acceptable is something that requires a discussion with each individual patient alongside the reassurance they are not immediately discharged from follow-up in either primary or secondary care.

There is much debate about the need to biopsy equivocal MRI score 3 lesions. This study suggests that 25% of Gleason >/=7 cancers would have been missed had these patients not undergone a biopsy. Even in those patients with a PSAD <0.15ng/ml/ml, 14% of GG >/=2 cancers would be missed; 14 (4%) would have GG >/=3. This is in line with the findings of Hansen et al. who found 18% GG >/=2 would have been missed with the inclusion of this PSAD cut-off [14]. Therefore, based on these findings, patients with MRI score 3 should probably still undergo a biopsy although a delayed surveillance strategy is unlikely to be significantly harmful from a cancer mortality perspective.

There is ongoing discussion about the value of PSA density as an additional piece of information in predicting biopsy outcomes – with many heralding it as an important missing piece of the puzzle to allow patients with a non-suspicious mpMRI to avoid a biopsy. Panebianco et al. recently showed that for patients with a non-suspicious mpMRI a hazard ratio of 7.57 (p<001) on multivariable cox regression analysis was found for PSAD <0.15ng/ml/ml in predicting a future csPCa diagnosis[15]. While Washino et al. found the addition of PSAD <0.15ng/ml/ml in conjunction with a MRI score <3 yielded 100% NPV csPCa, albeit in a study of 288 in whom these cut-offs applied to 38 patients [16].

In this large real-world series we found an increase in NPV from 88.1% to 90.1 when a PSAD cut-off of <0.15ng/ml was combined with a non-suspicious mpMRI (MRI score 1-2), this was further improved to 91.2% with a PSAD cut-off of <0.12ng/ml/ml. Furthermore, AUROC analysis found the inclusion of PSAD to be statistically significant. Although these findings are in line with the current literature, the improvement in NPV in the cases where it would be most important (MRI 1-2) was not as noteworthy in absolute terms as has been seen in

these previous studies and this should be taken into account if PSAD is being used as a defining factor in whether a patient undergoes a biopsy or not.

There is currently much support for an MRI-guided pathway in prostate cancer diagnostics, that includes no biopsy for non-suspicious mpMRI scans and targeted-only biopsy otherwise, as driven by studies such as PRECISION and 4M[1,2]. PRECISION showed a 12% increase in csPCa diagnosis and a 13% reduction in insignificant prostate cancer in the MRI-guided pathway despite not performing biopsies in patients with a negative MRI [1]. Our study (36% non-suspicious mpMRI) concurs with the findings of PRECISION (28% negative) and PROMIS (28%) that approximately one-third of patients could avoid an immediate biopsy if this pathway is followed. Further support for this has been provided by Panebianco et al. who reported on 1255 men with non-suspicious mpMRIs over 48months of follow-up that included a further mpMRI and biopsy [15]. This study found only a 5% risk of finding csPCa during follow-up, and there is now evidence showing a delay in treatment (and therefore diagnosis) of even higher risk prostate cancer is not necessarily associated with adverse outcomes [17].

However, much of this data comes from expert centres, for example the 4M study was performed using 3T MRI scanners, with two expert uroradiologists reporting by consensus [2]. There is no doubt that an MRI pathway could reduce the number of biopsies taken and therefore the associated complications, but the missed significant cancer rate reported in these studies may not be directly applicable to the real world. Our findings are consistent with NPVs that have previously been reported by the PROMIS and PICTURE studies, for instance, that utilised mapping biopsies for validate the imaging signal[4,18]. The MRI-First

trial, a prospective real-world study across 16 centres in France comparing systematic and targeted biopsy [3] also found 11.3% >/=Gleason 7 in their non-suspicious mpMRI group, including 2 (8.7%) tumours >/=ISUP GG3.

While the optimum biopsy strategy for prostate cancer diagnosis is developed, likely using multiple patient specific factors in conjunction with mpMRI and possibly the addition of biomarker testing, centres must be cautious in adopting novel strategies trialed at expert centres. It is essential that individual centres have good quality mpMRI scans reported by an expert uroradiologist reporting a high volume of prostate MRI's (this was a median of 300 per year in the PRECISION study[1]) and are aware of their own NPV. With this information an informed discussion can be had with patients at risk of prostate cancer about what they are willing to tolerate in terms of missed cancer weighed up against the toxicity of a biopsy. Furthermore, initially avoiding a biopsy does not mean discharge from any follow-up. A strict PSA follow-up protocol, which can utilise PSA density to inform thresholds for re-referral, must be in place to ensure those with false negative findings can be diagnosed at a later date whilst the cancer is still localised.

The major strength of this study is the real-world nature of the data. Patients are included from both district general hospitals and tertiary centres with 10 centres in total representing over 2,600 patient, with all providing reassuring results in terms of the accuracy of mpMRI in prostate cancer which seem consistent, on the whole. We report on what could be achieved by many centres in a healthcare setting that has shifted to pre-biopsy MRI following guideline change. One of the key criticisms of the change to pre-biopsy

MRI was the lack of real-world multicentre data and we believe this addresses this pertinent concern.

This study does have several limitations of note. First, due to the nature of data collection from multiple different sites with different record keeping systems in place the dataset is heterogenous with missing data points. Of note further detail of the biopsy technique such as standard TRUS or transperineal (Ginsberg, mapping, sectoral), and specifics of any targeted biopsies were not available. Second, whilst we believe these centres are more representative of the UK as a whole, there is also a possibility that such centres may be the exception too, considering they were so diligent in sharing their data for this analysis. Third, as with many such studies, a true negative cannot exist due to an imperfect reference test. This limitation is even more pertinent here as over 50% of the cohort underwent standard TRUS biopsy (in addition to any targeting) which was used as the reference test in those cases. Interestingly, the diagnostic metrics did not differ hugely between the TRUS biopsy and transperineal biopsy sub-groups. Finally, the retrospective analysis of the data could have led to selection and reporting bias, which may have either overstated or understated the diagnostic performance of mpMRI.

Conclusions

mpMRI when used in real-world setting is able to accurately rule-out csPCa, suggesting that about one-third of men might avoid an immediate biopsy. Men should be counselled about the risk of missing an early diagnosis of csPCa of around 9% when a negative mpMRI is used in combination with a PSAD cut-off of </=0.15ng/ml/ml.

Tables

Authorship

Stonier and Ahmed conceived the study.

Stonier and Simson recruited centres for participation in the study.

Stonier and [all other authors] collected the data for analysis.

Stonier, Mateen and Shah carried out the analysis.

Stonier, Simson, Shah and Ahmed wrote the first draft of the manuscript.

All authors carried out revisions to the manuscript and approved the final version.

Conflicts of interest

Ahmed's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) Imperial Biomedical Research Centre. Ahmed currently receives funding from the Wellcome Trust, Medical Research Council (UK), Prostate Cancer UK, Cancer Research UK, The BMA Foundation, The Urology Foundation, The Imperial Health Charity, Sonacare Inc., Trod Medical and Sophiris Biocorp for trials and studies in prostate cancer. Ahmed is a paid medical consultant for Sophiris Biocorp, Sonacare Inc. and BTG/Galil. Ahmed, is a paid proctor for HIFU, cryotherapy and Rezum water vapour therapy.

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