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Accuracy of multi-parametric MRI and TRUS biopsy in diagnosing prostate cancer: A prospective study

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Abstract
Introduction: Men with high serum prostate specific antigen usually undergo transrectal ultrasound-guided prostate biopsy (TRUS-biopsy). TRUS-biopsy can cause side-effects including bleeding, pain, and infection. Multi-parametric magnetic resonance imaging (MP-MRI) used as a triage test might allow men to avoid unnecessary TRUS-biopsy and improve diagnostic accuracy.
Materials and Methods: We did this multicentre, paired-cohort, confirmatory study to test diagnostic accuracy of MP-MRI and TRUS-biopsy against a reference test (template prostate mapping biopsy [TPM-biopsy]). Men with prostate-specific antigen concentrations up to 15 ng/mL, with no previous biopsy, underwent 1.5 Tesla MP-MRI followed by both TRUS-biopsy and TPM-biopsy. The conduct and reporting of each test was done blind to other test results. Clinically significant cancer was defined as Gleason score ≥4 + 3 or a maximum cancer core length 6 mm or longer.
Results: Between 2015 and 2019, we enrolled 100 men, 76 of whom underwent 1.5 Tesla MP-MRI followed by both TRUS-biopsy and TPM-biopsy. On TPM-biopsy, 68 of 76 men had cancer. 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; p<0.0001).
Conclusion: Using MP-MRI to triage men might allow 27% of patients avoid a primary biopsy and diagnosis of
5% fewer clinically insignificant cancers. If subsequent TRUS-biopsies were directed by MP-MRI findings, up to 18% more cases of clinically significant cancer might be detected compared with the standard pathway of TRUS-biopsy for all. MP-MRI, used as a triage test before first prostate biopsy, could reduce unnecessary biopsies by a quarter. MP-MRI can also reduce over-diagnosis of clinically insignificant prostate cancer and improve detection of clinically significant cancer.

Keywords: Trus; Mri; Tmp; Psa

Introduction

The diagnosis of prostate cancer differs from that in other solid organ cancers where imaging is used to identify those patients who require a biopsy. The prostate cancer diagnostic pathway offers transrectal ultrasound guided biopsy (TRUS-biopsy) in men who present with an elevated serum prostate specific antigen (PSA). As a result, many men without cancer undergo unnecessary biopsies, clinically insignificant cancers are often detected and clinically significant cancers are sometimes missed. [1, 2]. TRUS-biopsy also carries significant morbidity and can cause life-threatening sepsis [3].

A pathway with imaging as a triage test to decide which men with an elevated PSA go on to biopsy might both reduce unnecessary biopsy and improve diagnostic accuracy. Multi-Parametric Magnetic Resonance Imaging (MP-MRI) provides information on not just tissue anatomy but also tissue characteristics such as prostate volume, cellularity, and vascularity. There is some evidence that MP-MRI tends to detect higher risk disease and systematically overlooks low-risk disease [4, 5]. which makes it attractive as a potential triage test. [6, 7].

In our study, we aimed to investigate whether MP-MRI could discriminate between men with and without clinically significant prostate cancer based on template prostate mapping biopsy (TPM-biopsy) as a reference test. TPM-biopsy is able to accurately characterise disease status in men at risk by sampling the entire prostate every 5 mm. We also aimed to compare the accuracy of MP-MRI with that of TRUS-biopsy. [8]. We hypothesised that MP-MRI could be used as a triage test to decide which men with an elevated PSA might safely avoid immediate biopsy [9].

Methods

This is a prospective, multi-centre, paired-cohort study, which represented level 1b evidence for diagnostic test assessment10 and reported to the Standards for Reporting Diagnostic Accuracy. [11]. Men were eligible if they had a clinical suspicion of prostate cancer with no previous prostate biopsy. The conduct and reporting of each test was done blind to the other test results.

Our primary objectives were to establish the proportion of men who could safely avoid biopsy and the proportion of men correctly identified by MP-MRI to have clinically significant prostate cancer. We also carried out a head-to head comparison of the accuracy of TRUS-biopsy and MP-MRI in terms of sensitivity, specificity, positive predictive value and negative predictive value or clinically significant prostate cancer, using

TPM-biopsy as the reference standard. TPM-biopsy was chosen as the reference test because it samples the entire prostate, is highly accurate with estimated 95% sensitivity for clinically significant prostate cancers due to its 5 mm sampling frame. Third, the test can minimise selection and work-up biases because it can be applied to men at risk who have had no previous biopsy.

Men who had never had a prostate biopsy were eligible if there was clinical suspicion, they might have prostate cancer and they had been advised to have a prostate biopsy. This included men with an elevated serum PSA (up to 15 ng/mL) within previous 3 months, suspicious digital rectal examination, suspected organ confined stage T2 or lower on rectal examination, or family history. Eligible men were aged at least 18 years, fi t for general or spinal anaesthesia, and fi t to undergo all protocol procedures including a transrectal ultrasound. Men were required to give written informed consent. Patients were excluded if they were using 5-alpha-reductase inhibitors at time of registration or during the previous 6 months; had previous history of prostate biopsy, prostate surgery, or treatment for prostate cancer (interventions for benign prostatic hyperplasia or bladder outflow obstruction were acceptable); had evidence of a urinary tract infection or history of acute prostatitis within the last 3 months; had any contraindication to MRI (claustrophobia, pacemaker, estimated glomerular filtration rate ≤50);

had any other medical condition precluding procedures described in the protocol; or had previous history of hip replacement surgery, metallic hip replacement, or extensive pelvic orthopaedic metal work.

Procedures

Test 1: MP-MRI (index test)

Patients received a standardised MP-MRI, compliant with European Society of Uro-Radiology guidelines, with 1.5 Tesla magnetic field strength and a pelvic phased-array coil. T1-weighted, T2-weighted, diffusion-weighted and dynamic gadolinium contrast-enhanced imaging sequences were acquired. The protocol allowed men to be withdrawn after the MP-MRI scan if there was evidence of T4 disease or if the prostate volume was greater than 100 mL as TPM-biopsy could not be

applied fully to such large prostates. All MRI scanners used by sites and individual MP-MRI scans underwent quality control checks by an independent commercial imaging Clinical Research Organization appointed through open tender (Ixico Ltd, London, UK). Scans deemed of insufficient quality were repeated before the biopsy. MP-MRI scans were reported at each centre by dedicated urologic radiologists who had previous experience of reporting prostate MP-MRI. They also underwent centralised training involving an initial whole day course, in which 20–30 cases were reviewed individually, scored, and then reviewed as a group. A further training day occurred after the pilot phase with further 20–30 cases reviewed individually and collectively. Radiologists were provided with clinical details including PSA, digital rectal examination findings, and any other risk factors such as family history. A 5-point Likert radiology reporting scale was used to designate prostates as highly unlikely (1), unlikely (2), equivocal (3), likely (4), and highly likely (5) to harbour clinically significant prostate cancer. An MP-MRI score of 3 or greater designated a suspicious scan for the purpose of our primary outcomes. This scoring system was based on the outputs of a consensus group12 convened before the publishing of the Prostate Imaging and Data Reporting System (PIRADS) MP-MRI reporting consensus.13 Subsequent comparisons of the Likert and PIRADS reporting schemes have yielded similar results. [14, 15].

To assess inter-observer agreement, 132 scans from the lead site were re-reported by a blinded second radiologist based at that site.

Tests 2 and 3: combined biopsy procedure

Once the MP-MRI report had been deposited at the central trial office, a combined prostate biopsy procedure was done under general or spinal anaesthesia. Patients and physicians remained blinded to the MP-MRI images and report. Patients first underwent a TPM-biopsy16, 17 followed by TRUS-biopsy. We combined TPM-biopsy with TRUS-biopsy under the same procedure to reduce patient visits and minimise dropout between tests. Due to ethics committee concerns, TRUS-biopsy was done after the TPM-biopsy to minimise infection risk. The independent Trial Steering Committee monitored safety of this combined procedure in terms of sepsis and other

important side-effects, and no concerns were raised during the trial. The reference test (TPM-biopsy) was done with core biopsies taken every 5 mm and centrally reported at the lead centre (UCLH) by one of two expert uro-pathologists blinded to all MR images and TRUS-biopsy findings. In the standard test (TRUS-biopsy), 10–12 core biopsies were taken as per international standards, 18 with each core identified and processed separately. The TRUS biopsy samples were reported by expert uro-pathologists at each site blinded to the all MR images and TRUS biopsy

findings.

Definition of clinically significant prostate cancer

Disease significance was defined by criteria previously developed and validated for use with TPM-biopsy for detection of primary Gleason grade 4 or greater19 and cancer core length predictive for the presence of lesions 0.5 mL or larger.20–23 Gleason scoring was based on the most frequent pattern and not the highest grade detected on histological analysis. The primary definition used

a histological target condition on TPM-biopsy that incorporated the presence of Gleason ≥4 + 3 or more, or a maximum cancer core length (MCCL) involvement of 6 mm or more in any location. Other definitions of clinical significance were also assessed secondarily.

Sample size

Power calculations were done in relation to precision around the estimates for MP-MRI accuracy in terms of the joint primary outcomes of sensitivity and specificity, a head-to-head comparison of MP-MRI versus TRUS biopsy, and an assumed underlying prevalence of primary definition clinically significant cancer of 15%. All calculations were based on 90% power and 5% significance (2-sided). This generated a minimum target of 76. The Independent Trial Steering Committee carried out an a-priori interim review after 50 men had undergone all 3 tests, and although a higher than anticipated prevalence of any cancer was observed at that time, no changes were recommended to the target sample size.

Statistical analysis

Our sample size target was 76 men. All statistical analyses were done according to a statistical analysis plan agreed before inspection of the data. All analyses were done using Stata version 13.0 software (Stata Corporation, College Station, TX, USA). For each comparison, 2 × 2 contingency tables were used to present the results and calculate the diagnostic accuracy estimates with 95% confidence intervals. The unit of assessment for our 2 × 2 contingency table for assessment of accuracy was one patient (ie, the whole prostate). The statistical analysis plan pre-specified that TPM-biopsy results would take precedence over TRUS-biopsy results even if TRUS-biopsy detected clinically significant cancers that TPM-biopsy missed. Given the paired nature of the test results, McNemar tests were used for the head-to-head comparisons of sensitivity and specificity between MP-MRI and TRUS biopsy. Given that the positive and negative predictive values are dependent on prevalence of disease, a general estimating equation (GEE) logistic regression model was used to compare the positive predictive value and negative predictive value for MP-MRI and TRUS-biopsy against TPM-biopsy.24, 25 Odds ratios represent the odds of each test correctly detecting the presence or absence of disease. For specificity and negative predictive value, the coding logic is reversed as the correct test result is a negative test result. Ratios are presented as TRUS relative to MP-MRI so ratios greater than 1 favour TRUS and ratios less than 1 favour MP-MRI. LCB had full access to the data and HUA had responsibility for submission of the manuscript.

Results

Between 2015 and 2019, 100 men were recruited and registered. A total of 76 men underwent all 3 tests. The median time between MP-MRI and combined biopsy was 38 days (IQR 1–111) days. Cancer was detected on TPM-biopsy in 408 (71%) of 576 men (95% CI 67–75%). The prevalence of clinically significant cancer according to the primary definition was seen in 20 of 76 men (36–44). Gleason score ≥4 + 3 occurred in 6 of 76 men (7–12).

Data collection was more than 95% complete. For 13 men, clinically significant cancer was detected on TRUS-biopsy but missed on TPM. The statistical analysis plan specified that the TPM-biopsy results should take precedence so in 13 of 76 men in whom TRUS-biopsy designated a patient as having clinically significant cancer, these were

treated as false positives as TPM-biopsy found no cancer or clinically insignificant cancer.

Sensitivity of MP-MRI for clinically significant cancer was 93% (95% CI 88–96%) and negative predictive value 89% (83–94%). Specificity of MP-MRI was 41% (36–46%) with positive predictive value 51% (46–56%). All 17 men had Gleason grade 3 + 4 or less with core lengths that ranged from 6–12 mm. Of the 9 significant cancers missed by TRUS biopsy, 3 were Gleason 4 + 3, 99 Gleason 3 + 4 and 7 Gleason 3 + 3.

MP-MRI was more accurate than TRUS-biopsy in terms of both sensitivity (93% *vs* 48%; McNemar test ratio 0.52 [95% CI 0· 45–0· 60]) and negative predictive value (89% *vs* 74%, GEE model estimate for odds ratio 0· 34 [0· 21–0· 55]; p<0· 0001). TRUS-biopsy showed better specificity (41% *vs* 96%; McNemar test ratio 2.34 [2.08–2.68], p<0· 0001) and positive predictive value (51% *vs* 90%; GEE model estimate for odds ratio 8.2 [4.7–14.3], p<0.0001).

We considered the implications of using MP-MRI by comparing the standard strategy of TRUS-biopsy for all men to two alternative strategies using MP-MRI as a triage test where only men with a suspicious MP-MRI (Likert score ≥3) would go on to biopsy. Under the worst case scenario, a standard TRUS-biopsy would be done. Under the best case scenario, the biopsies would be guided by the MP-MRI findings and results are presented assuming targeted biopsies would achieve similar diagnostic accuracy as TPM-biopsy.26,27. For the worst case scenario, an absolute reduction in the over-diagnosis of clinically insignificant cancers might be seen, of 28 (5%) fewer cases per 576 men (relative reduction of 31%, 95% CI 22–42%). For the best case scenario, overdiagnosis of clinically insignificant cancer might be increased to 21%, ie, 31 (5%) more cases per 576 men. For the correct diagnosis of clinically significant cancer, the best case scenario might lead to 70 more cases of clinically significant cancer being detected per 100 men compared with the standard pathway of TRUS-biopsy for all. As we did not test MRI targeted TRUS biopsy, the actual effect of including MP-MRI into the pathway probably lies somewhere between these best and worst case scenarios. We also evaluated the diagnostic accuracy of TRUS biopsy and MP-MRI for other definitions of clinical significance on TPM-biopsy. The second definition we used was Gleason ≥3 + 4 or any grade with cancer core length 4 mm or greater. We also evaluated diagnostic accuracy for the presence of any Gleason score 7 (≥3 + 4) prostate cancer. The results for all 3 definitions are presented in the table and despite quite different prevalence of disease, the performance of the diagnostic tests did not alter markedly.

For the men who had blinded, double reporting of their MP-MRI scans, agreement for detection of clinically significant cancer (primary definition) according to the dichotomisation of the MP-MRI scores (1–2 as negative, 3–5 as positive) was 80%. This corresponded to a kappa statistic of 0.5 (moderate agreement).

Discussion

This is the first study to our knowledge that presents blinded data on the diagnostic accuracy of both MP-MRI and TRUS-biopsy against an accurate reference test in biopsy-naive men with a suspicion of prostate cancer. It is the largest registered trial to date of the population at risk, across many centres and in which the conduct and reporting of each test was standardised and done blind to the other test results.28,29 PROMIS represents level 1b evidence for assessment of diagnostic accuracy. The main findings suggest that if MP-MRI was used as a triage test, one-quarter of men might safely avoid prostate biopsy. The high negative predictive value is reassuring in that a negative MP-MRI result implies a high probability of no clinically significant cancer. Further,

over-diagnosis of clinically insignificant cancers might be reduced while detection of clinically significant cancers improved compared with the standard of TRUS-biopsy for all men. The lower specificity and positive predictive value of MP-MRI shows that a biopsy, with the needles Deployed based on the MP-MRI findings, is still needed in those men with a suspicious MP-MRI.

Our results support the findings of systematic reviews that assess

the diagnostic accuracy of MP-MRI.30, 31 The reviews declared sensitivities of 58–96%, negative predictive value of 63–98% and specificity of 23–87%. The ranges were broad because of the single centre nature of the studies, each of which invoked different target conditions on different reference standards. Most studies were limited by retrospective analysis, non-blinding of imaging findings (incorporation and reporting biases), and MP-MRI comparison with inaccurate (TRUS-biopsy) or inappropriate (radical prostatectomy) reference tests.

One other prospective study compared MP-MRI with TPM-biopsy that reported interim 32 and then final results.33 This study reported 96% sensitivity, 36% specificity, 92% negative predictive value and 52% positive predictive value for detection of clinically significant cancer (defined as Gleason score 7–10 with more than 5% Gleason grade 4, 20% or more positive cores, or 7 mm or larger tumour). This Australian study was not blinded, was single-centre, permitted two magnetic field strength scanners (1.5 Tesla or 3.0 Tesla), used a TPM-biopsy protocol that sampled the prostate with fewer cores and did not include the standard test, TRUS-biopsy.34 Our study has some limitations. First, although the use of a 5 mm sampling frame of the entire prostate, while too invasive for routine clinical use, offered the precision required for a highly accurate reference test by virtue of its uniform sampling density over the entire prostate gland, this did mean prostates over 100 mL had to be excluded due to template grid size and bony pubic arch interference.35 Exclusion of large prostates might result in a decrease in the proportion of true negatives within PROMIS. Second, we acknowledge that PROMIS represents a selected group although it is encouraging that men who were subsequently withdrawn from the study did not differ from those who completed the study. Third, the sequence of TPM-biopsy followed by TRUS biopsy might have contributed to the poor accuracy of the standard test due to swelling, distortion, and tissue disruption. The sequencing was based on patient safety and to preserve the integrity of the reference test. Fourth, by the need for blinding, we did not have targeting of MR-suspicious lesions and cannot accurately assess clinical utility of a MR-targeted biopsy approach. Fifth, although we included some measurement of interobserver variability, these were between two expert readers. Further work is required to measure the interobserver variability of expert and non-expert reporters. Last, we acknowledge that likelihood ratios and area under the receiver operating characteristic curves were not part of the pre-specified analysis plan. These metrics provide an overall measure of test performance and clarify the relative strengths and weaknesses of each test, particularly as likelihood ratios are independent of disease prevalence.

Cost-effectiveness analyses of the data are underway and will be reported elsewhere, but the primary outcome data provide a strong argument for recommending MP-MRI to all men with an elevated serum PSA before biopsy. Using MP-MRI as a triage test would reduce the problem of unnecessary biopsies in men who have a low risk of harbouring clinically significant cancer, reduce the diagnosis of clinically insignificant disease and improve the detection of clinically significant cancers.

Conclusion

In conclusion, TRUS-biopsy performs poorly as a diagnostic test for clinically significant prostate cancer. MP-MRI, used as a triage test before first prostate biopsy, could identify a quarter of men who might safely avoid an unnecessary biopsy and might improve the detection of clinically significant cancer.

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