Multiparametric MRI to improve detection of prostate cancer compared with transrectal ultrasound-guided prostate biopsy alone: the PROMIS study

Louise Clare Brown,[1] Hashim U Ahmed,[2,3]* Rita Faria,[4] Ahmed El-Shater Bosaily,[2,3] Rhian Gabe,[5] Richard S Kaplan,[1] Mahesh Parmar,[1] Yolanda Collaco-Moraes,[1] Katie Ward,[1] Richard Graham Hindley,[6] Alex Freeman,[7] Alexander Kirkham,[8] Robert Oldroyd,[9] Chris Parker,[10] Simon Bott,[11] Nick Burns-Cox,[12] Tim Dudderidge,[13] Maneesh Ghei,[14] Alastair Henderson,[15] Rajendra Persad,[16] Derek J Rosario,[17] Iqbal Shergill,[18] Mathias Winkler,[19] Marta Soares,[4] Eldon Spackman,[4] Mark Sculpher[4] and Mark Emberton[2,3] on behalf of the PROMIS Study Group

[1]Medical Research Council Clinical Trials Unit, University College London, London, UK
[2]Division of Surgery and Interventional Science, Faculty of Medical Sciences, University College London, London, UK
[3]Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK
[4]Centre for Health Economics, University of York, York, UK
[5]Hull York Medical School and Department of Health Sciences, University of York, York, UK
[6]Department of Urology, Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK
[7]Department of Histopathology, University College London Hospitals NHS Foundation Trust, London, UK
[8]Department of Radiology, University College London Hospitals NHS Foundation Trust, London, UK
[9]Public and patient representative, Nottingham, UK
[10]Department of Academic Urology, Royal Marsden Hospital, Sutton, UK
[11]Frimley Park Hospital, Frimley, UK
[12]Musgrove Park Hospital, Taunton, UK

[13]Southampton General Hospital, Southampton, UK
[14]Department of Urology, Whittington Hospital, London, UK
[15]Maidstone Hospital, Maidstone, UK
[16]Bristol Urological Institute, Southmead Hospital, Bristol, UK
[17]Royal Hallamshire Hospital, Sheffield, UK
[18]Wrexham Maelor Hospital, Wrexham, UK
[19]Charing Cross Hospital, Imperial College London, London, UK

*Corresponding author hashim.ahmed@imperial.ac.uk

Declared competing interests of authors: Hashim U Ahmed reports grants and personal fees from SonaCare Medical, Sophiris Bio Inc. and Galil Medical and grants from TROD Medical outside the submitted work. He conducts private practice in London for the diagnosis and treatment of patients with potential prostate cancer through insurance schemes and self-paying patients in addition to his NHS practice. Ahmed El-Shater Bosaily reports grants and non-financial support from University College London Hospitals/University College London Biomedical Research Centre, grants and non-financial support from The Royal Marsden NHS Foundation Trust and the Institute for Cancer Research Biomedical Research Centre and non-financial support from the Medical Research Council's Clinical Trials Unit during the conduct of the study. Mark Emberton reports grants from Sophiris Bio Inc., grants from TROD Medical, other support from STEBA Biotech, grants and other support from SonaCare Medical and other support from Nuada Medical and London Urology Associates, outside the submitted work. Rita Faria reports grants from the National Institute for Health Research during the conduct of the study. Richard Graham Hindley reports payment as a Clinical Director from Nuada Medical during the period of recruitment. Alexander Kirkham reports other support from Nuada Medical outside the submitted work. Derek J Rosario reports personal fees from Ferring Pharmaceuticals Ltd and grants from Bayer Pharmaceuticals Division, outside the submitted work. Iqbal Shergill reports grants from Ipsen and Astellas Pharma Inc. and non-financial support from Boston Scientific and Olympus, outside the submitted work. Eldon Spackman reports personal fees from Astellas Pharma Canada, Inc., outside the submitted work. Mathias Winkler reports grants and personal fees from Zicom-Biobot (Singapore), outside the submitted work.

Published July 2018
DOI: 10.3310/hta22390

Scientific summary

The PROMIS study

Health Technology Assessment 2018; Vol. 22: No. 39
DOI: 10.3310/hta22390

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Increasing numbers of men are being referred for prostate biopsy with suspected prostate cancer in the UK, mainly as a result of the increased use of serum prostate-specific antigen (PSA) testing in healthy men. Many of the cancers currently diagnosed are clinically non-significant (CNS) (i.e. are unlikely to have any clinical impact on the individual during his remaining life). If left unchecked, the existing diagnostic pathway will result in a further rise in the number of CNS cases identified and in the associated costs and harms of treatment, without necessarily reducing the risk of dying from the disease.

The standard diagnostic procedure is transrectal ultrasound (TRUS)-guided biopsy. Unlike procedures in other solid cancers, this technique is 'blind' to the location of the suspect lesion, because ultrasonography serves only to locate the prostate and cannot differentiate between cancerous and non-cancerous tissue. The unguided placement of the needles means that CNS cancers may be detected and clinically significant (CS) cancers may be missed.

A diagnostic method more specific to CS prostate cancer could reduce the unnecessary harms and costs associated with overdiagnosis and overtreatment of CNS cancers.

Objectives

The purpose of the PROstate Magnetic resonance Imaging Study (PROMIS) was to trial the use of multiparametric magnetic resonance imaging (mpMRI) in the diagnosis of prostate cancer. The main objectives were to:

- assess the ability of mpMRI to identify men who can safely avoid unnecessary biopsy
- assess the ability of a diagnostic pathway incorporating mpMRI to improve detection of CS cancer compared with TRUS-guided biopsy
- use economic modelling to identify the most efficient and cost-effective diagnostic strategy in men with suspected localised prostate cancer from the perspective of the UK NHS.

Methods

Diagnostic study

PROMIS was a validating paired-cohort study in men at risk of prostate cancer undergoing a first prostate biopsy, conducted at 11 NHS hospitals in England. To compare the diagnostic accuracy of mpMRI (the index test) and TRUS-guided biopsy (the current standard), both were individually compared with a reference standard: template prostate mapping (TPM) biopsy. All participants underwent all three tests (mpMRI, TPM-biopsy and TRUS-guided biopsy). Multiparametric magnetic resonance imaging was carried out first. TPM-biopsy followed by TRUS-guided biopsy was carried out as a combined biopsy procedure (CBP) at a subsequent visit. The CBP was carried out for the purposes of the study only and is not proposed for use in clinical practice. Each test was conducted blind to the results of the other tests and was reported independently of them.

The eligible population was adult men at risk of prostate cancer who had been advised to have a prostate biopsy and had a serum PSA level of $\leq$ 15 ng/ml within the previous 3 months, had a suspected stage of $\leq$ T2 on a rectal examination (i.e. organ confined) and were fit for general/spinal anaesthesia. Men with a

PSA level of > 15 ng/ml were excluded as the higher prevalence of prostate cancer in this subgroup means that mpMRI is unlikely to be used as a triage test in these men.

Multiparametric magnetic resonance imaging was carried out according to a standardised protocol in which T1-weighted, T2-weighted, diffusion-weighted (apparent diffusion coefficient maps and long-b scan) and dynamic gadolinium contrast-enhanced imaging was acquired using a 1.5-T scanner and a pelvic phased array. Radiologists used a standard reporting form to derive a 1–5 score on the Likert scoring system to indicate the suspicion level for CS cancer. TRUS-guided biopsies were taken as per international guidelines and incorporated 10–12 core biopsies. TPM-biopsy was carried out in accordance with a standardised protocol.

The primary definition of CS cancer in this trial used a histological target condition on TPM-biopsy that incorporated the presence of a Gleason score of $\geq 4 + 3$ and/or a cancer core length of ≥ 6 mm in any location. This was chosen because nearly all physicians would agree that any man with this burden of cancer would require treatment. A secondary definition was also investigated: cancer core length of ≥ 4 mm and/or a Gleason score of $\geq 3 + 4$. The primary magnetic resonance imaging (MRI) outcome measure (i.e. the threshold against which the Likert scores were given) was defined as a prostate cancer volume of ≥ 0.2 ml and/or a Gleason score of $\geq 3 + 4$. Two analyses were carried out: (1) using a Likert score of ≥ 3 to indicate a positive MRI result (primary analysis) and (2) using a cut-off point of ≥ 4.

The primary outcome measure was the diagnostic accuracy of mpMRI, TRUS-guided biopsy and TPM-biopsy as measured by sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using the primary definition of CS cancer. The same parameters using combinations of alternative definitions of disease for each test were investigated as secondary outcomes. The other outcomes reported were inter-rater agreement between tests and serious adverse events (SAEs). Information on health-related quality of life (HRQoL) was collected using the EuroQol-5 Dimensions, three-level version questionnaire after each test and at the final visit and was used in the economic evaluation.

The primary analysis was based on all evaluable data, excluding men without all three test results and any data rejected by the quality control/quality assurance process. For each comparison, 2×2 contingency tables were used to calculate the diagnostic accuracy estimates with 95% confidence intervals (CIs). McNemar's tests were used for the head-to-head comparisons of sensitivity and specificity between mpMRI and TRUS-guided biopsy. Because the PPVs and NPVs are dependent on disease prevalence, a generalised estimating equation logistic regression model was used to compare these values for mpMRI and TRUS-guided biopsy against those for TPM-biopsy.

Economic evaluation

The economic analysis aimed to identify the most efficient and cost-effective diagnostic strategy in men with suspected localised prostate cancer from the perspective of the UK NHS. It considered all feasible combinations of TRUS-guided biopsy, mpMRI and TPM-biopsy, within the various definitions and cut-off points for CS cancer.

The efficient diagnostic strategies were those that detected the most men with CS cancer (i.e. sensitivity) per £1 spent on testing. The cost-effective strategies were those that achieved the most health benefits, expressed as quality-adjusted life-years (QALYs), per £1 spent over the patients' expected lifetime. The cost-effective strategies were identified for the values of health opportunity cost, also known as cost-effectiveness thresholds, typically used in the UK NHS (i.e. £13,000, £20,000 and £30,000 per QALY). The cost-effective strategy for a given health opportunity cost is the strategy that achieves the most health benefits net of the health displaced given its additional costs.

A new decision-analytic model was developed to combine the information generated in PROMIS with external evidence as appropriate. For the short term, the model calculates the proportion of CS cancers detected by each strategy and the costs and HRQoL consequences of the tests. The model assumed that

biopsies, both TRUS-guided and TPM, detect only cancer, either CS or CNS, if cancer is present. Therefore, the specificity of each strategy is always perfect.

For the long term, the model calculates the health outcomes and costs of men with no cancer and low-risk, intermediate-risk and high-risk cancer, by diagnostic classification (no cancer, CNS cancer and CS cancer). Men classified as having CS cancer were assumed to receive radical treatment [radical prostatectomy (RP)], whereas men classified as having CNS cancer were monitored in secondary care (active surveillance) and men classified as having no cancer were followed in primary care. Therefore, the model calculates the health outcomes and costs of diagnosis and treatment of the men with CS cancer who were correctly identified, as well as misdiagnosis and delayed treatment of men with CS cancer who were not identified.

Results

Diagnostic study

A total of 740 men were registered to the trial, of whom 164 subsequently withdrew before completing all three tests. Most withdrawals took place before the combined biopsy and the most common reason for withdrawal was the discovery of a large prostate volume (> 100 ml). A total of 576 men were included in the final analysis.

The prevalence of any cancer as assessed by the reference test, TPM-biopsy, was 71% (95% CI 67% to 75%). The prevalence of CS cancer according to the primary definition (a Gleason score of $\geq 4 + 3$ and/or cancer core length of ≥ 6 mm) was 40% (95% CI 36% to 44%). TRUS-guided biopsy showed sensitivity for CS cancer of 48% (95% CI 42% to 55%) and specificity of 96% (95% CI 94% to 98%). The PPV was 90% (95% CI 83% to 94%) and the NPV was 74% (95% CI 69% to 78%). The sensitivity of mpMRI for CS cancer was high at 93% (95% CI 88% to 96%) and the NPV was 89% (95% CI 83% to 94%). However, its specificity was 41% (95% CI 36% to 46%), with a PPV of 51% (95% CI 46% to 56%). A negative mpMRI scan was recorded for 158 men (27%). Of these, 17 men were found to have CS cancer on TPM-biopsy.

We considered the implications of using mpMRI in clinical practice by comparing the current standard strategy (TRUS-guided biopsy for all men) with two alternative strategies: (1) mpMRI would be used as a triage test and only men with a suspicious mpMRI result (Likert score of ≥ 3) would go on to biopsy and (2) the remainder would receive active surveillance or would be discharged. Under the worst-case scenario, a standard TRUS-guided biopsy would be carried out but mpMRI would not be used to direct it. Under the best-case scenario, the TRUS-guided biopsies would be guided by the mpMRI findings and it would be assumed that targeted biopsies would achieve a similar diagnostic accuracy to that of TPM-biopsy. For both of these scenarios, 158 out of 576 men (27%) would avoid a primary biopsy, because they would be categorised by mpMRI as having either no cancer or CNS cancer, but 17 men in this group would have a CS cancer missed. For the worst-case scenario, an absolute reduction in the overdiagnosis of CNS cancers might be seen, with 28 out of 576 fewer cases (5%) [relative reduction of 31% (95% CI 22% to 42%) compared with the current standard]. Under the best-case scenario, overdiagnosis might be increased to 21% [i.e. there would be 31 out of 576 more cases (5%)]. However, it might also lead to 102 out of 576 more cases (18%) of CS cancer being detected compared with the standard pathway of TRUS-guided biopsy for all.

Agreement between radiologists for the detection of CS cancer according to the primary definition was 80%. This corresponded to a Cohen's kappa statistic of 0.5, indicating moderate agreement.

There were 44 reports of SAEs during the study, including 10 cases of sepsis (of which nine occurred after CBP, equating to a post-CBP risk of 1.5%). As emphasised earlier, CBP is not proposed for use in clinical practice.

Economic evaluation

Multiparametric magnetic resonance imaging, TRUS-guided biopsy and TPM-biopsy can plausibly be used in 32 different combinations to diagnose prostate cancer. These were evaluated for different diagnostic definitions and cut-off points, forming 383 diagnostic substrategies. Strategies using the secondary TRUS-guided biopsy definition (definition 2) and primary mpMRI definition (definition 2) detected more CS cancers. Of the 383 substrategies, 14 were efficient in that they detected the most CS cancers per £1 spent. Of these, four substrategies detected ≥ 80% of CS cancers. These substrategies involved mpMRI, either as the first or the second test, and up to two biopsies.

In the base case, the cost-effective strategy at the health opportunity costs of £13,000, £20,000 and £30,000 per QALY gained involves testing all men with mpMRI using definition 2 and cut-off point 2 for CS cancer (a less restrictive definition than used in the primary outcome of PROMIS, leading to more men receiving a biopsy, but fewer CS cancers being missed by the initial MRI) and using MRI-targeted, TRUS-guided biopsy and definition 2 to detect CS cancer and rebiopsying those men in whom CS cancer was not detected. This strategy detects 95% of CS cancers (95% CI 92% to 98%), achieves 8.72 discounted QALYs (95% CI 8.40 to 9.04 discounted QALYs) and costs £5367 (95% CI £4947 to £5876). This sequence of tests constitutes the proposed PROMIS strategy, albeit using the TRUS-guided biopsy definition 1 and mpMRI cut-off point 3. At this definition and cut-off point, this strategy detects 82% of CS cancers (95% CI 75% to 87%), achieves 8.65 discounted QALYs (95% CI 8.35 to 8.95 discounted QALYs) and discounted costs of £5027 (95% CI £4609 to £5512). The standard care strategy without mpMRI is TRUS-guided biopsy in all men and rebiopsy for those in whom CS cancer was not detected, both using definition 1. This strategy detects 52% of CS cancers (95% CI 45% to 61%), achieves 8.49 discounted QALYs (95% CI 8.19 to 8.80 discounted QALYs) and has discounted costs of £4603 (95% CI £4174 to £5044). The strategy recommended by the National Institute for Health and Care Excellence involves TRUS-guided biopsy in all men. Men in whom CS cancer using definition 1 is not detected receive mpMRI. Men with suspected CS cancer on mpMRI using definition 2 and cut-off point 3 receive a second TRUS-guided biopsy, evaluated using definition 1. This detects 85% of CS cancers (95% CI 78% to 91%), achieves 8.66 discounted QALYs (95% CI 8.36 to 8.97 discounted QALYs) and has discounted costs of £5173 (95% CI £4755 to £5664).

Sensitivity analysis suggests that the main drivers of cost-effectiveness are the unit cost of each test, the improvement in sensitivity of MRI-targeted, TRUS-guided biopsy compared with blind TRUS-guided biopsy and the cost-effectiveness of radical treatment and active surveillance.

Conclusions

The current standard, TRUS-guided biopsy, performs poorly as a diagnostic test for CS prostate cancer. Our findings suggest that if mpMRI were used as a triage test prior to biopsy in all men with an elevated serum PSA level then one-quarter of men might safely avoid a biopsy, thus reducing the problem of unnecessary biopsies in men with a low risk of harbouring CS cancer. A negative mpMRI result infers a high probability of no CS cancer. Triage with mpMRI might also reduce the diagnosis of CNS cancers and improve the detection of CS cancers compared with the current standard of TRUS-guided biopsy for all men with suspected localised prostate cancer. However, the lower specificity and PPV of mpMRI demonstrates that a biopsy, with the needles deployed based on the mpMRI findings, is still needed in those men with suspicious mpMRI findings.

The economic evaluation used the results from PROMIS alongside external evidence to ascertain the value of using these tests in sequence to support treatment decisions (when patients diagnosed with CS cancers would be referred for RP). It found that a strategy starting with mpMRI for all men and up to two TRUS-guided biopsies in men with suspected CS cancer using the most sensitive definitions (definition 2 and cut-off point 2) detects the most CS cancers per £1 spent and is cost-effective. These findings are sensitive to the costs of the tests and the assumptions made on the long-term management of men with unidentified cancers.

Trial registration

This study is registered as ISRCTN16082556 and NCT01292291.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research (NIHR). This project was also supported and partially funded by the NIHR Biomedical Research Centre at University College London (UCL) Hospitals NHS Foundation Trust and UCL and by The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research Biomedical Research Centre and was co-ordinated by the Medical Research Council's Clinical Trials Unit at UCL (grant code MC_UU_12023/28). It was sponsored by UCL. Funding for the additional collection of blood and urine samples for translational research was provided by Prostate Cancer UK.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.513

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 09/22/67. The contractual start date was in April 2016. The draft report began editorial review in November 2016 and was accepted for publication in July 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).