Multiparametric ultrasound versus multiparametric MRI to diagnose prostate cancer (CADMUS): a prospective, multicentre, paired-cohort, confirmatory study.

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Abstract

Background

Multiparametric MRI (mpMRI) of the prostate followed by targeted biopsy is recommended in patients at risk of prostate cancer. Multiparametric ultrasound (mpUSS) is more readily available. mpMRI and mpUSS visualise tissue anatomy, density and vascularity. Whilst there has been a large body of evidence supporting mpMRI incorporating paired cohort validation and randomised controlled trials, the evidence for ultrasound modalities on their own and mpUSS includes case series.

Methods

We conducted a prospective multicentre, paired-cohort, confirmatory study to compare mpUSS and mpMRI in diagnosing clinically-important prostate cancer. Patients at risk of prostate cancer underwent both tests at 7 UK hospitals, with conduct and reporting blinded to the results of the other. Patients with a positive mpUSS or mpMRI underwent targeted biopsies but were blinded to exact test results. If both tests were positive, the order of their targeting at biopsy was randomised. Co-primary outcomes were, a) proportion of positive mpMRI and mpUSS and b) detection of clinically-important cancer (Gleason>/=4+3 of any length or maximum cancer core length of >/=6mm of any grade). The study was registered on ISRCTN:38541912.

Findings

Between 15th/March/2016 and 7th/November/2019, 370 patients were enrolled, 306 completed both tests and 257 underwent a prostate biopsy. mpUSS and mpMRI were positive in 278/306 (88.9%; 95%CI=(84.8%, 92.2%)) and 238/306 (77.8%; 95%CI=(72.7%, 82.3%)) (difference +11.1% (95%CI=5.1,17.1%). Positive test agreement was 73.2% (95% CI=(67.9%, 78.1%), kappa=0.06). Cancer was detected in 133/257 (51.8%, 95%CI=(45.5%, 58.0%)) with 83/257 (32.3%; 95%CI=(26.6%, 38.4%)) clinically-important. Each test alone would result in mpUSS detecting

66/257 (25.7%; 95%CI=(20.5%, 31.5%)) clinically-important cancers and mpMRI detecting 77/257 (30.0%; 95%CI=(24.4%, 36.0%)) (difference -4.3%, 95%CI=(-8.3%, -0.3%). Combining both tests detected 83 clinically-important cancers (32.3%; 95%CI=(26.6%, 38.4%)); of these, mpUSS detected 6 (7.2%; 95%CI=(2.7%, 15.0%)) missed by mpMRI and mpMRI detected 17 (20.5%; 95% CI=(12.4%, 30.8%)) missed by mpUSS (agreement 91.1%; 95%CI=(86.9%, 94.2%); kappa=0.78). mpUSS and mpMRI detected 36/257 (14%; 95%CI=(10.0%-18.9%)) and 44/257 (17%; 95%CI=(12.7%, 22.3%)) clinically-unimportant cancers (by definition 1), respectively.

Interpretation

mpUSS detected 4.3% fewer clinically-important prostate cancers compared to mpMRI although would lead to 11.1% more patients being biopsied. Both modalities missed clinically-important cancers detected by the other so using both tests increased detection of clinically-important prostate cancers compared to each test alone.

Research in Context

The prostate cancer diagnostic pathway was previously reliant on transrectal ultrasound-guided biopsies without targeting of suspicious areas. This is because b-mode ultrasound alone was unable to accurately localise clinically-important cancers. Many healthcare settings now use multi-parametric MRI scans before biopsy because these have higher sensitivity for clinically-important prostate cancers. However, some healthcare settings are unable to access high quality MRI due to availability or cost, and some patients cannot have or tolerate MRI scans. This limits the dissemination of multi-parametric MRI globally.

Evidence before this study

We did not conduct a formal systematic review before this study given the paucity of published work at that point, in particular on multiparametric ultrasound. Evidence on the individual ultrasound modalities was garnered by medical database search including Medline, EMBASE, the Cochrane collection and PubMed as far back as 1990, using search terms ‘multi-parametric ultrasound’ ‘elastography’ ‘contrast enhanced ultrasound’ in combination with ‘prostate cancer’ or ‘prostate adenocarcinoma’ or ‘prostate biopsy’ or ‘prostate diagnosis’. Only one study reporting on multi-parametric ultrasound, a combination of different types of ultrasound imaging that can visualise prostate anatomy, cell density and vascularity, was identified. It has been reported to be more accurate than b-mode ultrasound alone and could be as accurate as multi-parametric MRI. The test is done on a device that is less expensive and mobile.

Added value of this study

The CADMUS trial compared multi-parametric ultrasound to multi-parametric MRI. It showed that patients at risk of prostate cancer had a similar chance of being diagnosed with clinically-important and unimportant prostate cancer with multi-parametric ultrasound or multi-parametric MRI. Ultrasound would lead to more men being biopsied if used on its own. However, some cancers were missed by both imaging types with more missed by ultrasound than MRI.

Using both tests together detected more clinically-important cancers although the chance of being biopsied was higher.

Implications of all the available evidence

Multi-parametric ultrasound should be used in patients at risk of prostate cancer in those healthcare settings which do not have ready access to high quality MRI and for those patients who have a contraindication or intolerance to MRI.

Introduction

Patients at risk of prostate cancer present with an elevated serum prostate specific antigen (PSA) level or a palpable abnormality on digital rectal examination (DRE). In many healthcare settings the strategy used to diagnose prostate cancer in such patients has changed from one using systematic biopsy to one using multiparametric MRI (mpMRI) in the first instance. In those patients advised to undergo biopsy the needle is targeted at areas of suspicion which improves detection [1,2,3,4].

For all the reported advantages of an mpMRI based pathway, there are limitations including availability and access in many healthcare systems. Data from the United States shows mpMRI pre-biopsy has risen slowly although remains very low overall [5,6,7] with reports of availability issues in Canada as well [8]. In Western Europe the picture has improved though with a focus on MRI in the re-biopsy or surveillance setting. Survey data shows pre-biopsy MRI in the biopsy naïve setting reported at 16% in Spain [9], 53% in France [10] and in Germany 41% [11] with cost cited as the concern when MRI was not employed for 78% of respondents. In the UK the situation is better with only 14% of centres not offering either multi or biparametric MRI to biopsy-naïve patients in 2018 [12]. Other factors include variability in scan quality or reporting [13] and contraindications to conducting mpMRI such as metal pelvic implants which degrade image quality or metallic fragments that might move in the magnetic field [14]. Cardiac implants require specialised facilities [15], and claustrophobia can lead to intolerance of the scan or movement causing artefact [16]. mpMRI also has a low specificity (overcome with a subsequent biopsy) and has moderate inter-reader variability as well as imaged conduct standardisation [4]. mpUSS itself may be unsuitable for some men however, for example in case of large or heavily calcified prostates, or where endorectal imaging is declined. Equally, whilst the initial capital outlay will be much lower, many centres may not have the correct equipment or expertise to carry out the full number of sequences.

Using a similar approach to mpMRI in which different types of MRI scans are combined, multi-parametric ultrasound (mpUSS) has been reported to have good accuracy in diagnosing prostate cancer. Similar to mpMRI, in which T2-weighted, diffusion-weighted, and dynamic contrast enhancement are used to visualise tissue structure, density and vascularity [17], mpUSS uses b-mode, elastography, Doppler, and contrast enhancement. We compared mpUSS and mpMRI in diagnosing clinically-important prostate cancer.

Methods

Trial Oversight: The confirmatory **CA**ncer **D**iagnosis by **M**ultiparametric **U**ltra**S**ound of the prostate **(**CADMUS) trial was a prospective paired cohort validation study set up to provide level one evidence on the diagnostic accuracy of mpUSS compared to mpMRI. It was conducted at 7 UK centres after approval by research ethics committee on 8^{th}/October/2015 (London - Brent Research Ethics Committee ref: 15/LO/1331). The trial protocol has been published [18] and includes a detailed description of mpUSS and mpMRI scan acquisition and reporting, as well as the biopsy procedure. A protocol amendment, approved on 28^{th}/March/2018, allowed either transperineal or transrectal biopsy. The trial was designed and is reported in line with the Standards in Reporting of Diagnostic studies (STARD) [19].

Following written informed consent, all eligible patients underwent both scans, mpUSS and mpMRI, at separate visits with each scan conducted and reported blind to the results of the other. Each scan was scored on a Likert scale from 1 to 5 with patients having lesions scoring >/=3 advised to undergo targeted prostate biopsy. Up to two suspicious lesions from each imaging modality were biopsied. Areas of the prostate that were not suspicious on either scan type were not biopsied. The trial was conducted and managed through the UCL Surgical and Intervention Trials Unit. Oversight was provided by an independent Trial Steering Committee and prospectively collected data entered into the regulator approved InferMed Macro secure electronic database.

Patients: Eligible patients were those presenting for the first time with a suspicion of prostate cancer based on an elevated serum PSA or abnormal DRE, a prior negative prostate biopsy or those with a prior positive biopsy requiring further risk stratification of cancer before entering active surveillance. Exclusion criteria included PSA >20ng/ml, prostate volume >/=60mls, contraindication to trial scans or biopsy and previous prostate cancer treatment or recent prostate surgery. No upper age limit was set, rather patients with fitness to undergo invasive testing or active prostate cancer treatment were considered.

Trial Procedures: mpUSS consisted of b-mode, real-time elastography, Doppler, and intravenous microbubble contrast enhanced ultrasound (CEUS) scans (Sonovue, Bracco). These were performed in sequence using end-fire transrectal probes on the 4 ultrasound models employed in the study; Hi Vision Preirus, Hitachi Medical-Tokyo, Japan, Logic E9 – GE Healthcare, Boston US Mylab Twice – Esaote, Genoa, Italy or Bk3000- BK Ultrasound, Boston US) with frequencies between 7 and 12 MHz across the machines. All mpUSS images were produced by one probe and machine at each centre. Videos were recorded of the prostate scanned along anatomical axes for each ultrasound modality. These images were reviewed separate from acquisition to provide the mpUSS report. Dynamic enhancement was recorded after the IV administration of a vial (45µg in 5ml saline) of sulphur hexafluoride, concentrating on the most suspicious area of the prostate for the first wash-in and the remainder using the 'bubble burst' function of the scanner. The reporting process was set in a Standard Operating Procedure using published guidance [20,21]. Scans were arranged in a 2x2 grid for review to allow cross referencing between ultrasound modalities in a similar manner to mpMRI reporting. Reporting generated a Likert score in an analogous manner to MRI and guidance for the scoring of the different ultrasound modalities can be found in Table 1. The overall lesion score was at the discretion of the reporter though determined by the number of positive ultrasound modalities and their degree of positivity, allowing equipoise with mpMRI reporting by the Likert scale. Reporting of mpUSS was by either expert uroradiologist or urologist dependent on site.

All operators had at least 7 years or transrectal ultrasound experience and image interpretation was carried out by the same person who acquired the images, though post hoc. A full description of the mpUSS scanning technique may be found in the previously published protocol paper [14].

mpMRI was acquired on either 1.5 or 3 Tesla machines and comprised high resolution T2-weighted, multiple b-value diffusion-weighting for generation of apparent diffusion coefficient maps (ADC), and dedicated high b of 1400 or 2000, as well as dynamic gadolinium contrast enhanced scans. Acquisition and reporting were compliant with contemporaneous standards [22,23]. MRI reporters were expert uroradiologists who had between 7 and 15 years of MRI reporting experience with each uroradiologist normally reporting between 100-300 prostate MRIs per year. The Likert system was used as this is common in the UK, was used in previous studies [1] we have conducted, has been shown to perform in a similar fashion to the PIRADS scoring system [24] and is the current recommended scoring system by the UK's National Institute of Clinical and Healthcare Excellence (NICE).

Conduct and reporting of each test were blinded to the results of the other. Patients with a positive mpUSS or mpMRI underwent targeted biopsies but were blinded to exact test results. Prostate biopsy was performed using either the transperineal (95%) or transrectal (5%) route and under local anaesthetic, sedation or general anaesthetic dependent on physician and patient preference at each site. Needle guidance was provided by b-mode ultrasound only with visual-estimation targeted biopsy employed, a technique of which all biopsy operators had between 2 and 9 years' experience conducting between 200-300 biopsies per year using visual-estimation. The use of visual estimation rather than MRI fusion ensured there was no bias in favour of mpMRI derived and mpUSS derived lesions, especially as the b-mode echo characteristics of the prostate during the biopsy did not form part of the targeting technique. Three biopsy cores were taken from the two most suspicious identified lesions on each scan type in a single procedure and formed the analysis for this report. If a lesion detected by mpMRI was determined to match one detected by mpUSS a single set of 3 biopsy cores were targeted. In cases where a lesion from either scan overlapped but did not match, separate biopsies were taken. Lesion matching was determined by the biopsy operator carrying out the prostate biopsy after each scan report was finalised. Any subsequent random or sampling biopsies performed as standard of care by some sites did not contribute to the CADMUS dataset. Histology reporting was by pathology specialists in urological cancer at each site with no centralised pathology review.

Randomisation: When both tests were positive, the order in which the targeted biopsies were taken from each scan type was randomised to avoid bias as targeting accuracy might decline due to bleeding or swelling resulting from the first set of biopsies. Prior computerised block randomisation was employed with randomisation order determined and communicated via the Kings Trials Unit Online Randomisation Service 11.4.1 to the biopsy operator on or prior to the day of biopsy, but not to the patient.

Outcomes: Co-primary outcomes were specified to reflect the two stages of the prostate cancer diagnostic pathway. The first was proportion of positive tests and agreement between mpMRI and mpUSS. The second was the detection of clinically-important prostate cancer at biopsy. For the primary outcome, clinically-important prostate cancer was defined as in the PROMIS trial [1], namely any amount of Gleason >/=4+3 (WHO grade group 3 or higher) or maximum cancer core length >/=6mm of any grade. Although there is broad agreement on the existence of clinically-important and unimportant prostate cancer, no threshold has gained widespread acceptance. As such, three other thresholds for cancer importance were used. The first was the PROMIS definition 2, namely any amount of Gleason score >/=3+4 (WHO grade group 2 or higher) or maximum cancer core length >/=4mm of any grade. The second was the presence of any Gleason >/=3+4. For completion, we also evaluated the detection of any prostate cancer. The core lengths of 6mm and 4mm specified in the 2 PROMIS definitions have been shown to relate to 0.5ml and 0.2ml tumours [25], volumes which themselves relate to likelihood of prostate cancer progression [26].

The primary analysis of the CADMUS trial reports at the per patient rather than per lesion level as this has the greatest clinical relevance. Per lesion analysis will form part of secondary reporting. Adverse events were reported continuously until the last patient last visit. Patients' participation in the study ended once the biopsy had been conducted. Only patients who complete mpUSS, mpMRI and biopsy data were regarded as assessable.

Sample size

Sample size was based on a precision of agreement (95%CI = +/-6%) in the detection of clinically-important cancer, by definition 1, at biopsy and also precision of agreement on lesion detection by each imaging modality. This required a key target of at least 245 to undergo biopsy and based on assumptions of agreement and estimates on the prevalence of positive tests, approximately 360 to have both mpUSS and mpMRI scans. The assumptions used were that i) mp-MRI identifies 80% of patients with a lesion to biopsy [27], ii) mp-USS identifies 75% of patients with a lesion to biopsy and iii) the same patients are identified using both methods as having the same lesion in 90% of the mp-USS cases (i.e. 68% of total).

An interim analysis was conducted at the request of the Independent Trial Steering Committee and funder to ensure that the original assumptions were correct. This was conducted by an independent statistician with the report issued on 14th/March/2018 when 196 patients were recruited and 143 had both tests; this confirmed recruitment targets. A statistical analysis plan was completed prior to final database lock on 1st/July/2019.

Statistical analysis

This trial is registered as ISRCTN: 38541912 and ClinicalTrials.gov Identifier: NCT02712684. Co-primary outcome 1 recorded proportions of positive mpMRI and mpUSS to calculate agreement between the imaging tests on the presence or absence of a lesion requiring a biopsy. The total number of patients undergoing each imaging test with the number and proportion of positive and negative scans (presence or absence of a lesion requiring biopsy) is reported, with differences in proportions of positive results accompanied by a 95%CI. The number and proportion of results on which the two techniques agree or disagree for the combinations of positive (P) and negative (N) results (PP, PN, NP, NN) were reported within a contingency table. Further, a statistical measure of agreement, the Cohen's kappa-statistic [28] was calculated (with 95%CI) to provide greater insight regarding the agreement between the two diagnostic tests. Cohen suggested the kappa result be interpreted as follows: values </=0 indicating no agreement and 0.01–0.20 none to slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1.00 almost perfect agreement. Co-primary outcome 2 was agreement between mpUSS and mpMRI in the detection of PROMIS definition 1 clinically important prostate cancer from a targeted biopsy. Analysis was carried out using the Stata software (version 15, StataCorp LLC, Texas, USA).

Role of the Funders

Neither the funders nor any commercial entity had any role in the protocol development, data analysis and interpretation or manuscript preparation. AG, HUA, BS, MP and RO had access to the raw data.

Results

Between 15th/March/2016 and 7th/November/2019, 370 were enrolled, (Table 2; Appendix-Page3). In total, 306 completed both mpMRI (67% at 1.5T and 33% at 3T) and mpUSS and 257 underwent a prostate biopsy, exceeding our key target of 245 (Figure-1; Appendix-Page1). Median (IQR) age, PSA, and prostate volume were 65.5 (59-70) years, 6.7 (5.2-9.45) ng/ml and 33 (25-43) ml, respectively. Thirty-two (10.5%) had previously undergone biopsy at least one year before enrolment. 15/257 (5.8%) had transrectal biopsy.

mpUSS was more likely to identify a suspicious lesion of score >/=3 ,272/306 [88.9%; 95%CI=(84.8%, 92.2%)] for mpUSS vs. 238/306 for mpMRI [77.8%; 95%CI=(72.7%, 82.3%)] (Table-3 and figure 2] a difference of 11.1% (95%CI=(5.1, 17.1%)) (Table-3 and figure 2). In 121/306 (39.5%; 95%CI=(34.0%, 45.3%)), the lesions on mpUSS and mpMRI requiring biopsy matched and in 185/306 (60.5%; 95%CI=(54.7%, 66.0%)) they did not match (Appendix-Page1).

A median (IQR) of 4 (3-4) targeted cores were taken overall, with median 3 (3-4) for mpUSS lesions and 4 (3-5) for mpMRI. mpUSS and mpMRI detected PROMIS definition 1 cancer in 66/257 (25.7%; 95%CI=(20.5%, 31.5%)) and 77/257 (30.0%; 95%CI=(24.4%, 36.0%)), respectively (-4.3%;95%CI=(-8.3%, -0.3%)) (Table 4). The combination of mpUSS and mpMRI used to target biopsies would have led to a detection of 83 PROMIS definition 1 clinically-important cancers (32.3%; 95%CI=(26.6%, 38.4%)); of these, mpUSS detected 6 (7.2%;95%CI=(2.7%, 15.1%)) missed by mpMRI and mpMRI detected 17 (20.5%; 95%CI=(12.4%, 30.8%)) that mpUSS missed (Table 4; Appendix-Page3). mpUSS and mpMRI detected 36/257 (14%;95%CI=(10.0%, 18.9%)) and 44/257 (17.1%; 95%CI=(12.7%, 22.3%))clinically-unimportant cancers (by this definition), respectively.

mpUSS and mpMRI detected 86/257 (33.5%; 95%CI=(27.7%, 39.6%)) and 102/257 (39.7% 95%CI=(33.7%, 46.0%)) PROMIS definition 2 cancers, respectively (-6.2%;95%CI=(-11%, -1.5%)). The combination of mpUSS and mpMRI would have led to detection of 111 (43.2%; 95%CI=(37.0%, 49.5%)) definition 2 cancers; of these, mpUSS detected 9 (8.1%; 95%CI=(3.8%, 14.8%)) missed by mpMRI and mpMRI detected 25 (22.5%; 95%CI=(15.1%, 31.4%)) that mpUSS missed. mpUSS and mpMRI detected 16/257 (6%; 95%CI=(3.6%, 9.9%)) and 19/257 (7%; 95%CI=(4.5%, 11.3%)) clinically-unimportant cancers (by this definition), respectively. (Table 4; Appendix-Page2; Appendix-Page3).

mpUSS and mpMRI detected 78 (30.4%; 95%CI=(24.8%, 36.4%)) and 92 (35.8%; 95%CI=(29.9%,42.0%)) Gleason >/=3+4 cancers, respectively. The combination of mpUSS and mpMRI would have led to a detection of 99 (38.5%; 95%CI=(32.5%, 44.8%,)) Gleason >/=3+4 cancers. mpUSS detected 7 (7%; 95%CI=(2.9%, 14.0%)) missed by mpMRI and mpMRI detected 21 (21%; 95%CI=(13.6%, 30.6%)) that mpUSS missed. mpUSS and mpMRI detected 24/257 (9%; 95%CI=(6%, 13.6%)) and 29/257 (11%; 95%CI=(8%, 15.8%)) clinically-unimportant cancers (any Gleason 3+3, ISUP 1), respectively (Supp. Table-4).

There were no serious adverse events related to CADMUS trial activity. One patient was admitted to hospital with acute kidney injury related to his pre-existing antihypertensive medication. He recovered fully but was withdrawn from the trial prior to biopsy (Appendix-Page2).

Discussion

In summary, the CADMUS trial has shown that mpUSS can detect most clinically-important prostate cancers in comparison to mpMRI, although a higher proportion of patients required a biopsy. Given that mpUSS might be more readily available and accessible in some healthcare settings, or used in patients who cannot undergo MRI scans, mpUSS should be considered in patients at risk of prostate cancer. It might also be used in combination with mpMRI to maximise cancer detection. The strengths of our study were the validating paired cohort design, blinding of the conduct and reporting of each test to the other, blinding of patients to the indication for biopsy and randomisation in the order of biopsy targeting.

Ultrasound has been employed for some years to examine the architecture of the prostate gland and new ultrasound techniques evaluated as potential diagnostic tests. Greyscale or b-mode ultrasound is used for biopsy targeting. Halpern and Strup [29] demonstrated a detection rate of 50% and a recent review [30] commented that the number of any cancers detected on greyscale ultrasound ranged from 11-35%, with cancer present in 17-57% of lesions [31].

The angiogenesis and microvascular proliferation associated with prostate cancer can be seen as a disturbed perfusion pattern on Doppler ultrasound [32]. A recent prospective series of 111 patients undergoing transrectal systematic biopsy reported a sensitivity of 81% and specificity of 68% [33] for power Doppler. Colour Doppler ultrasound was examined by Cheng and colleagues in 500 patients with 11.7% of detected cancers identified by colour Doppler alone [34].

Contrast-enhanced ultrasound (CEUS) is a more recent approach to investigating organ perfusion. Intravenous injection of agents containing microbubbles (1µm- 1mm) of a gas, usually a perfluorocarbon, increase the echogenicity of circulating blood and detection of abnormal tissue perfusion. In a randomized trial of 272 patients, Halpern and colleagues quantified prostate cancer detection with CEUS showing area under the receiver operating characteristic curve of 0.80 for CEUS compared to 0.74 for b-mode ultrasound in the detection of Gleason >/=3+4 prostate cancer. When high cancer volume (>50% biopsy core) as well as Gleason >/=3+4 was considered, in a similar manner to our use of PROMIS definition 2, this rose to 0.90 for CEUS and 0.83 for b-mode [35].

Elastography assesses the stiffness of tissues by its deformation in response to an applied force [36], with cancer being less elastic than normal tissue due to increased cell density or differing collagen distribution [37,38]. Pozzie et al reported a sensitivity of 61% for real time elastography (RTE) alone in a retrospective cohort of 460 patients. Interestingly, the results for the combined approach of b-mode and RTE was improved with sensitivity 80% [39].

Most recent efforts have turned towards combining ultrasound modalities to optimize diagnostic accuracy [8,40,41]. Brock et al reported on 86 patients who underwent both RTE and CEUS before whole-mount analysis of their radical prostatectomy specimens. They showed an increase in the positive predictive value from 65.1% using b-mode with RTE to 89.7% using b-mode, CEUS and RTE in combination. False positives were reduced from 34.9% to 10.3% [16]. Recently, Mannaerts et al evaluated the sensitivity of mpUSS (Likert >/=3) in comparison to radical whole-mount prostatectomy. For clinically important prostate cancer (any Gleason >/=3+4, cancer volume >/=0.5ml, extraprostatic extension or nodal involvement) sensitivity was 74% (95%CI 67-80) compared to 55% (95%CI 47-63), 55% (95%CI 47-63) and 59% (95%CI 51-67) when b-mode, shear wave elastography and CEUS were used, respectively [42]. Novel image processing software approaches show promise, but more data is awaited [43].

Ultrasound devices capable of mpUSS are approximately one-twentieth to one-tenth the purchase cost of a modern MRI body scanner, though at the upper end of the price range for ultrasound scanners The cost differential and availability issues could be particularly impactful in healthcare systems where MRI is not readily available, with the innate mobility of ultrasound machines adding to this advantage, potentially allowing for transfer between institutions. The democratisation of accurate imaging for diagnosing prostate cancer in all healthcare settings is of considerable importance given the increased risks of prostate cancer in the Black or ethnic minority populations. Given the similar, though slightly lower cancer detection rates demonstrated for mpUSS, we consider the most likely first role for mpUSS to be situations where MRI is not available, likely still the majority of instances of prostate cancer diagnosis internationally at present [9,10,11]. We believe these results are very encouraging and could allow for wider access of a high quality diagnostic pathway for many patients whether in developed or developing nations, given that accessibility to mpMRI is actually still poor.

We were unable to evaluate high resolution or micro-ultrasound technology which has recently shown encouraging results although this does not yet offer the multiparametric modalities used in CADMUS. [44,45]. Cancer detection for mpUSS targeted biopsies was not compared to an independent set of systematic samples, although a number of studies have done this robustly for mpMRI. The exclusion of patients with large prostates (>60cc) prevents the application of our results in this cohort and it is likely that ultrasound performs less well in large prostates. Further, due to the use of a Likert reporting scheme, in the absence of a something similar to the PIRADS for mpUSS, there are likely to be limitations in terms of inter-reader variability and quality reporting during dissemination. Seventy-five per cent of our study population was from academic centres so CADMUS is limited in that respect. Our study findings are limited to those patients with a PSA of up to 20ng/ml. Further, the visual estimation targeting technique used in CADMUS and in our wider practice is dependent on anatomical landmarks to determine the position of lesions identified on prebiopsy imaging, and not echo characteristics of the prostate as b-mode ultrasound alone has been shown to lack both sensitivity or specificity in prostate cancer detection [21]. It is still possible that some operators may have used hypoechoic lesions visible at time of biopsy for targeting. CADMUS was a study of diagnostic performance in a single round of testing. Consent was taken however for linkage to national data records to allow for longer term follow up in future work.

The agreement between mpUSS and mpMRI was substantial at all three thresholds of cancer important as well as for any cancer, with over 91% agreement at definition 1. At this definition, mpUSS detected 4.3% fewer clinically-important cancers compared to what may be regarded as best practice in current clinical care, mpMRI. This difference increased when using less stringent definitions of clinically-important cancer pointing to a quality of mpUSS akin to that of mpMRI, with higher grade and large lesions better visualised and smaller, lower grade cancers, which are more likely to be clinically indolent, avoiding detection. In fact, the strategy of mpMRI and biopsy also lead to a very small increase in over-diagnosis of clinically-unimportant cancers compared to mpUSS. Interestingly, at all levels of clinical importance on biopsy, mpUSS detected cancer not found by mpMRI meaning a diagnostic strategy employing both scans over mpMRI alone will increase clinically-important cancer detection. However, this will lead to a greater number of patients undergoing a prostate biopsy. Further work will be needed on the acceptability to patients and physicians of a combined test approach, the use of additional risk factors and cost-effectiveness.

In conclusion, mpUSS detected 4.3% fewer clinically-important prostate cancers compared to mpMRI although would lead to 11.1% more patients being biopsied. Both modalities missed clinically-important cancers detected by the other so using both tests increased detection of clinically-important prostate cancers compared to each test alone.

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Declaration

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Author contributions

Hashim Ahmed and Alistair Grey had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: HUA, ME, AG

Acquisition of data: RS, PA, SL, FC, PP, TS, SH, MG, HG, AG, NA, AC, AF, DEE, AK, ZA, LM, DC, MBT, MW, MA

Analysis and interpretation of data: AG, RO, MP

Drafting of the manuscript: AG, HUA

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: RO, MP

Obtaining funding: HUA, ME, FC

Administrative, technical, or material support: CBG, BS,

Supervision:HUA

Other: None

HUA, ME, SM, FC and RO are full professors

The Independent Trials Steering Committee was composed of the following members: Professor Marcus Drake (Bristol), Professor Jayant Vaidya (UCL), Christopher Langley, Dr Alastair Henderson (Maidstone and Kent), Professor Haleema Shakur (London School of Hygiene and Tropical Medicine), Anne Millman (Patient and Public Involvement representative)

Data Sharing

All anonymised data will be shared following publication of the cost-effectiveness analysis that will be published subsequent to the primary outcomes in this manuscript. Access will be by writing to the Chief Investigator with a proposal and this will be considered by an Imperial Prostate Oversight Committee for research data sharing.

Tables and Figures

Figure Legends

Figure 1: Enrolment and outcomes

Figure 2: Distribution of positive lesion scores for mpMRI and mpUSS

Appendix attached.

Protocol attached as appendix.

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