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The Prostate Cancer Diagnostic Pathway: Reporting a Pilot of a One-Stop Cognitive Magnetic Resonance Imaging Targeted Service

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Abstract

Objectives

To evaluate the suitability and feasibility of a novel multiparametric magnetic resonance imaging (mpMRI) and cognitive fusion transperineal targeted biopsy led prostate cancer (PCa) diagnostic service with regard to cancer detection and reducing time to diagnosis and treatment.

Patients & Methods

Men referred with a raised prostate specific antigen (PSA) or abnormal digital rectal examination (DRE) between 02/2015 and 03/2016 were investigated for PCa. An mpMRI was performed prior to patients attending clinic, on the same day. If required, MRTB was offered. Results were available within 48 hours and discussed at a specialist multidisciplinary team (MDT) meeting. Patients returned for counselling within 7 days.

Results

112 men were referred to the service. 111 (99.1%) underwent mpMRI. Median PSA was 9.4ng/mL [IQR 5.6-21.0]. 87 patients had a target on mpMRI with 25 scoring Likert 3/5 for likelihood of disease, 26 4/5 and 36 5/5.

57 (51%) patients received a local anaesthetic, MRTB. Cancer was detected in 45 (79%). 43 (96%) had University College London (UCL) definition 2 disease or greater. The times to diagnosis and treatment were a median of 8 and 20 days respectively.

Conclusion

This approach greatly reduces the time to diagnosis and treatment. Detection rates of significant cancer are high. Similar services may be valuable to patients with a potential diagnosis of PCa.

Strengths and limitations of this study

- First prospective study demonstrating the clinical feasibility of a 'one stop', rapid diagnostic prostate cancer pathway, using both multiparametric magnetic resonance imaging and transperineal targeted biopsy.
- Inclusion criteria reflecting 'real world' practice in the United Kingdom.
- This study incorporates a standardised multiparametric MRI acquisition and a validated system for defining clinically significant prostate cancer.
- Cognitive targeted biopsy performed only, rather than mpMRI / ultrasound fusion.
- Transperineal, rather than transrectal approach offers minimal septic complications post biopsy.

Introduction

Accurate risk stratification for men presenting with localised prostate cancer is vitally important. In its absence, patient centred management cannot be offered. Men with low-risk disease can be safely managed with active surveillance, whereas men with a good life expectancy and intermediate to high-risk disease are likely to benefit from interventional treatment[1-2]. Currently, standard practice uses prostate-specific antigen (PSA) value, digital rectal examination (DRE) and transrectal ultrasound guided biopsy (TRUSGB). However, TRUSGB is inherently random. The tumour cannot be visualised with certainty, and thus leads to overdiagnosis of insignificant disease in up to 50% of men[3], and missing significant disease in 18% of men, especially if cancer is located in anterior or apical regions of the prostate[4]. This creates difficulty for urologists and adds anxiety to patients[5] who have to undergo a repetitive cascade of diagnostic tests, which inevitably has cost implications for healthcare providers.

Transperineal mapping or zonal biopsies (TPM) of the prostate offer a diagnostic alternative to TRUS biopsy with demonstrable diagnostic success. However, the burden on patients is high. Firstly, the extensive biopsies demand general anaesthesia. Secondly, the rates of urinary retention following the procedure are

high, making postoperative catheterization commonplace. Thirdly, the large number of cores taken requires many hours of labour to assess. Thus, a patient may have to wait significantly longer for a result, adding to their anxiety. This may also delay necessary treatment. Whether this results in adverse outcomes is not known. However, all of these established difficulties do confer added costs. Indeed, if every patient undergoing TRUSGB instead underwent a TPM, the cost of such a move would likely be exceedingly high. Therefore, the challenge presents itself as biopsy offering superior clinically significant detection rates to the existing standard, whilst not conferring an added cost.

Multiparametric magnetic resonance imaging (mpMRI) of the prostate has proved a useful tool in the diagnosis and risk stratification of prostate cancer. MpMRI has demonstrated its ability to detect significant cancers, whilst not detecting those which are insignificant[4]. Suspicious areas on mpMRI can be targeted with subsequent transperineal biopsy (MRTB). MRTB has demonstrated greater sampling efficiency and accuracy when compared with standard TRUS-guided protocols[6-8], and has demonstrated accuracy when compared to the reference standard of radical prostatectomy (RP)[9]. This allows for a more accurate assessment of Gleason grade, and therefore an improved risk stratification and treatment plan at diagnosis[10]. Furthermore, the efficiency advantage, i.e. taking fewer cores at biopsy, confers significant benefits in cost, patient tolerability and post biopsy sepsis rates.

Three methods of transperineal MRTB currently exist. First and most common is 'cognitive targeting'. This approach requires the urologist to review the mpMRI images and aim the needle toward the corresponding area on ultrasound (US) imaging[11]. Alternatively, the reporting uroradiologist draws a diagrammatic representation of the gland and any suspicious area contained within, which guides the urologist to potential cancer. Second, 'in-bore MRTB' is performed whilst the patient is in the MRI scanner, allowing for real time targeting of suspicious areas with MRI compatible biopsy equipment. Third, 'fusion targeting' uses specifically designed software to allow combination of the mpMRI images with real time US imaging[4]. The latter two methods have implications in terms of equipment

availability and cost, and as of yet the question of superiority of any one over another remains elusive[4].

Currently, prostate cancer diagnostic pathways remain built around TRUSGB. MpMRI is more commonly being used prior to TRUSGB. However, the use of an mpMRI and MRTB pathway remains a rarity despite the potential advantages of such an approach. The reasons for this are multiple and commonly relate to the techniques being in their relative infancy. The lack of standardised mpMRI reporting[12], a learning curve for operators[13], mpMRI availability and cost[14] and concern regarding missed diagnosis from not sampling the whole gland have all been cited as reasons not to accept widespread adoption. Despite this, MRI-guided targeted biopsy pathways have been utilised before, albeit via the transrectal rather than the transperineal route[15-17]. The recent findings of the PRECISION [18] trial has clearly addressed concerns in regard to superiority of an MRI-targeted biopsy approach over systematic TRUS biopsy, demonstrating superiority in clinically significant cancer detection rate and a reduction in the detection of insignificant disease.

Thus, the objective of this study was primarily to determine the suitability and feasibility of a transperineal MRI-targeted biopsy pathway for prostate cancer in 'real-world' clinical practice. Outcome measures in this regard included the time to diagnosis and treatment of patients referred with a suspicion of prostate cancer. Quality control outcome measures included clinically significant and total cancer detection rates.

Patients and Methods

This prospective study analyses the clinical and service outcomes of an mpMRI and MRTB led prostate cancer diagnostic pathway (*figure 1*) from 02/2015 to 03/2016. Inclusion criteria were men presenting with a biochemical or clinical suspicion of prostate cancer under the United Kingdom two week wait program and undergoing mpMRI and if necessary subsequent cognitive targeted prostate biopsy. Patients

without negative urine cultures or with estimated glomerular filtration rates of <30 micromol/L were excluded. The patient was contacted on referral and an mpMRI was arranged. This was reported before the patient attended clinic in the early afternoon of the same day. If a targetable lesion was identified (Likert >/=3), a transperineal-targeted biopsy was offered. Results were available within 48 hours and were discussed at a specialist MDT. Patients returned for counselling within seven days.

MpMRI acquisition was performed according to the European guidelines of Uro-radiology previously described by the University College London (UCL) group[12,19,20]. In summary this includes the use of a 1.5 or 3.0 Tesla MRI scanner acquiring T2-weighted axial and coronal, axial diffusion weighted coefficient and high *b*-value as well as T1 weighted dynamic contrast enhancement (intravenous Gadolinium) images. Each scan was reported by an experienced uro-radiologist as previously described [21,22] and a pictorial diagrammatic map drawn (*figure 2*). Regions of interest (ROIs) were scored using a Likert-like scale of 1-5[22] using the overall impression of the radiologist to characterise the level of suspicion for prostate cancer. ROIs scoring 4 or 5 were thought 'likely' or 'highly likely' to contain a malignant lesion, which was either ≥0.2mL in volume and/or had high-grade components within (Gleason ≥3+4)[23]. ROIs 3 were rated as indeterminate for such disease and this score of 3, or higher, was chosen as the threshold for a positive mpMRI. Our choice of scoring system was based on the outcomes of the 2011 European Consensus Meeting[12] which met prior to the Prostate Imaging and Data Reporting System (PIRADS) MP-MRI reporting consensus meeting[19] and has demonstrated equivalency with the PIRADS system[24].

The procedure was performed as a day case under local anaesthesia and antimicrobial prophylaxis in the lithotomy position, by either a consultant urologist or urology clinical fellow as previously described[25]. This biopsy technique has demonstrated a median procedure length of 30 minutes and good patient toleration, with median visual analogue pain scores of 1.0[26].

Data was collected on a case report form compliant with the Standards of Reporting

for MRI-targeted Biopsy Studies (START) of the prostate[11]. Included data were patients demographics, indications for biopsy, PSA value, prostate volume, number of targets per patient, and Likert score per target[11]. Additionally, for each biopsy collected the total number of cores taken, biopsy density, number of positive cores, maximum and overall Gleason scores and the maximum cancer core length (MCCL). Biopsy efficiency was calculated by the number of cores demonstrating clinically significant disease divided by the number of cores taken. For the purpose of this study, clinically significant disease was defined using the University College London (UCL) classification for interpreting transperineal biopsy findings, which sets the significance threshold at Gleason score >/= to 3 + 4 and/or MCCL >/= 4 mm for definition 2 and >/= to 4 + 3 and/or MCCL >/= 6 mm for definition 1[26] (*figure 3*).

Finally, to assess the time to diagnosis and treatment as well as the treatments elected by men were determined by examination of the hospital trust's electronic data system.

Patient and Public Involvement

This study received approval from the local audit committee. An informative consent process was performed for each patient prior to biopsy.

Results

Table 1

A. *Patient Demographics*		
Men included		112
Median Age (years)		68 [IQR 62-78]
Median PSA (ng/mL)		9.4 (IQR 5.6 - 21.0)
B. *MpMRI Outcomes*	n	%
Men undertaking mpMRI	111	99%
Median Prostate Volume (mL)	50 (IQR 35 - 78)	
Positive mpMRI (Men)	87	78%
Negative mpMRI (Men)	24	22%
Total ROIs	162	

1 ROIs / man		39	35%			
2 ROIs / man		25	23%			
3 ROIs / man		22	20%			
4 ROIs / man		1	1%			
Likert score per man						
Likert 3		25	23%			
Likert 4		26	23%			
Likert 5		36	32%			
Total ROIs		162				
Median ROI volume (mL)		0.5 (IQR 0.2 - 1.0)				
Likert score per lesion						
Likert 3		71	44%			
Likert 4		49	30%			
Likert 5		42	26%			
***C.** Biopsy Outcomes*	n		%			
Men undertaking biopsy		57	51%			
Median cores per patient		9 (IQR 5 - 12)				
Total cores		514				
Cores positive (UCL 2)		241	47%			
Biopsy efficiency		47%				
Median cores per lesion		4 (IQR 4 - 5)				
Median biopsy density (cores / ROI mL)		10 (IQR 3.5 - 20)				
Cancer detection by man						
Any Cancer		45	79%			
UCL 2		43	75%			
UCL 1		34	60%			
Gleason >/=3+4		43	75%			
Gleason >/=4+3		23	40%			
Median MCCL (mm)		7 (IQR 3 - 10)				
Cancer detection by lesion			Any cancer	UCL 2		UCL 1
Likert 3 (lesions biopsied)		40	13	10		4
Likert 4 (lesions biopsied)		38	24	19		15
Likert 5 (lesions biopsied)		35	35	35		28
***D.** Diagnosis and Treatment Outcomes*						
Median time to diagnosis (days)		8 (IQR 5 - 12)				
Median time to treatment (days)		20 (IQR 8 - 40)				

Treatment type (Post Biopsy)	n	%
Discharged	4	7%
PSA Surveillance	6	11%
Active Surveillance	5	9%
Focal therapy	6	11%
Robotic Prostatectomy	9	16%
External Beam Radiotherapy	10	18%
Brachytherapy	2	4%
Androgen Deprivation Therapy	9	16%
Chemotherapy	4	7%
Antibiotics	1	2%
Repeat biopsy	1	2%

Patient demographics

In total, 112 consecutive biopsy naive men with a median age of 68 attended the prostate cancer one stop clinic between 02/2015 and 03/2016 *(Table 1A*). All but one man (99%) received an mpMRI scan prior to clinic. The patient in question had an MRI incompatible cardiac pacemaker.

MpMRI Outcomes

The median prostate volume was 50mL. Eighty-seven men (78%) had a positive mpMRI (Likert score >/=3) and 24 (22%) had a negative scan (Likert score </=2) and did not go on to biopsy. Twenty-five men (29%) had an mpMRI scan with an overall Likert score of 3, 26 (30%) an overall score of 4 and 36 (41%) an overall Likert score of 5. There were 162 ROIs identified on mpMRI with a median volume of 0.5mL when measured on T2 MRI sequencing. Thirty-nine men (45%) had a single ROI on mpMRI, 25 men (29%) had two, 22 men (25%) had three and a single man (1%) had four. Seventy-one lesions (30%) were Likert 3, 49 (30%) at Likert 4 and 42 (26%) and Likert 5. After mpMRI, nine with negative mpMRIs (38%) were discharged for PSA surveillance in the community, 10 (42%) remained on PSA surveillance in secondary care, four (17%) underwent investigations for lower urinary tract symptoms and one (4%) underwent a full template biopsy under general anaesthetic *(Table 1B*).

Biopsy Outcomes

Fifty-seven men (51%) underwent a local anaesthetic MRTB as described following mpMRI *(Table 1C*). Fifteen (17%) men chose not to undergo biopsy under local anaesthetic and were listed for a biopsy under sedation. Thirteen men (15%) did not have a biopsy due to clinical reasons. Any cancer was detected in 45 (79%) of men. Of these, 43 (96%) satisfied the UCL 2 criteria for clinical significance and 34 (76%) satisfying the UCL 1 criteria. The median MCCL of positive biopsies was 7mm. The calculated biopsy efficiency for UCL 2 disease was 47%. The median number of cores taken per ROI was 4, with a median calculated biopsy density of 10 cores/mL of ROI. Of the 20 men who had more than one lesion on mpMRI and underwent biopsy, two had a secondary lesion, which harboured either higher grade or volume disease. In only one of these men was the secondary lesion a lower Likert score. Both such men went on to radical prostatectomy.

Diagnosis and Treatment Outcomes

The median time to a man being told his diagnosis was eight days, and the median time by which treatment had been started was 20 days, although in five cases this time period was not clear *(Table 1D*). The treatment outcomes are shown in table 1D. Of note, 20 (18%) men were discharged after biopsy with 19 (17%) men starting PSA surveillance. Forty-four (40%) went on to undergo treatment and nine (8%) men underwent a further biopsy either due a perceived false negative or diffuse disease requiring a biopsy under sedation or general anaesthetic. Eleven (10%) patients underwent further assessment or treatment for benign disease.

Discussion

An optimal PCa diagnostic strategy should encapsulate maximal significant cancer detection whilst avoiding insignificant disease or repeat biopsy. Furthermore, it should convey enough information for urologists and patients to accurately devise a treatment plan according to the risk of progression. However, as things stand, the diagnostic pathway is still commonly led by TRUSGB, despite its accepted inaccuracy, especially for disease located in the anterior or apical regions of the prostate[27]. In

particular the negative predictive value (NPV) of the originally described six core TRUSGB is poor, with false negative rates of around 35%[28,29]. This inherent disadvantage is somewhat mitigated by extending the biopsy to a 12 or even 24 core technique, however increasing the number of cores past 12 leads to increased numbers of insignificant cancers being detected[30,31] which is present in 40% of men over the age of 50[32]. These cancers are rarely affect life expectancy or its quality in any meaningful way and revealing them simply adds unnecessary burdens to patients. Furthermore, increasing the number of cores may increase incidence of post TRUSGB sepsis[33] and with the incidence already on the rise alongside increasing prevalence of colonisation with resistant organisms such strategies pose an increasing potential for harm[34] for which our clinical options are worryingly limited. As a result, transperineal zonal or mapping biopsies (TPM) have become more popular. In particular, one recent series reported a 0% readmission rate for infective complications after targeted transperineal biopsy[35], in comparison to rates of sepsis of up to 6.3% after TRUSGB[36]. However, there are significant concerns regarding its cost, need for general anaesthetic, increased complications and patient burden. Such concerns have justly prevented its wider use and certainly a TPM led diagnostic pathway has not been seriously suggested.

However, the development and refinement of mpMRI demands that its use in leading an approach to diagnosis must be contemplated. MpMRI has demonstrated high levels of accuracy for the detection of clinically significant cancer when compared to both TPM[37] and whole-mount prostatectomy specimens[9]. Indeed, a systematic review by Fütterer et al found that mpMRI detected clinically significant disease in up to 84% of men with a NPV of up to 98% where either TPM or prostatectomy was used as the reference standard[20]. More recently the results of the PROMIS trial demonstrate the sensitivity and negative predictive value of mpMRI in detecting clinically significant disease as 93% and 89% respectively[38]. Furthermore, the PROMIS trial demonstrated that 27% of men could avoid a biopsy[38]. Despite these findings, both the European Association of Urology (EAU)[39] and National Institute of Clinical Excellence (NICE)[40] still do not recommend mpMRI prior to an initial set of biopsies. In this study, leading with

mpMRI allowed 24 (21.6%) men to avoid a biopsy entirely. However, the majority would remain on PSA surveillance due to the small – but understood - risk of a false negative mpMRI. There is perhaps a concern that in less experienced centres overcall images as PIRADS 3 is an issue that will expose men to unnecessary biopsies and thus reducing the benefit of an image-guided pathway. However, as the PIRADS v2[41] scoring system is increasingly adopted, with its ability to define a PIRADS 4 lesion over a 3 by utilisation of the second parameter (DCE and DWI for peripheral zone and transition zone lesions respectively), alongside its more easily understood and applicable design, should reduce such an effect going forward.

Clearly, there is enough evidence now to introduce an image-guided biopsy to the PCa diagnostic pathway, bringing it in line with the current practice in other solid organ malignancies. However, currently there is concern that targeted biopsies alone risk missing areas of significant disease that appear normal on mpMRI. This may be viewed as a limitation. However, our current approach to this cohort of men was introduced after our paired analyses of mpMRI versus template biopsies demonstrated that mpMRI cognitive biopsies had equivalent detection rates to zonal mapping biopsies[37]. Furthermore, numerous centres have now reported improved cancer detection rates of MRTB strategies when compared to systematic approaches [42,43], as well as improved biopsy efficiency and reduced false negative rates for significant cancer[8]. To underline this, another series of men who underwent both fusion MRTB and systematic TPM showed a difference of clinically significant cancer detection rates of 4% (28% for MRTB and 24% for systematic biopsy), although combined biopsies outperformed each approach in isolation[44]. Naturally, such results have been reported by specialist centres and as such, concern remains in regard to the level of operator dependency with targeted biopsy techniques. However, authors have found no difference between cancer detection rates with targeted techniques regardless of the experience of the operator, albeit with TRUSGB[45].

As with mpMRI, MRTB is not a perfect test, both can miss significant disease. However, this is an improvement on our current standard diagnostic test which is demonstrably poor[27-30]. As recent studies have shown, in comparison to TRUSGB,

MRTB is more likely to detect disease once a suspicious area has been identified[6,17]. Furthermore, the recently published PRECISION randomised controlled trial clearly demonstrated the superior clinically significant cancer detection rate of MRTB and a reduced insignificant cancer detection rate when compared to systematic TRUS biopsy[18].

A potential limitation of the MRTB technique in this study is the use of 'cognitive fusion' rather than US/mpMRI fusion or 'in-bore' targeting. However, no superiority of one technique over another has been clearly demonstrated, whilst 'cognitive fusion' is clearly a less costly option[46]. Another potential limitation of the targeted biopsy strategy is the 'satisfaction of search' bias. Essentially, this means that after the primary lesion is scored, less attention to detail is given to subsequent lesions, which may therefore be undercalled or undersampled. However, in this series this occurred twice, only once where the secondary lesion was attributed a lower score than the primary, and in no cases did this change the proposed management. Further, in the vast majority of centres where radical treatments – rather than focal – remain the standard of care, there would likely be no change in the approach to curative therapy, save for planning for prostatectomy in the case of nerve-sparing procedures.

The cost of mpMRI has been cited as a reason for persisting with TRUSGB led diagnostic pathways [47], using it instead for a second investigation in the case of a negative biopsy in a patient in whom suspicion of cancer remains. Whilst mpMRI is indeed useful in this scenario, recent cost effectiveness analyses have shown the long term cost benefits of mpMRI led pathways when various outcomes are accounted for[14,48,49] due to a reduction in overdiagnosis and higher detection rates of clinically significant disease at primary biopsy. In particular, the cost-analysis of the PROMIS trial cohort demonstrated that MpMRI first followed by two MRTBs detects more cancer per pound spent than a TRUS first biopsy strategy[49].

A major advantage of our pathway is the low time to diagnosis and treatment. At a median of 8 and 20 days respectively the time a patient waits is significantly below the 31 and 62-day targets set by the United Kingdom National Health Service. The

meeting of these targets is a persistent challenge nationally[50]. Moreover, performing an mpMRI prior to primary biopsy negates the risk of an initial false negative biopsy significantly delaying a subsequent mpMRI due to post biopsy haemorrhage within the prostate. This makes it difficult to localise cancer or accurately determine its size or border[51]. In such circumstances, the delay in diagnosis can be up to eight weeks.

Conclusions

This novel pathway offers an alternative to standard prostate cancer diagnostic services. Attendance and cancer detection rates are high. The use of an mpMRI led pathway allows for a significant proportion of men to avoid a biopsy and for those who do, the time to diagnosis and definitive treatment is kept particularly low. The integration of both mpMRI and MRTB in the prostate cancer diagnostic pathway has shown cost-effectiveness in the long-term. This is especially true where rapid diagnostics are mandated or desirable. Furthermore, today, where septic complications are of grave concern, the transperineal route is particularly advantageous. This pilot study demonstrates, that similar services can be provided in appropriate centres and may be valuable to patients with a potential diagnosis of prostate cancer

Contributorship statement

Edward J Bass drafted the manuscript and approved the final version.

Alex Freeman contributed to the conception of the work presented, revised the manuscript critically and approved the final version.

Charles Jameson contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

Shonit Punwani contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

Caroline Moore contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

Manit Arya revised the manuscript critically and approved the final version.

Mark Emberton contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

Hashim U. Ahmed contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

All authors are accountable for all aspects of the work in terms of accuracy and integrity.

Competing Interests

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Emberton receives funding from NIHR-i4i, MRC, Sonacare Inc., Trod Medical, Cancer Vaccine Institute and Sophiris Biocorp for trials in prostate cancer. Emberton is a medical consultant to Sonacare Inc., Sophiris Biocorp, Steba Biotech, Exact Imaging and Profound Medical.

Moore receives funding from the National Institute for Health Research, The European Association of Urology Research Foundation, Prostate Cancer UK, Movember and the Cancer Vaccine Institute, for clinical prostate cancer research. She has received advisory board fees for Genomic Health.

Ahmed, Emberton, and Moore are all proctors for HIFU and are paid for training other surgeons in this procedure.

Emberton and Freeman have loan notes/stock options in Nuada Medical Ltd (UK).

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Data sharing statement

Supplementary data is available in the reference tables in the appendix.

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Figure and Table legends

Figure 1: The One-Stop mpMRI led, MRTB prostate cancer diagnostic pathway.

Figure 2: A pictorial prostate mpMRI diagrammatic report, as drawn by the uroradiologist.

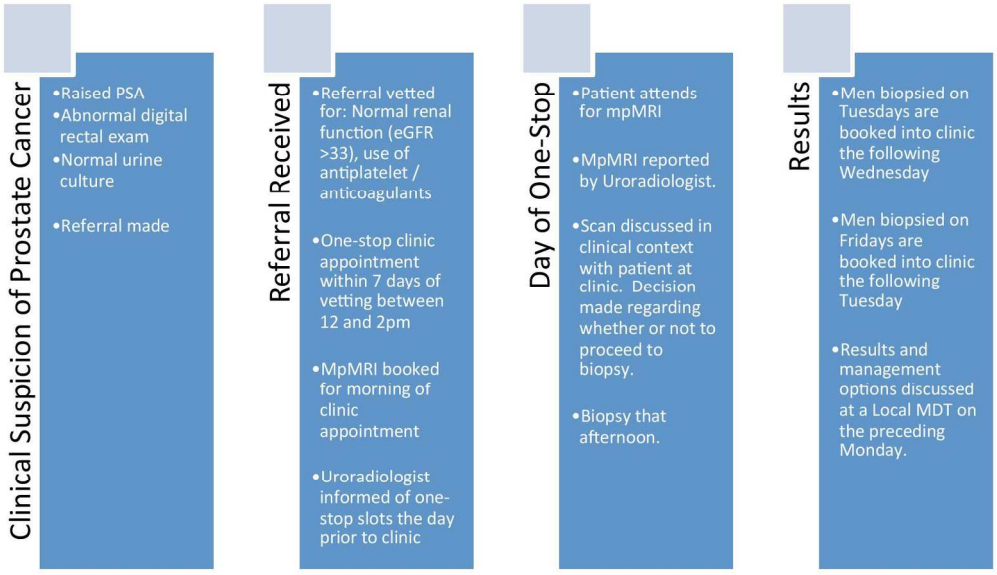
Figure 3: The University College London 'traffic light like' system to define significant prostate cancer.

Table 1A: Baseline demographics for the cohort.

Table 1B: MpMRI outcomes.

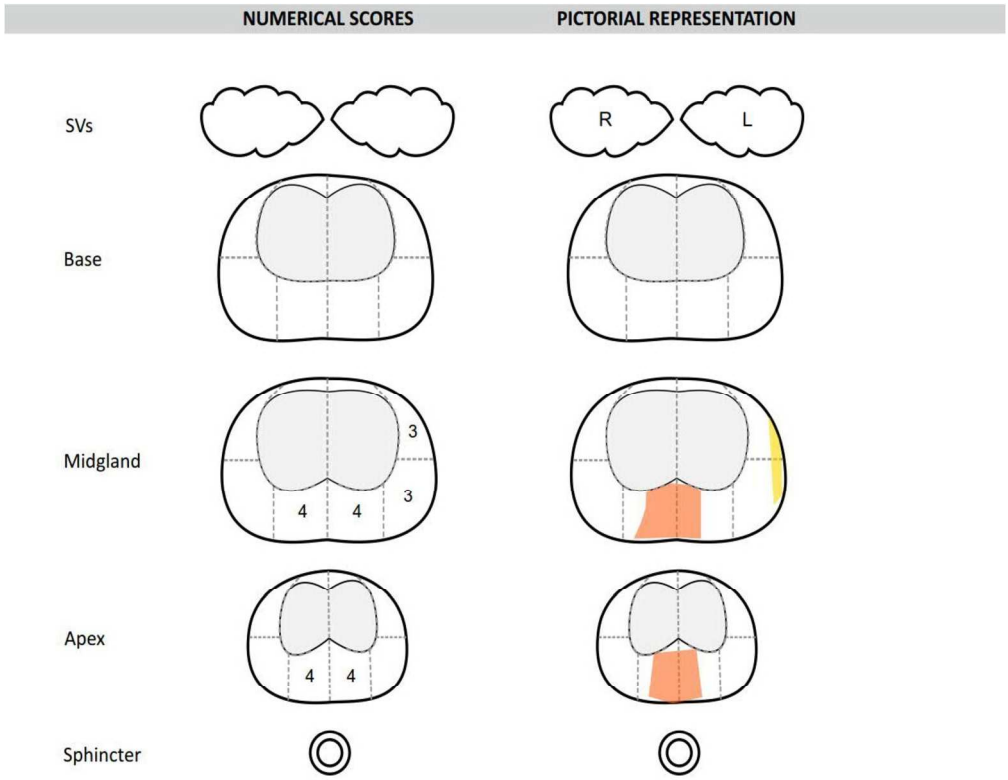
Table 1C: Biopsy outcomes.

Table 1D: Diagnosis and treatment outcomes.



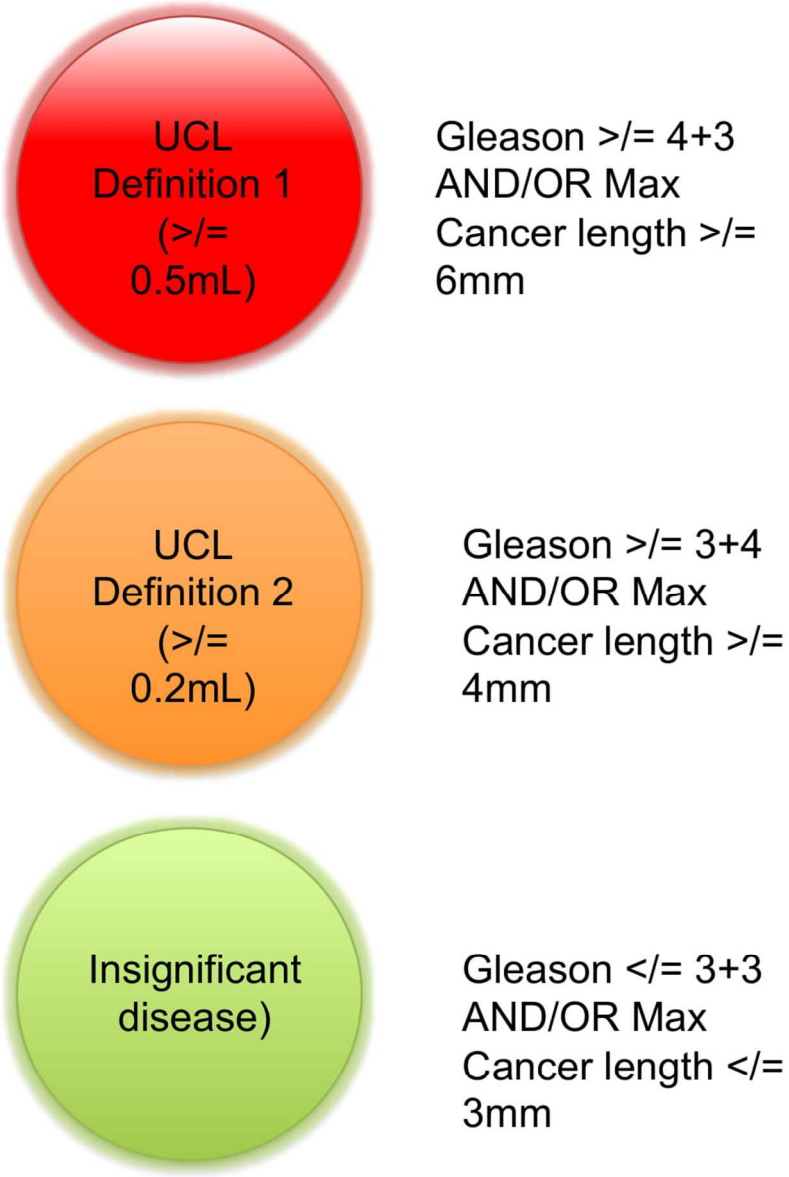
The One-Stop mpMRI led, MRTB prostate cancer diagnostic pathway.

168x97mm (300 x 300 DPI)



A pictorial prostate mpMRI diagrammatic report, as drawn by the uroradiologist.

261x230mm (300 x 300 DPI)



The University College London 'traffic light like' system to define significant prostate cancer.

89x125mm (300 x 300 DPI)

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The Prostate Cancer Diagnostic Pathway: Is a One-Stop Cognitive Magnetic Resonance Imaging Targeted Biopsy Service A Realistic Goal in Everyday Practice? A pilot cohort in a Tertiary Referral Centre in the United Kingdom.

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The Prostate Cancer Diagnostic Pathway: Is a One-Stop Cognitive Magnetic Resonance Imaging Targeted Biopsy Service A Realistic Goal in Everyday Practice? A pilot cohort in a Tertiary Referral Centre in the United Kingdom.

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Abstract

Objectives

To evaluate the feasibility of a novel multiparametric magnetic resonance imaging (mpMRI) and cognitive fusion transperineal targeted biopsy led prostate cancer (PCa) diagnostic service with regard to cancer detection and reducing time to diagnosis and treatment.

Design

Consecutive men being investigated for possible prostate cancer under the United Kingdom two week wait guidelines.

Setting

Tertiary referral centre for prostate cancer in the United Kingdom.

Participants

Men referred with a raised prostate specific antigen (PSA) or abnormal digital rectal examination (DRE) between 02/2015 and 03/2016 under the United Kingdom two week rule guideline.

Interventions

An mpMRI was performed prior to patients attending clinic, on the same day. If required, MRTB was offered. Results were available within 48 hours and discussed at a specialist multidisciplinary team (MDT) meeting. Patients returned for counselling within 7 days

Primary and Secondary Outcome Measures

Outcome measures in this regard included the time to diagnosis and treatment of patients referred with a suspicion of prostate cancer. Quality control outcome measures included clinically significant and total cancer detection rates.

Results

112 men were referred to the service. 111 (99.1%) underwent mpMRI. Median PSA was 9.4ng/mL [IQR 5.6-21.0]. 87 patients had a target on mpMRI with 25 scoring Likert 3/5 for likelihood of disease, 26 4/5 and 36 5/5.

57 (51%) patients received a local anaesthetic, MRTB. Cancer was detected in 45 (79%). 43 (96%) had University College London (UCL) definition 2 disease or greater. The times to diagnosis and treatment were a median of 8 and 20 days respectively.

Conclusions

This approach greatly reduces the time to diagnosis and treatment. Detection rates of significant cancer are high. Similar services may be valuable to patients with a potential diagnosis of PCa.

Strengths and limitations of this study

- First prospective study demonstrating the clinical feasibility of a 'one stop', rapid diagnostic prostate cancer pathway, using both multiparametric magnetic resonance imaging and transperineal targeted biopsy.
- Inclusion criteria reflecting 'real world' practice in the United Kingdom.
- This study incorporates a standardised multiparametric MRI acquisition and a validated system for defining clinically significant prostate cancer.
- Cognitive targeted biopsy performed only, rather than mpMRI / ultrasound fusion.
- Transperineal, rather than transrectal approach offers minimal septic complications post biopsy.

Introduction

Accurate risk stratification for men presenting with localised prostate cancer is vitally important. In its absence, patient centred management cannot be offered. Men with low-risk disease can be safely managed with active surveillance, whereas men with a good life expectancy and intermediate to high-risk disease are likely to benefit from interventional treatment[1-2]. Currently, standard practice uses prostate-specific antigen (PSA) value, digital rectal examination (DRE) and transrectal ultrasound guided biopsy (TRUSGB). However, TRUSGB is inherently random. The tumour cannot be visualised with certainty, and thus leads to overdiagnosis of insignificant disease in up to 50% of men[3], and missing significant disease in 18% of men, especially if cancer is located in anterior or apical regions of the prostate[4]. This creates difficulty for urologists and adds anxiety to patients[5] who have to undergo a repetitive cascade of diagnostic tests, which inevitably has cost implications for healthcare providers.

Transperineal mapping or zonal biopsies (TPM) of the prostate offer a diagnostic alternative to TRUS biopsy with demonstrable diagnostic success. However, the burden on patients is high. Firstly, the extensive biopsies demand general anaesthesia. Secondly, the rates of urinary retention following the procedure are high, making postoperative catheterization commonplace. Thirdly, the large number of cores taken requires many hours of labour to assess. Thus, a patient may have to wait significantly longer for a result, adding to their anxiety. This may also delay necessary treatment. Whether this results in adverse outcomes is not known. However, all of these established difficulties do confer added costs. Indeed, if every patient undergoing TRUSGB instead underwent a TPM, the cost of such a move would likely be exceedingly high. Therefore, the challenge presents itself as biopsy offering superior clinically significant detection rates to the existing standard, whilst not conferring an added cost.

Multiparametric magnetic resonance imaging (mpMRI) of the prostate has proved a useful tool in the diagnosis and risk stratification of prostate cancer. MpMRI has demonstrated its ability to detect significant cancers, whilst not detecting those

which are insignificant[4]. Suspicious areas on mpMRI can be targeted with subsequent transperineal biopsy (MRTB). MRTB has demonstrated greater sampling efficiency and accuracy when compared with standard TRUS-guided protocols[6-8], and has demonstrated accuracy when compared to the reference standard of radical prostatectomy (RP)[9]. This allows for a more accurate assessment of Gleason grade, and therefore an improved risk stratification and treatment plan at diagnosis[10]. Furthermore, the efficiency advantage, i.e. taking fewer cores at biopsy, confers significant benefits in cost, patient tolerability and post biopsy sepsis rates.

Three methods of transperineal MRTB currently exist. First and most common is 'cognitive targeting'. This approach requires the urologist to review the mpMRI images and aim the needle toward the corresponding area on ultrasound (US) imaging[11]. Alternatively, the reporting uroradiologist draws a diagrammatic representation of the gland and any suspicious area contained within, which guides the urologist to potential cancer. Second, 'in-bore MRTB' is performed whilst the patient is in the MRI scanner, allowing for real time targeting of suspicious areas with MRI compatible biopsy equipment. Third, 'fusion targeting' uses specifically designed software to allow combination of the mpMRI images with real time US imaging[4]. The latter two methods have implications in terms of equipment availability and cost, and as of yet the question of superiority of any one over another remains elusive[4].

Currently, prostate cancer diagnostic pathways remain built around TRUSGB. MpMRI is more commonly being used prior to TRUSGB. However, the use of an mpMRI and MRTB pathway remains a rarity despite the potential advantages of such an approach and the novel approach of both diagnostic interventions in one day exceptionally so. The reasons for this are multiple and commonly relate to the techniques being in their relative infancy. The lack of standardised mpMRI reporting[12], a learning curve for operators[13], mpMRI availability and cost[14] and concern regarding missed diagnosis from not sampling the whole gland have all been cited as reasons not to accept widespread adoption. Despite this, MRI-guided targeted biopsy pathways have been utilised before, albeit via the transrectal rather

than the transperineal route[15-17]. The recent findings of the PRECISION [18] trial has clearly addressed concerns in regard to superiority of an MRI-targeted biopsy approach over systematic TRUS biopsy, demonstrating superiority in clinically significant cancer detection rate and a reduction in the detection of insignificant disease.

Thus, the objective of this pilot study was primarily to determine the suitability and feasibility of a 'One-Stop', transperineal MRI-targeted biopsy pathway for prostate cancer in 'real-world' clinical practice. Outcome measures in this regard included the time to diagnosis and treatment of patients referred with a suspicion of prostate cancer. Quality control outcome measures included clinically significant and total cancer detection rates.

Patients and Methods

This prospective study analyses the clinical and service outcomes of an mpMRI and MRTB led prostate cancer diagnostic pathway (*figure 1*) from 02/2015 to 03/2016. Inclusion criteria were men presenting with a biochemical or clinical suspicion of prostate cancer under the United Kingdom two week wait program and undergoing mpMRI and if necessary subsequent cognitive targeted prostate biopsy. Patients without negative urine cultures or with estimated glomerular filtration rates of <30 micromol/L were excluded. The patient was contacted on referral and an mpMRI was arranged. This was reported before the patient attended clinic in the early afternoon of the same day. If a targetable lesion was identified (Likert >/=4), a transperineal-targeted biopsy was advised. If a target was rated as equivocal (Likert =3), the discussion was more nuanced including risk factors for a subsequent biopsy being positive such as a positive family history of prostate cancer, high PSA density or concordant positive DRE findings. Further, in this group of men, those with diffuse equivocal changes requiring a greater number of cores to be taken for a positive result, the option of full template biopsies under general anaesthetic was discussed. Results were available within 48 hours and were discussed at a specialist MDT. Patients returned for counselling within seven days.

MpMRI acquisition was performed according to the European guidelines of Uro-radiology previously described by the University College London (UCL) group[12,19,20]. In summary this includes the use of a 1.5 or 3.0 Tesla MRI scanner acquiring T2-weighted axial and coronal, axial diffusion weighted coefficient and high *b*-value as well as T1 weighted dynamic contrast enhancement (intravenous Gadolinium) images. Each scan was reported by an experienced uro-radiologist as previously described [21,22] and a pictorial diagrammatic map drawn (*figure 2*). Regions of interest (ROIs) were scored using a Likert-like scale of 1-5[22] using the overall impression of the radiologist to characterise the level of suspicion for prostate cancer. ROIs scoring 4 or 5 were thought 'likely' or 'highly likely' to contain a malignant lesion, which was either ≥0.2mL in volume and/or had high-grade components within (Gleason ≥3+4)[23]. ROIs 3 were rated as indeterminate for such disease and this score of 3, or higher, was chosen as the threshold for a positive mpMRI. Our choice of scoring system was based on the outcomes of the 2011 European Consensus Meeting[12] which met prior to the Prostate Imaging and Data Reporting System (PIRADS) MP-MRI reporting consensus meeting[19] and has demonstrated equivalency with the PIRADS system[24].

The procedure was performed as a day case under local anaesthesia and antimicrobial prophylaxis in the lithotomy position, by either a consultant urologist or urology clinical fellow as previously described[25]. This biopsy technique has demonstrated a median procedure length of 30 minutes and good patient toleration, with median visual analogue pain scores of 1.0[26].

Data was collected on a case report form compliant with the Standards of Reporting for MRI-targeted Biopsy Studies (START) of the prostate[11]. Included data were patients demographics, indications for biopsy, PSA value, prostate volume, number of targets per patient, and Likert score per target[11]. Additionally, for each biopsy collected the total number of cores taken, biopsy density, number of positive cores, maximum and overall Gleason scores and the maximum cancer core length (MCCL). Biopsy efficiency was calculated by the number of cores demonstrating clinically significant disease divided by the number of cores taken. For the purpose of this study, clinically significant disease was defined using the University College London

(UCL) classification for interpreting transperineal biopsy findings, which sets the significance threshold at Gleason score >/= to 3 + 4 and/or MCCL >/= 4 mm for definition 2 and >/= to 4 + 3 and/or MCCL >/= 6 mm for definition 1[26] (*figure 3*).

Finally, to assess the time to diagnosis and treatment as well as the treatments elected by men were determined by examination of the hospital trust's electronic data system.

Patient and Public Involvement

Participants were not involved in the design of the study. However, conclusions gleaned from the study are to be disseminated amongst patients newly referred to the service.

Results

Table 1

A. *Patient Demographics*		
Men included		112
Median Age (years)		68 [IQR 62-78]
Median PSA (ng/mL)		9.4 (IQR 5.6 - 21.0)
B. *MpMRI Outcomes*	n	%
Men undertaking mpMRI	111	99%
Median Prostate Volume (mL)		50 (IQR 35 - 78)
Positive mpMRI (Men)	87	78%
Negative mpMRI (Men)	24	22%
Total ROIs	162	
1 ROIs / man	39	35%
2 ROIs / man	25	23%
3 ROIs / man	22	20%
4 ROIs / man	1	1%
Likert score per man		
Likert 3	25	23%
Likert 4	26	23%
Likert 5	36	32%
Total ROIs	162	

Median ROI volume (mL)		0.5 (IQR 0.2 - 1.0)				
Likert score per lesion						
Likert 3		71	44%			
Likert 4		49	30%			
Likert 5		42	26%			
***C.** Biopsy Outcomes*	n	%				
Men undertaking biopsy		57	51%			
Median cores per patient		9 (IQR 5 - 12)				
Total cores		514				
Cores positive (UCL 2)		241	47%			
Biopsy efficiency		47%				
Median cores per lesion		4 (IQR 4 - 5)				
Median biopsy density (cores / ROI mL)		10 (IQR 3.5 - 20)				
Cancer detection by man						
Any Cancer		45	79%			
UCL 2		43	75%			
UCL 1		34	60%			
Gleason >/=3+4		43	75%			
Gleason >/=4+3		23	40%			
Median MCCL (mm)		7 (IQR 3 - 10)				
Cancer detection by lesion			Any cancer	UCL 2		UCL 1
Likert 3 (lesions biopsied)		40	13	10		4
Likert 4 (lesions biopsied)		38	24	19		15
Likert 5 (lesions biopsied)		35	35	35		28
***D.** Diagnosis and Treatment Outcomes*						
Median time to diagnosis (days)		8 (IQR 5 - 12)				
Median time to treatment (days)		20 (IQR 8 - 40)				
Treatment type (Post Biopsy)	n	%				
Discharged		4	7%			
PSA Surveillance		6	11%			
Active Surveillance		5	9%			
Focal therapy		6	11%			
Robotic Prostatectomy		9	16%			
External Beam Radiotherapy		10	18%			
Brachytherapy		2	4%			
Androgen Deprivation Therapy		9	16%			
Chemotherapy		4	7%			
Antibiotics		1	2%			

Repeat biopsy	1	2%

Patient demographics

In total, 112 consecutive biopsy naive men with a median age of 68 attended the prostate cancer one stop clinic between 02/2015 and 03/2016 *(Table 1A*). All but one man (99%) received an mpMRI scan prior to clinic. The patient in question had an MRI incompatible cardiac pacemaker.

MpMRI Outcomes

The median prostate volume was 50mL. Eighty-seven men (78%) had a positive mpMRI (Likert score >/=3) and 24 (22%) had a negative scan (Likert score </=2) and did not go on to biopsy. Twenty-five men (29%) had an mpMRI scan with an overall Likert score of 3, 26 (30%) an overall score of 4 and 36 (41%) an overall Likert score of 5. There were 162 ROIs identified on mpMRI with a median volume of 0.5mL when measured on T2 MRI sequencing. Thirty-nine men (45%) had a single ROI on mpMRI, 25 men (29%) had two, 22 men (25%) had three and a single man (1%) had four. Seventy-one lesions (30%) were Likert 3, 49 (30%) at Likert 4 and 42 (26%) and Likert 5. After mpMRI, nine with negative mpMRIs (38%) were discharged for PSA surveillance in the community, 10 (42%) remained on PSA surveillance in secondary care, four (17%) underwent investigations for lower urinary tract symptoms and one (4%) underwent a full template biopsy under general anaesthetic *(Table 1B*).

Biopsy Outcomes

Fifty-seven men (51%) underwent a local anaesthetic MRTB as described following mpMRI *(Table 1C*). Fifteen (17%) men chose not to undergo biopsy under local anaesthetic and were listed for a biopsy under sedation. Thirteen men (15%) did not have a biopsy due to clinical reasons. Any cancer was detected in 45 (79%) of men. Of these, 43 (96%) satisfied the UCL 2 criteria for clinical significance and 34 (76%) satisfying the UCL 1 criteria. The median MCCL of positive biopsies was 7mm. The calculated biopsy efficiency for UCL 2 disease was 47%. The median number of cores

taken per ROI was 4, with a median calculated biopsy density of 10 cores/mL of ROI. Of the 20 men who had more than one lesion on mpMRI and underwent biopsy, two had a secondary lesion, which harboured either higher grade or volume disease. In only one of these men was the secondary lesion a lower Likert score. Both such men went on to radical prostatectomy.

Diagnosis and Treatment Outcomes

The median time to a man being told his diagnosis was eight days, and the median time by which treatment had been started was 20 days, although in five cases this time period was not clear *(Table 1D*). The treatment outcomes are shown in table 1D. Of note, 20 (18%) men were discharged after biopsy with 19 (17%) men starting PSA surveillance. Forty-four (40%) went on to undergo treatment and nine (8%) men underwent a further biopsy either due a perceived false negative or diffuse disease requiring a biopsy under sedation or general anaesthetic. Eleven (10%) patients underwent further assessment or treatment for benign disease.

Discussion

An optimal PCa diagnostic strategy should encapsulate maximal significant cancer detection whilst avoiding insignificant disease or repeat biopsy. Furthermore, it should convey enough information for urologists and patients to accurately devise a treatment plan according to the risk of progression. However, as things stand, the diagnostic pathway is still commonly led by TRUSGB, despite its accepted inaccuracy, especially for disease located in the anterior or apical regions of the prostate[27]. In particular the negative predictive value (NPV) of the originally described six core TRUSGB is poor, with false negative rates of around 35%[28,29]. This inherent disadvantage is somewhat mitigated by extending the biopsy to a 12 or even 24 core technique, however increasing the number of cores past 12 leads to increased numbers of insignificant cancers being detected[30,31] which is present in 40% of men over the age of 50[32]. These cancers are rarely affect life expectancy or its quality in any meaningful way and revealing them simply adds unnecessary burdens

to patients. Furthermore, increasing the number of cores may increase incidence of post TRUSGB sepsis[33] and with the incidence already on the rise alongside increasing prevalence of colonisation with resistant organisms such strategies pose an increasing potential for harm[34] for which our clinical options are worryingly limited. As a result, transperineal zonal or mapping biopsies (TPM) have become more popular. In particular, one recent series reported a 0% readmission rate for infective complications after targeted transperineal biopsy[35], in comparison to rates of sepsis of up to 6.3% after TRUSGB[36]. However, there are significant concerns regarding its cost, need for general anaesthetic, increased complications and patient burden. Such concerns have justly prevented its wider use and certainly a TPM led diagnostic pathway has not been seriously suggested.

However, the development and refinement of mpMRI demands that its use in leading an approach to diagnosis must be contemplated. MpMRI has demonstrated high levels of accuracy for the detection of clinically significant cancer when compared to both TPM[37] and whole-mount prostatectomy specimens[9]. Indeed, a systematic review by Fütterer et al found that mpMRI detected clinically significant disease in up to 84% of men with a NPV of up to 98% where either TPM or prostatectomy was used as the reference standard[20]. More recently the results of the PROMIS trial demonstrate the sensitivity and negative predictive value of mpMRI in detecting clinically significant disease as 93% and 89% respectively[38]. Furthermore, the PROMIS trial demonstrated that 27% of men could avoid a biopsy[38]. Despite these findings, both the European Association of Urology (EAU)[39] and National Institute of Clinical Excellence (NICE)[40] still do not recommend mpMRI prior to an initial set of biopsies. In this study, leading with mpMRI allowed 24 (21.6%) men to avoid a biopsy entirely. However, the majority would remain on PSA surveillance due to the small – but understood - risk of a false negative mpMRI. There is perhaps a concern that in less experienced centres overcall images as PIRADS 3 is an issue that will expose men to unnecessary biopsies and thus reducing the benefit of an image-guided pathway. However, as the PIRADS v2[41] scoring system is increasingly adopted, with its ability to define a PIRADS 4 lesion over a 3 by utilisation of the second parameter (DCE and DWI for peripheral

zone and transition zone lesions respectively), alongside its more easily understood and applicable design, should reduce such an effect going forward.

Clearly, there is enough evidence now to introduce an image-guided biopsy to the PCa diagnostic pathway, bringing it in line with the current practice in other solid organ malignancies. However, currently there is concern that targeted biopsies alone risk missing areas of significant disease that appear normal on mpMRI. This may be viewed as a limitation. However, our current approach to this cohort of men was introduced after our paired analyses of mpMRI versus template biopsies demonstrated that mpMRI cognitive biopsies had equivalent detection rates to zonal mapping biopsies[37]. Furthermore, numerous centres have now reported improved cancer detection rates of MRTB strategies when compared to systematic approaches [42,43], as well as improved biopsy efficiency and reduced false negative rates for significant cancer[8]. To underline this, another series of men who underwent both fusion MRTB and systematic TPM showed a difference of clinically significant cancer detection rates of 4% (28% for MRTB and 24% for systematic biopsy), although combined biopsies outperformed each approach in isolation[44]. Naturally, such results have been reported by specialist centres and as such, concern remains in regard to the level of operator dependency with targeted biopsy techniques. However, authors have found no difference between cancer detection rates with targeted techniques regardless of the experience of the operator, albeit with TRUSGB[45]. Of course, advocating for a rapid uptake of such techniques in centres with no prior experience would be optimistic. Instead, envisage a step-wise, quality controlled uptake of transperineal approach biopsies, mpMRI reporting before adopting targeted strategies.

As with mpMRI, MRTB is not a perfect test, both can miss significant disease. However, this is an improvement on our current standard diagnostic test which is demonstrably poor[27-30]. As recent studies have shown, in comparison to TRUSGB, MRTB is more likely to detect disease once a suspicious area has been identified[6,17]. Furthermore, the recently published PRECISION randomised controlled trial clearly demonstrated the superior clinically significant cancer

detection rate of MRTB and a reduced insignificant cancer detection rate when compared to systematic TRUS biopsy[18].

A potential limitation of the MRTB technique in this study is the use of 'cognitive fusion' rather than US/mpMRI fusion or 'in-bore' targeting. However, no superiority of one technique over another has been clearly demonstrated, whilst 'cognitive fusion' is clearly a less costly option[46]. Another potential limitation of the targeted biopsy strategy is the 'satisfaction of search' bias. Essentially, this means that after the primary lesion is scored, less attention to detail is given to subsequent lesions, which may therefore be undercalled or undersampled. However, in this series this occurred twice, only once where the secondary lesion was attributed a lower score than the primary, and in no cases did this change the proposed management. Further, in the vast majority of centres where radical treatments – rather than focal – remain the standard of care, there would likely be no change in the approach to curative therapy, save for planning for prostatectomy in the case of nerve-sparing procedures.

The cost of mpMRI has been cited as a reason for persisting with TRUSGB led diagnostic pathways [47], using it instead for a second investigation in the case of a negative biopsy in a patient in whom suspicion of cancer remains. Whilst mpMRI is indeed useful in this scenario, recent cost effectiveness analyses have shown the long term cost benefits of mpMRI led pathways when various outcomes are accounted for[14,48,49] due to a reduction in overdiagnosis and higher detection rates of clinically significant disease at primary biopsy. In particular, the cost-analysis of the PROMIS trial cohort demonstrated that MpMRI first followed by two MRTBs detects more cancer per pound spent than a TRUS first biopsy strategy[49].

A major advantage of our pathway is the low time to diagnosis and treatment. At a median of 8 and 20 days respectively the time a patient waits is significantly below the 31 and 62-day targets set by the United Kingdom National Health Service. The meeting of these targets is a persistent challenge nationally[50]. Moreover, performing an mpMRI prior to primary biopsy negates the risk of an initial false negative biopsy significantly delaying a subsequent mpMRI due to post biopsy

haemorrhage within the prostate. This makes it difficult to localise cancer or accurately determine its size or border[51]. In such circumstances, the delay in diagnosis can be up to eight weeks.

Conclusions

This novel pathway offers an alternative to standard prostate cancer diagnostic services. Attendance and cancer detection rates are high. The use of an mpMRI led pathway allows for a significant proportion of men to avoid a biopsy and for those who do, the time to diagnosis and definitive treatment is kept particularly low. The integration of both mpMRI and MRTB in the prostate cancer diagnostic pathway has shown cost-effectiveness in the long-term. This is especially true where rapid diagnostics are mandated or desirable. Furthermore, today, where septic complications are of grave concern, the transperineal route is particularly advantageous. This pilot study demonstrates, that similar services can be provided in appropriate centres and may be valuable to patients with a potential diagnosis of prostate cancer.

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Figure and Table legends

Figure 1: The One-Stop mpMRI led, MRTB prostate cancer diagnostic pathway.

Figure 2: A pictorial prostate mpMRI diagrammatic report, as drawn by the uroradiologist.

Figure 3: The University College London 'traffic light like' system to define significant prostate cancer.

Table 1A: Baseline demographics for the cohort.

Table 1B: MpMRI outcomes.

Table 1C: Biopsy outcomes.

Table 1D: Diagnosis and treatment outcomes.

Footnotes

Contributorship statement

Edward J Bass drafted the manuscript and approved the final version.

Alex Freeman contributed to the conception of the work presented, revised the manuscript critically and approved the final version.

Charles Jameson contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

Shonit Punwani contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

Caroline Moore contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

Manit Arya revised the manuscript critically and approved the final version.

Mark Emberton contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

Hashim U. Ahmed contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

All authors are accountable for all aspects of the work in terms of accuracy and integrity.

Competing Interests

Hashim Ahmed's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) Imperial Biomedical Research Centre. This paper is independent research funded by the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre (BRC). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Ahmed currently receives funding from the Wellcome Trust, Prostate Cancer UK, Sonacare Inc., Trod Medical and Sophiris Biocorp for trials in prostate cancer. Ahmed is a paid medical consultant for Sophiris Biocorp for trials work.

Mark Emberton's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research Centre. He was awarded NIHR Senior Investigator in 2015.

Emberton receives funding from NIHR-i4i, MRC, Sonacare Inc., Trod Medical, Cancer Vaccine Institute and Sophiris Biocorp for trials in prostate cancer. Emberton is a medical consultant to Sonacare Inc., Sophiris Biocorp, Steba Biotech, Exact Imaging and Profound Medical.

Moore receives funding from the National Institute for Health Research, The European Association of Urology Research Foundation, Prostate Cancer UK, Movember and the Cancer Vaccine Institute, for clinical prostate cancer research. She has received advisory board fees for Genomic Health.

Ahmed, Emberton, and Moore are all proctors for HIFU and are paid for training other surgeons in this procedure.

Emberton and Freeman have loan notes/stock options in Nuada Medical Ltd (UK).

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Data sharing statement

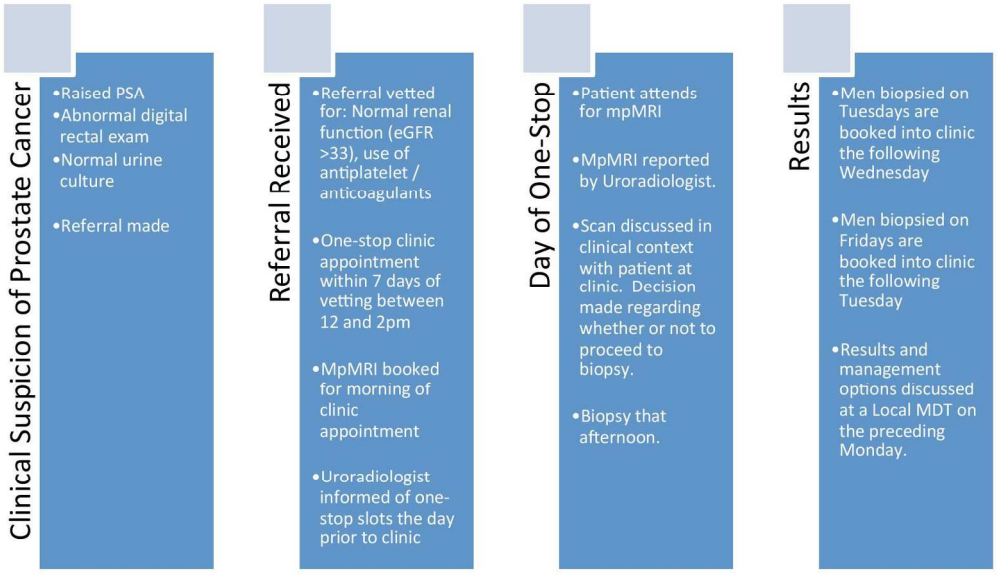
We declare there is no unpublished data from etc study.

Patient Consent

Consent was obtained prior to mpMRI and biopsy.

Ethics approval

Local ethical approval was attained through the Hospital Trust's audit commitee



The One-Stop mpMRI led, MRTB prostate cancer diagnostic pathway.

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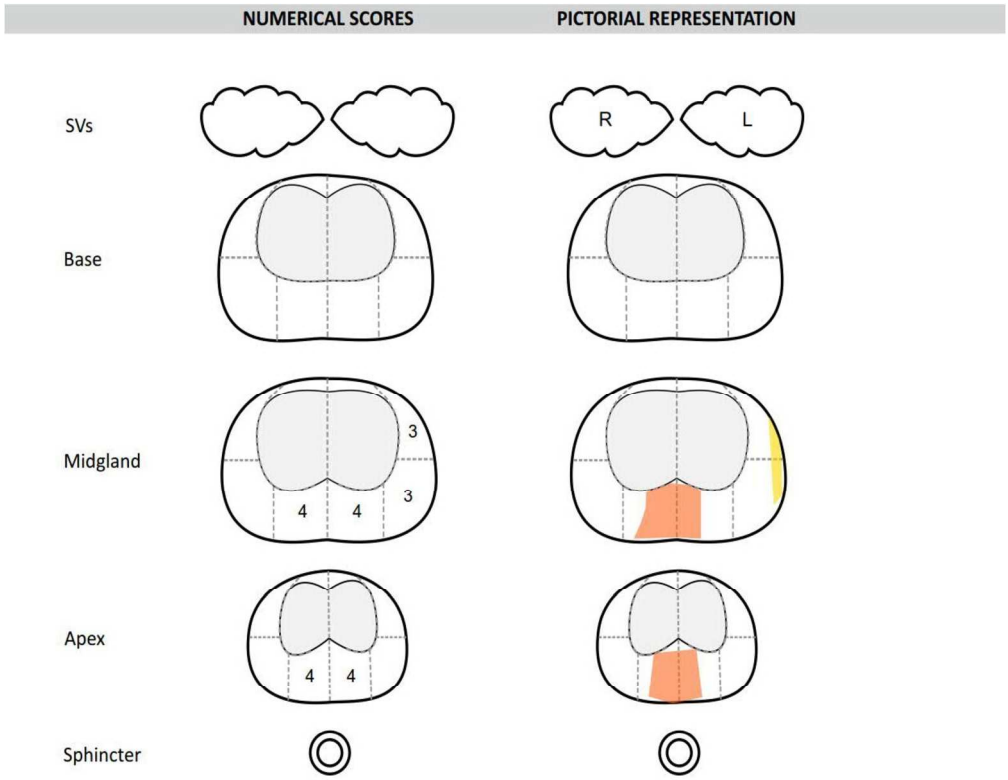
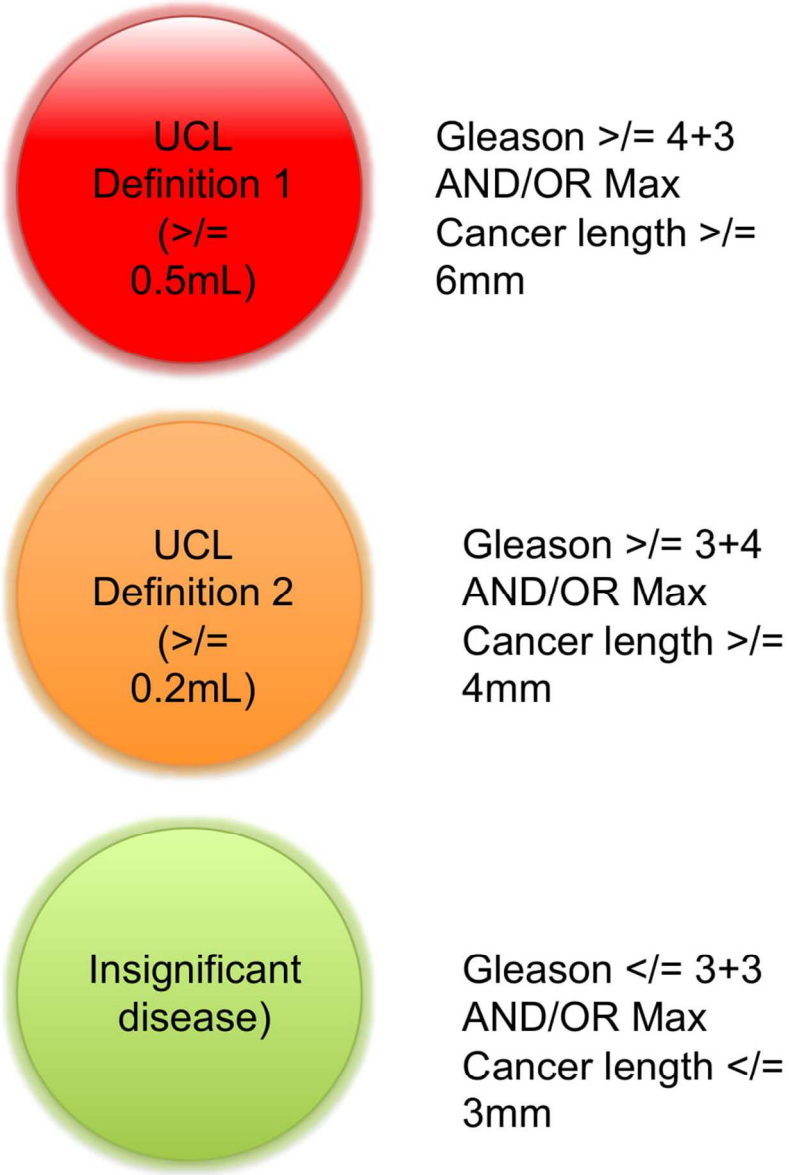


A pictorial prostate mpMRI diagrammatic report, as drawn by the uroradiologist.

261x230mm (300 x 300 DPI)



The University College London 'traffic light like' system to define significant prostate cancer.

89x125mm (300 x 300 DPI)

Item	Extension for pilot trials	Reported	Page	Line
Title	Identification of study as randomised pilot or feasibility trial	✓	7	6
Trial design	Description of pilot trial design (eg, parallel, cluster)	✓	7	14 - 29
Methods:				
Participants	Eligibility criteria for participants and the settings where the pilot trial was conducted	✓	7	17 - 20
Interventions	*Interventions intended for each group*	✓	8	1 - 22
Objective	Specific objectives of the pilot trial	✓	7	6 - 11
Outcome	Prespecified assessment or measurement to address the pilot trial objectives*	✓	7	10 - 11
Randomisation	*How participants were allocated to interventions*	N / A	N / A	N / A
Blinding (masking)	*Whether or not participants, care givers, and those assessing the objectives were blinded to group assignment*	N / A	N / A	N / A
Results:				
Numbers randomised	Number of participants screened and randomised to each group for the pilot trial objectives*	N / A	N / A	N / A
Recruitment				
Numbers analysed	Number of participants analysed in each group for the pilot objectives*	✓	11	2 - 3
Outcome	Results for the pilot objectives, including any expressions of uncertainty*	✓	12 & 13	19 - 26 & 1 - 15
Harms	*Important adverse events or side effects*	✗	✗	✗

Conclusions	General interpretation of the results of pilot trial and their implications for the future definitive trial	✓	15	23 - 26
Trial registration	Registration number for pilot trial and name of trial register	N / A	N / A	N / A
Funding	Source of funding for pilot trial	N / A	N / A	N / A