**Clinico-pathological outcomes of men with initial Likert 2 Multiparametric Magnetic Resonance Imaging of the Prostate: findings from a case series in a non-teaching hospital in UK.**

**ABSTRACT**

**Introduction:** With the recent introduction of Multiparametric MRI (MP-MRI) for suspected prostate cancer, we investigated the clinic-pathological outcome of men who were suspected to have prostate cancer but in whom initial MP-MRI was negative (Likert 2).

**Methods:** Demographic and clinico-pathological outcomes data were analysed in men, with minimum 2 year follow up, who had undergone investigation for suspected prostate cancer with a negative (Likert 2) initial MP-MRI. The primary outcome was subsequent identification of prostate cancer in this cohort. Secondary outcome measures included correlation of prostate volume, presence of previous prostate biopsy, age, Prostate Specific Antigen (PSA) dynamics (pre and post MP-MRI scan), Digital Rectal Examination (DRE) findings and follow-up in months with the primary outcome.

**Results:** With respect to the primary outcome of this study, prostate cancer was identified in 8.7% of men only (n=4). Of these, two cases were low risk and two were high risk. With regards the secondary outcome measures, there was a positive correlation between PSA dynamics, age at MP-MRI and follow-up in months with subsequent diagnosis of prostate cancer, although this was not statistically significant. There was no prostate cancer specific mortality or morbidity in this cohort.

**Conclusions:** In this study, despite initial negative MP-MRI scan, prostate cancer was subsequently diagnosed in 4 men (8.7%). Reassuringly, this compares very favourably to the negative predictive value (89%) from the PROMIS trial, and as

such, adds an important body of work to the contemporary literature on modern diagnosis of suspected prostate cancer.

*Key words: Prostate, MRI, Diagnosis, Biopsy, Cancer*

# 1. INTRODUCTION

Prostate cancer is the commonest cancer in the UK with over 40,000 cases diagnosed per year and around 12,000 deaths per annum [1], figures which are only expected to increase significantly over the next decade. Recently, a paired validating confirmatory study – the PROMIS trial – assessed the diagnostic accuracy of MultiParametric MRI (MP-MRI) and TRUS (Transrectal UltraSound) biopsy against the reference test, Template Prostate Mapping (TPM) biopsy [2-4]. This multicentre trial concluded that a "negative" MP-MRI may allow 27% of patients to avoid an unnecessary prostate biopsy. It was also shown that MP-MRI could reduce over-diagnosis of clinically insignificant prostate cancer and improve detection of clinically significant cancer. These results were replicated in a second study, which also reported that MP-MRI before biopsy improves detection of clinically significant prostate cancer [5].The landmark PROMIS study resulted in a change in clinical practice and was subsequently endorsed in the updated international guidance for prostate cancer [6, 7]. In these documents, guidance was given to clinicians to offer MP-MRI as the first-line investigation for men with suspected clinically localised prostate cancer, with the result to be reported using the 5-point Likert scale. Importantly, this guidance was the first to formally advise clinicians to consider omitting a prostate biopsy for patients with MP-MRI Likert score of 2, but only after discussing the risks and benefits with the patient and reaching a shared decision. Prior to the PROMIS trial, there were several reports investigating outcomes of negative MRI scans [8-11]. However, all of these studies had limitations, specifically including use of PIRADS 1 [8,9] and patients proceeding to biopsy, despite negative MRI scan [10]. These reports also

included use of TRUS biopsy [9, 10] which PROMIS Trial had revealed to be associated with poor sensitivity and negative predictive value for identifying significant prostate cancer. Certainly, one could argue that none of these studies reported modern contemporary management of men with suspected prostate cancer. Hence, since the publication of PROMIS Trial, to our knowledge there have been no studies reporting the clinical outcome of men with negative MRI scan, who did not undergo biopsy. As such, in this descriptive paper, we investigated the clinico-pathological outcomes of men who were suspected to have prostate cancer but initial MP-MRI was negative, with the aim of adding to the contemporary literature on this important global topic.

## 2. METHODS

We reviewed our prospectively kept database of men who had undergone investigation for suspected prostate cancer with initial MP-MRI, and extracted data on patients with report of Likert 2 since 2017, with at least 2 year follow up. Inclusion criteria for the purposes of our study was men with MRI scan reported as Likert 2, while exclusion criteria was those with Likert 3-5 and/or previous treatment. Demographic and clinico-pathological data (indication for MP-MRI, initial and subsequent PSA results, examination findings and outcomes of subsequent MP-MRI and biopsies, if performed) were obtained from the Picture Archiving and Communication System and review of digital patient records. Data was cross checked via formal medical case notes review. As per local clinical guidelines, patients were followed up with clinical examination and PSA, every 6 months, until a clinical decision was made for discharge to primary care setting. Consecutive rises in PSA resulted in subsequent MRI scan.

## 2.1 - Outcomes

The primary outcome was subsequent identification of prostate cancer in this cohort. As per the original PROMIS report [2], the primary definition (Definition 1) for clinically significant prostate cancer (csPCa) was overall Gleason score ≥4+3 of any length and/or maximum cancer core length (MCCL) ≥6 mm of any grade, whereas the secondary definition (Definition 2) was overall Gleason ≥3+4 of any length and/or MCCL ≥4 mm of any grade. Secondary outcome measures were correlation of prostate volume, presence of previous prostate biopsy, age, PSA dynamics (pre and post MP-MRI scan), Digital Rectal Examination (DRE) findings and follow-up time in months, with the subsequent risk of detecting prostate cancer. We also assessed outcomes of subsequent MP-MRI and prostate biopsies, if performed, as well as prostate cancer mortality and overall mortality.

## 2.2 – Ethical Considerations
There was no formal ethical committee approval performed for this study, as this was deemed an audit of newly introduced service review.

## 2.3 – Statistical Analysis
Descriptive statistical tests were used to calculate mean, median, minimum and maximum values. Comparative statistical tests were two-sided with alpha=.05. The Wilcoxon test was used due to the non-paired, non-parametric nature of the data. Relationships between parameters were determined employing the Pearson Correlation test. All analyses were conducted using GraphPad Prism 8 (Graph-Pad Software, Inc., La Jolla, CA, USA) and the R statistical package. Patients received a standardised MP-MRI, compliant with European Society of Uro-Radiology guidelines, with a 1.5 Tesla magnetic field strength and a pelvic phased-array coil. T1-weighted, T2-weighted, diffusion-weighted and dynamic gadolinium contrast-enhanced imaging sequences were acquired [2].

# 3. RESULTS

46 men were identified to meet the inclusion criteria for this study. Average age at MP-MRI scan was 67 years (Range 51-80) and the average follow up since MP-MRI scan was 32 months (Range 24-42). Of the 46 patients, 29 were undergoing investigation in the absence of previous investigation (n= 25 for raised PSA and n=4 for abnormal DRE with normal PSA). The remaining 17 patients had previously had a negative TRUS biopsy but were still undergoing follow for suspicion of prostate cancer due to persistently elevated PSA. The overall Median PSA value was 6.95 (Range 1.2 to 44.1), Median prostate volume was 59.5ml (20-166ml) and median PSAD was 0.12 (Range 0.04 to 0.6). The median prostate volume (70ml) and median PSA levels (8.2ng/ml) were higher in patients who had previously had a TRUS biopsy, although this was not statistically significant ($p$=.068). With regards to median PSAD this was lower in patients with abnormal DRE (0.06ng/ml$^2$) but again were not statistically significant ($p$=.066). With respect to the Primary outcome of this study, prostate cancer was identified in 4 patients (8.7%). Table 1 summarises the demographics of these patients. Table 2 shows the pathological outcomes data for these patients.

## 3.1 – Table 1 – Demographic data for the 4 men subsequently diagnosed with prostate cancer

| Case Number | Age | PSA at Baseline | PSA Density at Baseline | PSA at Diagnosis | PSA Density at Diagnosis | Time Interval between Index and Diagnostic MRI |
|---|---|---|---|---|---|---|
| 27 | 58 | 3.4 | 0.06 | 9.1 | 0.04 | 23 months |
| 29 | 68 | 6.4 | 0.09 | 8.4 | 0.12 | 27 months |
| 36 | 82 | 7.8 | 0.37 | 9.7 | 0.73 | 24 months |
| 40 | 60 | 8.1 | 0.41 | 10.7 | 0.71 | 28 months |

## 3.2 - Table 2 - Pathological outcome data for those subsequently diagnosed with prostate cancer

| Case No. | Clinical Indication | Prostate Volume | PSA (Baseline) | PSAD (Baseline) | Clinico-pathological outcome | Risk Category |
|---|---|---|---|---|---|---|
| Case 27 | Raised PSA with initial MRI negative but PSA continued to rise. Subsequent MRI PIRADS 4 prompted TPM | 55 | 3.4 | 0.06 | Subsequent MRI PIRADS 4 (RIGHT) LP: 1 core positive Gleason 3+3=6 (GG2). Longest continuous length of tumour = 2 mm. Percentage of involvement of relevant core = 12%. Percentage of involvement of whole specimen < 2% of specimen. All other cores negative. | LOW |
| Case 29 | Raised PSA with previous negative TRUS biopsy and then initial MRI negative but PSA continued | 69 | 6.4 | 0.09 | RA: 1 core positive Gleason 3+3=6 (GG1). Longest continual length of carcinoma <1 mm. Largest deposit <1mm in 16mm core. % involvement of most involved core | LOW |

| | | | | | <1% | |
|---|---|---|---|---|---|---|
| to rise, prompting TPM | | | | | % involvement of whole specimen <1% | |
| | | | | | RP: 1 core positive Gleason 3+3=6 (GG1). | |
| | | | | | Longest continual length of carcinoma 4 mm. | |
| | | | | | Largest deposit 4mm in 17mm core. | |
| | | | | | % involvement of most involved core 23%. | |
| | | | | | % involvement of whole specimen 5%. | |
| | | | | | LP: 1 core positive Gleason 3+3=6 (GG1). | |
| | | | | | Longest continual length of carcinoma <1 mm. | |
| | | | | | Largest deposit <1mm in 14mm core. | |
| | | | | | % involvement of most involved core <1%. | |
| | | | | | % involvement of whole specimen <1%. | |
| Case | Raised PSA - clinical | 21 | 7.8 | 0.37 | LEFT: 3/6 cores | HIGH |

| | | | | | | |
|---|---|---|---|---|---|---|
| 36 | suspicion LEFT lobe prompted TRUS Biopsy | | | 8 | Gleason 4+4=8 (GG4). The core with largest volume shows 85% (10mm) involvement and overall, the tumour represents approximately 30% of the aggregate length of the cores. There is no perineural invasion. RIGHT: all cores Negative. | |
| Case 40 | Raised PSA - continued to rise prompting TPM | 20 | 8.1 | 0.41 | RP: One core positive Gleason 4+5=9 (GG5) 5mm. Percentage of involvement of relevant core 40%. Percentage of involvement of whole specimen 18%. LL: One core positive Gleason 4+3=7 (GG3) 2mm. Percentage of involvement of relevant core 15%. Percentage of whole specimen less than 2%. | HIGH |

| | | | | | All other cores negative. | |
|---|---|---|---|---|---|---|

Table 2 shows that while three cases were subsequently diagnosed with clinically significant prostate cancer (Cases 29, 36 and 40) as per PROMIS trial criteria [2], only two cases were actually stratified as high risk prostate cancer [6]. Cases 36 and 40 had subsequent radiotherapy treatment and PSA remains undetectable for both. Case 29 had clinically significant prostate based on Definition 2 in PROMIS Trial [2] and subsequently had radical prostatectomy (patient choice). His PSA remains un-recordable at <0.1. Case 27 remains on Active Surveillance (with no significant change in clinical findings). With respect to Case 27, the subsequent MRI revealed PIRADS 4, but this did not correlate with location of positive biopsy at TPM. None of these four patients who were subsequently diagnosed with prostate cancer had prior abnormal DRE findings or previous TRUS biopsy.

With regards the secondary outcome measures, although not statistically significant, there was a positive correlation for PSA dynamics (Pearson Correlation $p=.17$), age at MP-MRI (Pearson Correlation $p=.106$) and Follow up in months (Pearson Correlation $p=.18$), for the subsequent diagnosis of prostate cancer. There was no significant correlation for pre MP-MRI PSA (Pearson Correlation $p=.32$) and Prostate Volume (Pearson Correlation $p=.63$).

In this study, two patients have subsequently received a histological diagnosis of benign prostatic disease. Case 25 developed worsening LUTS and underwent HOLEP 12 months after MP-MRI scan. Histology revealed 62g BPH only, with no evidence of prostate cancer. Case 42 subsequently had a repeat MP-MRI scan at 18 months, due to rising PSA levels, and went on to have TPM which was negative, with no evidence of prostate cancer. Case 14 had a PSA of 44.1 at

presentation. Interestingly, his PSA has remained elevated at follow up, as per protocol, but he has not been diagnosed with prostate cancer. His PSA has hovered between 38-46 ng/ml. He continues under regular follow-up.

In this study, to date, there have been no prostate cancer specific mortality or morbidity. Two patients (Cases 15 and 20) died of unrelated causes - Case 15 from delayed presentation of severe cellulitis of the groin, resulting in sepsis and multi-organ failure, while Case 20 developed multiple myeloma for which medical therapy was sadly unsuccessful. Case 24 was diagnosed with lymphoma (lymph nodes at MP-MRI scan) and to date has been treated successfully with standard chemoradiotherapy.

## 4. DISCUSSION

In this study, despite an initially negative MP-MRI scan, prostate cancer was subsequently diagnosed in only 8.7% of men (n=4), which compares very favourably to the negative predictive value (89%) from the PROMIS trial [2]. This is a reassuring conclusion and we feel that this study adds an important body of work to the contemporary literature on modern diagnosis of suspected prostate cancer.

All MP-MRI scans in this study were reported by a single dedicated Uro-Radiologist, who had previous experience of reporting prostate MP-MRI in the PROMIS trial. Prior to the trial they had undergone centralised training of 20–30 cases individually reported, and then reviewed as a group. A further training day occurred after the pilot phase with further 20–30 cases reviewed individually and collectively [2]. Significantly, it appears that lessons learned before and during the PROMIS trial have been consolidated in our unit, especially as our centre is not a formal teaching hospital or academic centre, inferring that PROMIS trial outcomes may be applicable in all health-

care settings, and reflect "real-life" urological practice. All MP-MRI imaging in this study was based on the LIKERT scoring system. There have been some recent studies comparing the LIKERT system with the PI-RADS system, and perhaps this is an area we could look to develop this current work [12, 13].

In this study, with an average follow up of 32 months, there was no prostate cancer mortality or morbidity, indicating that this population with Likert 2 on MP-MRI are likely to follow a benign pathway, or at worse, a clinically non aggressive outcome. Of course, it was ethically not possible to biopsy men with negative MP-MRI scans (apart from "for cause" clinical indications) and so we believe this study reflects "real-life" clinical practice in Urology.

Of the four cases who were diagnosed subsequently with prostate cancer, two were actually low risk, of which one chose undergo radical surgery. The other remains on active surveillance with no significant change in PSA levels and has also avoided potential complications of radical treatment. With regards the two high risk cases, our Uro-Radiologist colleague subsequently re-reviewed their MP-MRI scans. One of them (Case 40) had significant artefact due to the presence of bilateral hip replacements, making it difficult to disagree with the original report findings. The other, Case 26, was still reported as Likert 2 on this (retrospective) review. Fortunately, both patients had effective treatment and did not suffer mortality or morbidity after their initial MP-MRI.

There was no clinical correlation in men who were subsequently diagnosed with prostate cancer, with regards pre MP-MRI PSA, Prostate Volume, PSA dynamics, age at MRI and follow-up in months. Although not statistically significant

there was a positive correlation for PSA dynamics, age at MRI and follow-up in months – this raises the possibility that changes may have been significant in these subgroups if larger numbers were studied, and this is something we are aiming to study in multi-centre trials in the UK.

In this study, there were only two other patients (4.3%), who underwent subsequent histological sampling of their prostate. Case 25 developed worsening symptoms and underwent Holmium Laser Enucleation of Prostate, twelve months after MP-MRI scan. Histology revealed 62g BPH only, with no evidence of prostate cancer. In addition, Case 42 subsequently had a repeat MP-MRI scan at 18 months, due to rising PSA levels, and went on to have TPM, but no prostate cancer was detected. This provides some further histological evidence, albeit small numbers, that significant prostate cancer was not missed in these patients.

None of the cases who subsequently were diagnosed with prostate cancer in our study had previously had a TRUS biopsy or had an abnormal DRE - the most likely inference is due to small numbers, especially with regards to DRE. However, one could argue that patients with previous negative TRUS biopsy and subsequent Likert 2 at MP-MRI are more likely to have larger prostate volumes and hence unlikely to have significant cancer. Similarly, one could hypothesise that negative MRI is more sensitive than abnormal DRE [2]. There were no deaths from prostate cancer reported in this study. This may not be surprising as minimum follow up was only two years, but is nevertheless a reassuring finding. Indirectly, this study also picked up alternative diagnoses. Case 20 was diagnosed with multiple myeloma and in Case 24 lymph nodes at MRI scan were found to be positive for lymphoma, which were subsequently successfully treated with standard chemo-radiotherapy.

## 5. CONCLUSION

In this study, despite an initially negative MP-MRI scan, prostate cancer was subsequently diagnosed in 4 men (8.7%). Reassuringly, this compares very favourably to the negative predictive value (89%) from the PROMIS trial, and as such, adds an important body of work to the contemporary literature on modern diagnosis of suspected prostate cancer.

## CONSENT AND ETHICAL APPROVAL

There was no formal ethical committee approval performed for this study, and informed patient consent was not sought, as this was deemed an audit of newly introduced service review.

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