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Combination of multiparametric MRI and transperineal template-guided mapping biopsy of the prostate to identify candidates for hemi-ablative focal therapy

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Objective

To evaluate the accuracy of combined multiparametric magnetic resonance imaging (mpMRI) and transperineal template-guided mapping biopsy (TTMB) for identifying lobes with significant prostate cancer (PCa) for the application of hemi-ablative focal therapy (FT).

Patients and Methods

From January 2012 to January 2014, 89 consecutive patients, aged ≥40 years, with a PSA level ≤15 ng/mL, underwent in sequential order: mpMRI, TTMB and radical prostatectomy (RP) at a single centre. Analysis was performed on 50 patients who met consensus guidelines for FT. Lobes were stratified into lobes with significant cancer (LSC), lobes with insignificant cancer and lobes with no cancer. Using histopathology at RP, the predictive performance of combined mpMRI + TTMB in identifying LSC was evaluated.

Results

The sensitivity, specificity and positive predictive value for mpMRI + TTMB for LSC were 97, 61 and 83%, respectively. The negative predictive value (NPV), the primary variable of interest, for mpMRI + TTMB for LSC was 91%. Of the 50 patients, 21 had significant unilateral disease on mpMRI + TTMB. Two of these 21 patients had significant bilateral disease on RP not identified on mpMRI + TTMB.

Conclusions

In the selection of candidates for FT, a combination of mpMRI and TTMB provides a high NPV in the detection of LSC.

Keywords

prostate cancer, focal therapy, transperineal template-guided mapping biopsy, MRI

Introduction

Prostate cancer (PCa) is the most commonly diagnosed non-cutaneous cancer in Western men, and the second most common cause of cancer death in men [1]. PSA screening and extended biopsy templates have reduced PCa mortality but have also resulted in a stage migration towards overdetection and overtreatment of low-risk PCa [1]. Whole-gland treatment of PCa is associated with significant morbidity, particularly incontinence and impotence.

Focal therapy (FT) has emerged as a treatment option for patients with localized low- to intermediate-risk PCa to reduce the morbidity of therapy. Current consensus guidelines recommend consideration of FT in patients with a life expectancy ≥10 years, PSA ≤ 15 ng/mL, clinical stage ≤T2a, Gleason ≤3 + 4 and no evidence of extracapsular extension (ECE) or seminal vesicle invasion (SVI) on biopsy or imaging [2]. FT refers to organ-sparing ablative techniques, and a number of FT techniques are available, including cryosurgery, high-intensity focused ultrasonography, photodynamic therapy, radiofrequency ablation, laser-induced interstitial thermotherapy and irreversible electroporation.

The challenge for FT is the known multifocality of PCa, even in its early stages [3]. It has been reported that, in multifocal PCa, it is the index lesion that determines clinical outcome and satellite lesions are unlikely to affect overall disease

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progression and mortality [4]; however, this index lesion hypothesis remains controversial [5].

Focal therapy is based on the concept that destruction of the index lesion may be adequate to alter the clinical course of PCa and satellite lesions can be subsequently managed by active surveillance. For FT to achieve acceptable oncological outcomes, clinicians must accurately identify and localize clinically significant lesions within the prostate to ensure appropriate patient selection and an adequate treatment field.

Transperineal template-guided mapping biopsy (TTMB) is currently the standard diagnostic tool to qualify patients for FT [2,6]. Recent studies at our institution and elsewhere have shown that multiparametric MRI (mpMRI) is an accurate tool in identifying clinically significant tumour foci [7,8]. The aim of the present study was to evaluate the accuracy of combined mpMRI and TTMB for identifying lobes with significant prostate cancer for the application of hemi-ablative FT.

Patients and Methods

Patients

From January 2012 to January 2014, 89 consecutive patients aged ≥40 years with a PSA level ≤15 ng/mL underwent, in sequential order: mpMRI and TTMB as part as a standardized protocol, and radical prostatectomy (RP) at a single centre.

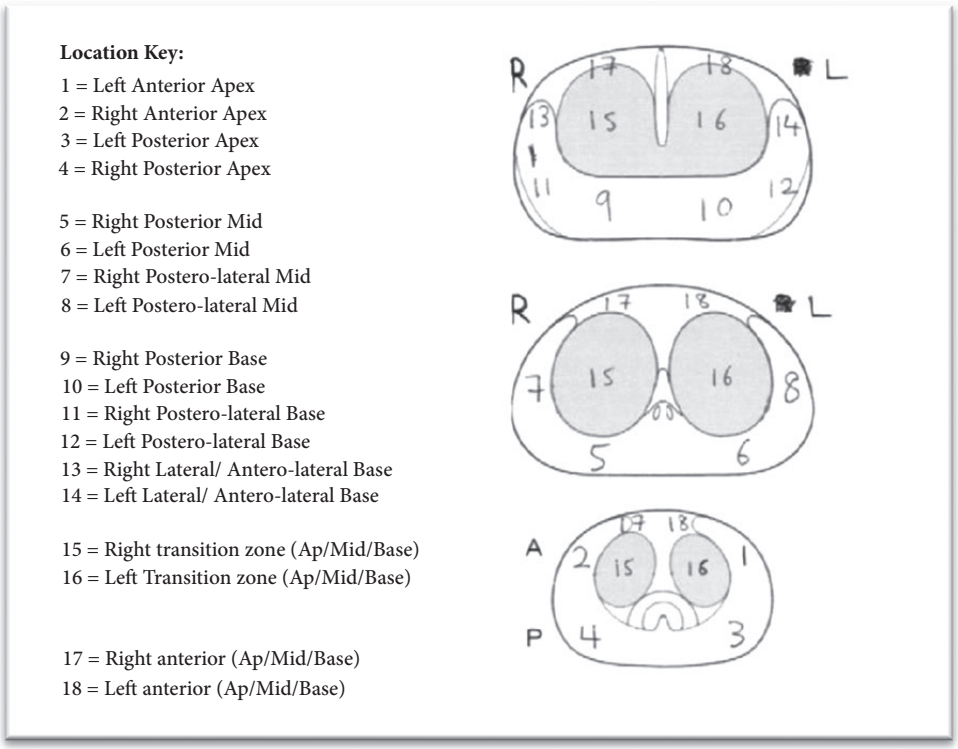
Multiparametric MRI Reporting Protocol

Patients underwent a mpMRI, for abnormal DRE or PSA result, at one of two radiology practices. A 1.5-Tesla (1.5T) magnet was used at one centre and a 3-Tesla (3T) magnet at the other. All mpMRI was reported by expert sub-specialized radiologists (D.M., R.S.) before this study, and clinical data (DRE, PSA and family history) were obtained as per routine clinical practice. All mpMRI was reported as per the standardized Prostate Imaging Reporting and Data System (PIRADS v1) guidelines developed by the European Society of Urogenital Radiology (ESUR) [9]. This scoring comprised a five-point scale on which the presence of clinically significant cancer was defined as: 1, extremely unlikely; 2, unlikely; 3, equivocal; 4, likely; or 5, extremely likely. A total of 18 regions of interest (ROIs) were indicated on a topographic map corresponding to biopsy template locations (Fig. 1) and were assigned a PIRADS score.

Biopsy and Prostatectomy Methodology

Patients underwent a TTMB with a 5-mm sampling frame in the peripheral zone and limited sampling of the transition zone from 18 template locations (Fig. 1) using a modified Barzell technique [10] by two urologists (P.B., P.S.) at a single centre. Urologists reviewed the mpMRI images and reported and collected an additional 3–4 targeted cores from all ROIs

Fig. 1 Regions of interest for standardised multiparametric MRI reports corresponding to biopsy template locations using modified Barzell biopsy technique. Ap, apex.



that were potentially undersampled by template biopsy using two methods: (1) MRI/TRUS fusion biopsy was performed with a floor-mounted transperineal grid TRUS platform (BK Medical, Herlev, Denmark) combined with Biojet rigid MRI/TRUS fusion software (Meditron, Melbourne, Australia) for ROIs potentially missed by cognitive targeted biopsy as a result of having a diameter of <10 mm and a site outside the template, e.g. midline, junction of peripheral and transitional/anterior fibromuscular zones, extreme anterolateral horn or adjacent to bladder/seminal vesicles and (2) cognitive (manual MRI-informed) transperineal grid-directed, TRUS-guided biopsy was carried out for ROIs that had a diameter of >100 mm and were at an easily accessible location, but that were potentially undersampled by template biopsy. Such ROIs were visible on TRUS as a hypoechoic area, aiding cognitive targeted biopsy. Targeted biopsy was unnecessary for large ROIs, >15 mm in diameter, that spanned multiple template locations as they were easily accessible by template cores.

Patients underwent open or robot-assisted RP. Biopsies and RP specimens were processed according to International Society of Urological Pathology protocols by a single subspecialist uropathologist (W.D.).

Stratification of Lobes Based on mpMRI and TTMB

Lobes were stratified into lobes with no cancer (LNC), lobes with insignificant cancer (LIC) or lobes with significant cancer (LSC) based on combined mpMRI and TTMB findings. Because of controversy regarding the biopsy definition of significant PCa, three definitions were selected based on strict criteria (definitions 1 and 2) [11,12] and less restrictive criteria (definition 3) [13] (Table 1). Because of the risk of undertreating significant cancer, definition 2 [12] was selected prospective to data analysis. Lobes with Gleason score 6 with ≤3 mm maximum core length PCa were considered LIC. Lobes with Gleason score 6 with >3 mm maximum core length PCa as well as lobes with Gleason score ≥7 were considered LSC. Alternative definitions accounted for controversy and facilitated comparison. If a lobe had a PIRADS score ≥4 on mpMRI, regardless of biopsy findings, it was defined as LSC. Additionally, if a lesion visible on mpMRI that crossed the midline was found to be significant on biopsy, both lobes were considered to be LSC.

Stratification of Lobes Based on RP

Final histopathology from stitched whole-mount RP specimens was used as our endpoint. Differentiation between LSC and LIC was based on a recent study [13]. LSC at RP was defined as any of the following: (1) Gleason score 6 with tumour volume ≥1.3 mL; (2) Gleason score 7 with >5% grade 4 or Gleason 8–10 with tumour volume ≥0.7 mL; or (3) presence of ECE or SVI. If a lesion with significant cancer extended into the contralateral lobe, both lobes were defined as LSC.

Statistical Analysis

Analysis was performed only on patients eligible for hemi-ablative FT based on consensus guidelines (T-stage ≤T2a, Gleason score ≤3 + 4 on TTMB and no evidence of ECE or SVI on mpMRI or TTMB). A positive predictive value (PPV) for a LSC was defined as the probability that a side contained LSC at RP when the lobe was reported as LSC on mpMRI + TTMB. A negative predictive value (NPV) for LSC was defined as the probability that a side did not contain LSC when the lobe was negative for LSC on combined mpMRI + TTMB.

Results

A total of 89 consecutive men underwent mpMRI and TTMB as per the standardized protocol and had an RP. Of the 89 patients, 39 patients were excluded from analysis, as they did not meet consensus guidelines for FT (Table 2). The baseline characteristics of the 50 patients included in the analysis are outlined in Table 3. In the 100 lobes, there were 54 ROIs with a PIRADS score 4–5 in 37 of the 50 patients. The median number of cores collected was 32, with a median of 7 positive cores per patient. The rates of LSC on mpMRI + TTMB were 69, 78 and 70% according to biopsy definitions 1, 2 and 3, respectively. Using biopsy definition 2 in addition to mpMRI, of the total 100 lobes, 78 were LSC, eight were LIC and 14 were LNC. On RP specimens, 67 were LSC, 27 were LIC and six were LNC.

Table 1 Three proposed definitions of biopsy based risk categories.

Definition	Lobes with no cancer	Lobes with insignificant cancer	Lobes with significant cancer
1: More strict, grade only criteria	No positive biopsies	Gleason score 6	Gleason score 7–10
2: More strict, grade + volume criteria	No positive biopsies	Gleason score 6 and ≤3 mm maximum core length PCa	Gleason score 6 and >3 mm maximum core length PCa. Gleason score 7–10
3: Less strict, grade + volume criteria	No positive biopsies	Gleason score 6–7 with ≤5% Gleason pattern 4 and <30% of cores positive and <8 mm maximum core length PCa	Gleason score 6–7 with >5% Gleason pattern 4 or ≥30% of cores positive or ≥8 mm max core length of PCa. Gleason score 8–10

PCa, prostate cancer.

Table 2 Patients excluded from analysis.

Reason for exclusion	Number of patients
T-stage ≥ T2b	1
Gleason pattern ≥4 + 3 on TTMB	17
Evidence of ECE or SVI on TTMB or mpMRI	3
T-stage ≥ T2b and Gleason pattern ≥4 + 3 on TTMB	4
T-stage ≥ T2b and evidence of ECE or SVI on TTMB or mpMRI	1
T-stage ≥ T2b and Gleason pattern ≥4 + 3 on TTMB and evidence of ECE or SVI on TTMB or mpMRI	3
Gleason pattern ≥4 + 3 on TTMB and evidence of ECE or SVI on TTMB or mpMRI	10
Total number of patients excluded from analysis	39

TTMB, transperineal template-guided mapping biopsy; ECE, extracapsular extension; SVI, seminal vesicle invasion; mpMRI, multiparametric MRI.

Table 3 Baseline patient and lobe characteristics.

Characteristic	Value
Number of patients	50
Mean (median) age, years	61.8 (63)
Mean (median) PSA, ng/mL	5.5 (5.1)
Clinical tumour stage, *n* (%)	
T1b	1 (2)
T1c	29 (58)
T2a	20 (40)
MRI, *n* (%)	
Magnet strength 1.5T	23 (46)
Magnet strength 3.0T	27 (54)
ROIs with PIRADS 4–5	54
Patients with positive MRI PIRADS 4–5	37 (74)
Biopsy	
Mean (median) number of cores collected	31.0 (32.0)
Mean (median) number of positive cores	7.6 (7.0)
Number of lobes	100
MpMRI and TTMB lobe category (definition 2), *n* (%)	
Lobes with significant PCa	78 (78)
Lobes with insignificant PCa	8 (8)
Lobes with no PCa	14 (14)
RP method, *n* (%)	
Open	3 (6)
Robot-assisted	47 (94)
RP surgeon	
P.S.	37 (74)
P.B.	13 (26)
RP lobe category, *n* (%)	
Lobes with significant PCa on RP	67 (67)
Lobes with insignificant PCa on RP	27 (27)
Lobes with no PCa on RP	6 (6)

mpMRI, multiparametric MRI; TTMB, transperineal template-guided mapping biopsy; RP, radical prostatectomy; PIRADS, Prostate Imaging Reporting and Data System; ROI, region of interest.

The accuracy estimate for each biopsy definition is shown in Table 4. The sensitivity and specificity for LSC using definition 2 were 97 and 61%, respectively. The PPVs for LSC were 86, 83 and 89% for definitions 1, 2 and 3 respectively. The NPVs for LSC were 74, 91 and 83% for definitions 1, 2 and 3, respectively.

From the 50 patients, 21 had unilateral significant disease on mpMRI + TTMB and were thus candidates for hemi-ablative FT. Of these 21 patients, two had bilateral significant disease on final histopathology on RP. Both of these patients had a significant lesion crossing the midline from the contralateral lobe with margins of 4 and 6 mm, respectively. One of these two patients also had a 5-mm diameter (0.1 mL) Gleason 3 + 4 lesion with 10% Gleason pattern 4 that was not detected on mpMRI + TTMB (Fig. 2).

Discussion

Recent long-term data suggest many patients with low- to intermediate-risk PCa are being overtreated [14], with an associated reduction in quality of life secondary to the side effects of radical treatment. For this reason, FT is a promising treatment option for selected men with localized low- to intermediate-risk PCa, with the potential for similar oncological outcomes and reduced morbidity compared with whole-gland therapy. A recent review evaluating the functional outcomes of FT reported a pad-free continence rate of 95–100% and a potency sufficient for intercourse rate of 54–100%, with or without use of phosphodiesterase-5 inhibitor medication [15].

One of the biggest concerns with FT is the multifocal nature of PCa. In a review of 12 contemporary RP series totalling 2 988 patients, the incidence of multifocal PCa ranged from 67 to 87% [3]. It has been reported that in multifocal PCa, it is the index lesion, rather than the satellite lesions, that determines clinical outcome. Central to this index lesion hypothesis was a study by Liu et al. [4], who analysed 94 samples of malignant tissue from metastatic sites in 30 men whose death was attributable to metastatic PCa. Through genome-wide survey of single-nucleotide and copy-number polymorphisms, the investigators showed that different, anatomically distinct metastases within the same patient originated from a single precursor cell; however, this index lesion hypothesis remains controversial. Haffner et al. [5] reported one case of metastatic PCa, which through genomic and pathological analysis was attributed to a small (2.2 × 1.3 mm) focus of Gleason 3 separate to the index lesion.

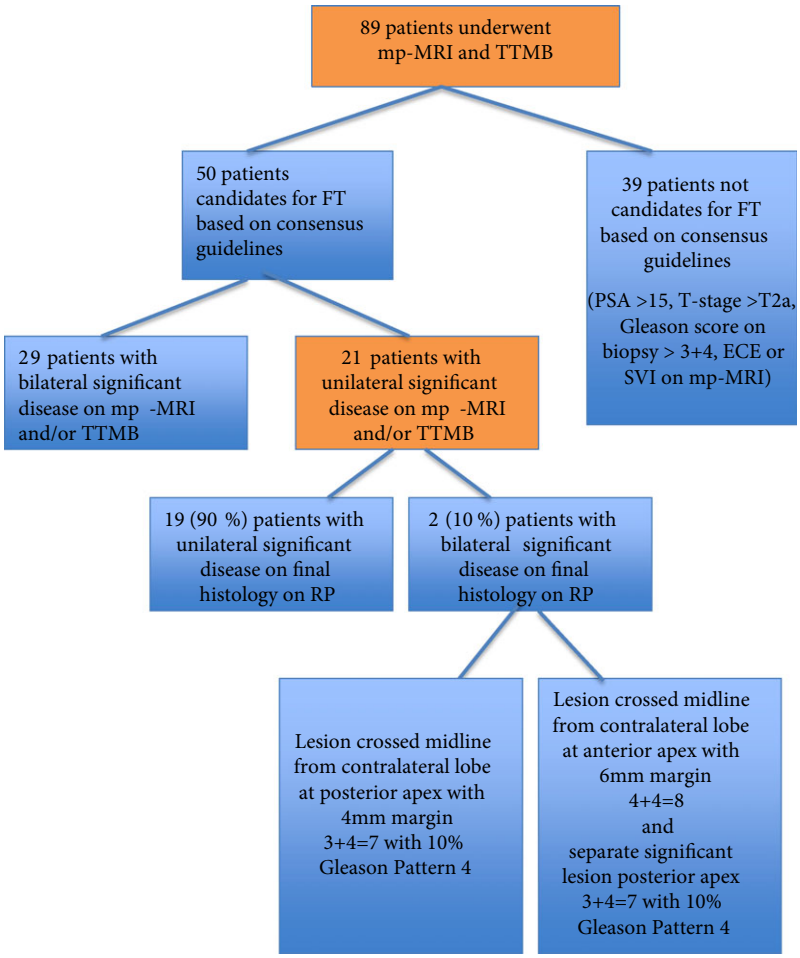
If the index lesion hypothesis holds true in the vast majority of cases, the successful administration of FT requires accurate identification and localization of clinically significant lesions within the prostate.

A number of studies have shown that standard 6–12-core TRUS-guided biopsy of the prostate is inaccurate in detecting unilateral disease with a NPV < 50% [16–19]. For this reason, TTMB rather than TRUS-guided biopsy of the prostate is considered to be the diagnostic tool to qualify patients for FT [6]. TTMB involves the use of a grid being placed against the perineum to guide biopsies with the patient placed in the lithotomy position. With regard to FT, there are a number of advantages of TTMB over TRUS-guided biopsy. TTMB allows

Table 4 Accuracy in detecting lobes with significant cancer according to biopsy risk definition based on 2 × 2 chi-squared analysis.

Biopsy definition	Sensitivity, % (*n*/*N*)	Specificity, % (*n*/*N*)	NPV, % (*n*/*N*)	PPV, % (*n*/*N*)
1. More strict, grade only criteria	88 (59/67)	69 (23/33)	74 (23/31)	86 (59/69)
2. More strict, grade and volume criteria	97 (65/67)	61 (20/33)	91 (20/22)	83 (65/78)
3. Less strict, grade and volume criteria	93 (62/67)	76 (25/33)	83 (25/30)	89 (62/70)

Fig. 2 Flow diagram of patients.



systematic sampling of the entire prostate, providing a precise three-dimensional representation of the lesion [20], the use a grid allows a fixed set of reproducible coordinates during the administration of FT and TTMB has been shown to be superior in detecting anterior lesions [21].

Crawford et al. [20] showed that TTMB with a 5-mm sampling frame could rule in and rule out PCa foci of 0.5 and 0.2 mL with 90% certainty. In a separate study, Crawford et al. [22] also showed that TTMB using a 5-mm sampling frame missed only one clinically significant lesion, defined as either Gleason ≥7 or tumour volume ≥0.5 mL, from 25 men with 64 PCa lesions in their RP specimens.

Multiparametric MRI using T2-weighted high-resolution anatomical imaging combined with functional parameters is gaining momentum as a clinically useful tool to identify and localize significant cancer foci within the prostate. A recent meta-analysis showed that mpMRI has a sensitivity of 66–81% and specificity of 82–92% for prostate cancer detection [7]. Given the moderate sensitivity and high specificity of contemporary mpMRI for significant lesions and the ability to anatomically localize these lesions, mpMRI in addition to TTMB could assist in the selection of patients for hemi-ablative FT, as shown in the present study.

To our knowledge, only one study has looked at the accuracy of specifically identifying unilateral PCa with use of mpMRI before biopsy. Matsouka et al. [23] reported that diffusion-weighted imaging and a combined TRUS/transperineal technique with 14 cores has a NPV of 95.7% for predicting lobes with significant PCa. In a re-analysis of these patients, Matsouka et al. [24] reported that diffusion-weighted imaging and the combined TRUS/transperineal technique had NPVs of 91.1 and 91.7% in detecting significant lesions in anterior and posterior quadrants of the prostate, respectively. In both studies, however, insignificant PCa included Gleason score 3 + 4 PCa. Although there is no consensus on insignificant PCa, a Gleason score of 3 + 4, without taking into account percentage of Gleason 4 present, seems too high to accept as insignificant PCa. A recent large study using European Randomized Study of Screening for Prostate Cancer data recommended that the tumour volume threshold for significant Gleason score 6 be 1.3 mL [13] rather than 0.5 mL [11]. We included Gleason score 3 + 4 disease as insignificant PCa, if there was <5% Gleason pattern 4 with a tumour volume <0.7 mL.

The most important risk of FT is undertreating significant PCa, thus NPV is the most clinically relevant accuracy measure. Our results show that, with a NPV of 91%, the combination of mpMRI with TTMB provides the clinician with a reliable assessment of laterality of significant PCa.

Of the 50 patients, 21 had significant unilateral disease on mpMRI + TTMB and were thus potential candidates for hemi-ablative FT. Only two of the 21 patients had a significant lesion crossing the sagittal midline with contralateral extensions of 4 and 6 mm, respectively. One of these two patients additionally had a separate small but moderate risk lesion undetected by mpMRI + TTMB. The significance of a 0.1 mL Gleason score 3 + 4 lesion with 10% Gleason pattern 4 is uncertain, given that RP studies have suggested lesions <0.5 mL may be insignificant [13,25], but the risk of metastasis may be significant over a 10–15-year period; therefore, if a wider treatment margin crossing the midline, rather than a strict hemi-ablative approach, was applied in these 21 patients, only one patient would have had inadequate initial therapy with FT, and that patient's missed <0.1 mL Gleason score 3 + 4 lesion may have been clinically insignificant.

Given our findings, we suggest for lesions close to the sagittal midline, a wider treatment field be applied to ablate tumour extending beyond the known location, with peri-urethral sparing. Furthermore, as patients that are treated with hemi-ablative FT undergo active surveillance with routine DRE, PSA and TTMB, we suggest taking additional cores on TTMB at the margin of the treatment field, to improve the likelihood of detecting positive margins. Salvage treatment with RP, radiotherapy or repeat FT could then be performed, with early studies showing that salvage FT is both feasible and safe [26,27]. Long-term outcomes with FT have not yet been reported and are needed before FT can be considered a treatment option for carefully selected patients.

The present study has several limitations. Firstly, given the small sample size of 50 patients, it is difficult for these findings to be generalized into the broader community based on this study alone. The definition of insignificant cancer on biopsy used in this paper is per the University College London (UCL) traffic-light system, allowing findings from this study to be amenable to subsequent meta-analysis [12]. Secondly, there is a selection bias because this study only includes those men at higher risk who underwent RP, as this was used as our reference test. Many patients who had low- to intermediate-risk PCa underwent alternative management options, particularly active surveillance, FT or low dose rate brachytherapy; thus, our analysis excluded many of those men considered most suitable for FT. Thirdly, there is heterogeneity in the MRI performed in this study with both 1.5T and 3T MRIs being used. The mpMRI and the accompanying reports performed in the present study were based on the ESUR guidelines for prostate MRI known as PIRADS v1 [9]. Collaboration between the ESUR, the American College of Radiology and the AdMeTech Foundation recently updated these guidelines and developed PIRADS v2 [28]. A change in this updated guideline is the recommendation of 3T over 1.5T MRI because of its superior signal-to-noise ratio, enabling higher quality imaging. Although we used 1.5T MRI in the present study, to date no study has shown an advantage of 3T over 1.5T for detection of PCa [26] and this is also supported by our data [8]. Future studies assessing the diagnostic accuracy of mpMRI should, however, follow PIRADS v2 protocol and preferentially use 3T over 1.5T. Lastly, the observational nature of mpMRI is a limitation, but all mpMRI was reported on by two expert radiologists, with each having reported on >1 000 prostate mpMRIs.

In conclusion, in potential candidates for FT based on consensus guidelines using an RP cohort, mpMRI reported by expert radiologists and TTMB provides a high NPV in the application of hemi-ablative FT. The findings of the present study need to be validated in a larger series with other centres in a screening population.

Acknowledgements

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Conflict of Interest

None declared.

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Abbreviations: mpMRI, multiparametric MRI; TTMB, transperineal template-guided mapping biopsy; FT, focal therapy; RP, radical prostatectomy; 1.5T, 1.5-Tesla; 3T, 3-Tesla; LSC, lobes with significant cancer; LIC, insignificant cancer; LNC, lobes with no cancer; PPV, positive predictive value; NPV, negative predictive value; ECE, extracapsular extension; SVI, seminal vesicle invasion; ESUR, European Society of Urogenital Radiology; PIRADS, Prostate Imaging Reporting and Data System; ROI, region of interest.