Negative mpMRI rules out extra-prostatic extension in prostate cancer before robot-assisted radical prostatectomy.

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Abstract

Background: The accuracy of multi-parametric MRI (mpMRI) in pre-operative staging of prostate cancer (PCa) remains controversial.

Objective: To evaluate the ability of mpMRI to accurately predict PCa extra-prostatic extension (EPE) on a side-specific basis using a risk-stratified 5-point Likert scale. This study also aimed to assess the influence of mpMRI scan quality on diagnostic accuracy.

Patients and Methods: We included 124 men who underwent robot-assisted RP (RARP) as part of the NeuroSAFE PROOF study at our centre. Three radiologists retrospectively reviewed mpMRI blinded to RP pathology and assigned a Likert score (1-5) for EPE on each side of the prostate. Each scan was also ascribed a Prostate Imaging Quality (PI-QUAL) score for assessing the quality of the mpMRI scan, where 1 represents poorest and 5 represents best diagnostic quality.

Outcome measurements and statistical analyses: Diagnostic performance is presented for binary classification of EPE including 95% confidence intervals and area under the receiver operating characteristic curve (AUC).

Results: A total of 231 lobes from 121 men (mean age 56.9 years) were evaluated. 39 men (32.2%), or 43 lobes (18.6%) had EPE. Likert score ≥3 had sensitivity (SE), specificity (SP), NPV, PPV of 90.4%, 52.3%, 96%, 29.9%, respectively, and AUC was 0.82 (95% CI: 0.77-0.86). AUC was 0.76 (95% CI: 0.64-0.88), 0.78 (0.72-0.84) and 0.92 (0.88-0.96) for biparametric scans, PI-QUAL 1-3 and PI-QUAL 4-5 scans, respectively.

Conclusions: MRI can be used effectively by genitourinary radiologists to rule out EPE and help inform surgical planning for men undergoing RARP. EPE prediction was more reliable when the MRI scan was a) multi-parametric and b) of a higher image quality according to the PI-QUAL scoring system.

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Introduction

Multi-parametric magnetic resonance imaging (mpMRI) of the prostate is a valuable tool in the prostate cancer (PCa) diagnostic pathway (1). Once diagnosis of PCa has been made on biopsy, correct assessment of the tumour stage, particularly identifying pathological extra-prostatic extension (EPE), is crucial for directing correct surgical planning, including nerve-sparing (NS), bladder neck sparing, and the extent of apical dissection (2-4). These decisions are pivotal in promoting optimal post-operative functional outcomes without compromising cure from PCa(5). Moreover, EPE of tumour is associated with a higher risk of positive surgical margins (PSM), biochemical recurrence, metastatic disease and cancer-specific mortality(6-8).

In 2016, de Rooij et al. reported their diagnostic meta-analysis on the accuracy of mpMRI for local staging of PCa(9). Overall, MRI had a sensitivity (SE) of 55% (95% CI: 47-63%) and specificity (SP) of 91% (95% CI: 88-93%) for the prediction of stage pT3a disease, though the authors noted considerable heterogeneity in the studies included. Since this review, use of mpMRI for pre-operative staging has evolved considerably, especially as mpMRI has become more prominent in the diagnostic pathway around the world. Although now widely used for pre-operative staging, variation in the use of mpMRI is still huge and, as such, its role in surgical planning remains controversial.

The objective of this study was to assess the accuracy of mpMRI for pre-operative local staging of PCa for men undergoing RARP at a high-volume UK academic centre whose scans were performed within the regional referral network. A key secondary objective was to evaluate the effect of technical scan quality on diagnostic accuracy of EPE prediction.

Materials & Methods

Study Design & Patient Population

We undertook retrospective review of mpMRI performed in men who had already undergone robot-assisted RP (RARP) at our centre as part of the NeuroSAFE PROOF trial

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(NCT03317990, ethics approval 17/LO/1978, Supplementary Material S1 for full inclusion/exclusion criteria). The STROBE checklist for reporting of observational studies is included as an online Supplementary Material. Though all men included in this study were participants in the NeuroSAFE PROOF trial, mpMRI scans were performed as part of their routine clinical care. All participants provided written informed consent.

Standard of Reference

RARP was performed by three experienced surgeons (GS, SN, TB). Histopathologic examination was performed by a consultant genitourinary pathologist according to the International Society of Urological Pathology (ISUP) 2014 consensus statement (10, 11). Pathologic EPE was diagnosed separately for each side of the prostate where cancer cells were seen outside of the prostate capsule or pseudo-capsule. Seminal vesicle invasion (pT3b) on its own was not classified as EPE. Where an intraprostatic PSM was observed with no evidence of ipsilateral EPE elsewhere, the lobe was excluded from analysis as it is not possible to know whether this focus of PCa extended beyond the limit of the prostate.

Imaging Protocols and Evaluation

Standard of clinical care mpMRI were performed at 13 different locations in the north and east of London as part of the regional NHS hub and spoke model for the referral of PCa cases for surgery at our centre (Supplementary Material Figure S2). mpMRI was performed without endorectal coil. Scans were performed using a variety of magnets (1.5T and 3T) from different vendors (Philips, GE and Siemens).

All mpMRI scans were reviewed independently by 3 genitourinary radiologists (CA, DH, TS) who were blinded to the RP final pathology results and who reviewed images under invigilated circumstances in the same room at the same time. Reporting was performed on a bespoke MRI EPE case reporting form (Supplementary Material Figure S3). Images were reviewed and reported in locked sequential manner such that T2WI was reported first, then DWI, then DCE, then blood serum prostate specific antigen (PSA) level was provided, and finally prostate biopsy information was provided. Where DCE sequences were not available

for a given scan (biparametric scans), the score for DCE specifically was omitted by radiologists, but scores were still provided after PSA and biopsy information. At each point, the 3 radiologists separately rated likelihood of EPE using a risk-stratified 5-point Likert scale: 1, highly unlikely; 2, unlikely; 3, equivocal or indeterminate; 4, likely; and 5, highly likely. Once a score had been assigned and the next imaging sequence or information was provided, the radiologist was not allowed to change any preceding score. Radiologists scored for EPE specifically, but not seminal vesicle invasion (pT3b).

The 3 radiologists (CA, DH, TS) were all fellowship trained and had 20, 5, and 1 years of experience as a consultant, reading >3,000, >750, >750 scans per year, respectively. Before initiating interpretation, radiologists attended an in-person training session where examples of the MRI scans of patients with and without EPE were reviewed alongside whole mount pathological images from the RP specimen.

Separate to the process described above, the quality of all scans was assessed by means of the Prostate Imaging Quality (PI-QUAL) score from 1 to 5, where 1 represents poorest and 5 represents best quality scan (Supplementary Material S4 and S5), by two radiologists (CA and FG)(12). The PI-QUAL score is derived by evaluating mpMRI scans against a defined set of objective quality criteria in line with Prostate Imaging-Reporting and Data System (PI-RADS) v2 guidelines (13) that cover the adequacy of all three of the mpMRI sequences and additional objective criteria considered to be consistent with a high-quality scan. PI-QUAL scores were given blinded to EPE Likert score and RP pathology after a wash-out period >4 months. In case of discordance, PI-QUAL score was discussed until consensus.

Sample size and power calculation

Based on the performance reported within the meta-analysis by Rooij et al. (9), 217 prostate lobes reviewed by three readers within this study provides 90% power to detect a sensitivity of 80% (95% CI 65-95) and a specificity of 90% (95% CI 80-100), assuming 19% EPE prevalence and 10% loss to follow-up. The sample size and power were calculated in Stata 16 (College Station, TX, USA).

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Statistical analysis

The prostate lobe was the unit of analysis as treatment planning incorporating mpMRI occurs on a lobe basis. A Likert score ≥3 was considered positive for EPE. Diagnostic accuracy measures (sensitivity, specificity, NPV, PPV, and AUC) were calculated for each reader and combined. We based statistical significance on 95% CIs derived from the exact binomial method. All analyses were conducted in SPSS (version 27, IBM)

Results

1,125 men underwent RARP at our centre between June 2018 and December 2019. 127 were participants in NeuroSAFE PROOF study and eligible for inclusion. 4 men were excluded because their mpMRI was not available for review. Of the remaining 123 men, 36 (29.3%) had PSM, of which 13 (10.6%) were ≤1mm, 3 (2.4%) were 1-3mm, and 20 (16.3%) were >3mm or multifocal. Of the 246 lobes available for the purposes of evaluating whether EPE was present or not, a further 15 lobes were excluded because of intra-prostatic PSM (Figure 1), meaning that 121 men and 231 lobes were included in the final analysis. Representative mpMRI and matched patient RP pathology images can be seen in Figure 2.

Clinical, radiological and final pathological characteristics of the patient cohort are shown in Table 1. Mean age was 56.9 years, mean PSA level was 8.9 ng/mL and mean prostate volume on mpMRI was 36.6cc ± 15. On final pathology, 82 of 121 (67.8%) men had organ-confined disease (pT2a-pT2c). EPE was seen in 39 of 121 men (32.2%), including in all 7 men who had pT3b disease, and 43 of 231 lobes (18.6%). In 35 of 39 men (89.7%) EPE was unilateral.

112 of the scans used for EPE assessment were original pre-biopsy mpMRI, whilst 9 men had mpMRI repeated after their prostate biopsy (Supplementary Material Table S6). Of these 9 men, mean number of days from biopsy to repeat scan was 163 (range; 63 - 475). All 9 men had their repeat mpMRI scan performed at the academic centre and had a mean of 13 days (range; 2 - 25) from repeat scan until RARP.

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mpMRI prediction of EPE

The detection rates of pathological EPE according to Likert scale and diagnostic accuracy are presented in Table 2 and depicted in Figure 3. For Likert ≥3 on final read (i.e. once all imaging sequences, PSA and biopsy information was available) there was SE 90.4% (CI: 83.8-94.9), SP 52.3% (48-56.5), PPV 29.9% (25.3-34.8), and NPV 96% (93.2-97.9). When analysis was instead performed on a per patient level, for Likert ≥3 on final read there was SE 97.4%, SP 24.4%, PPV 38% and NPV 95.2% (see Supplementary Material S8).

Scan quality and diagnostic performance

18 scans were biparametric and therefore could not be assigned a PI-QUAL score (Figure 1 and Supplementary Material S9). 103 scans were scored according to PI-QUAL; 63 and 40 scans were classified score 1-3 and 4-5, respectively. Diagnostic accuracy is presented in Table 3 and Supplementary Material Figure S9, showing that biparametric scans performed least well, followed by PI-QUAL 1-3 scans, and PI-QUAL 4-5 scans were best interpreted. AUC were 0.76 (95% CI: 0.64-0.88), 0.78 (0.72-0.84) and 0.92 (0.88-0.96) for biparametric scans, PI-QUAL 1-3 and PI-QUAL 4-5 scans, respectively. PI-QUAL 4-5 scans had SE 100% (90.3-100) and SP 57% (49.7-64.1).

Accuracy of EPE with additional sequences and clinical information

Diagnostic accuracy improved with the addition of each imaging sequence and then further with provision of PSA and biopsy information. The AUC for T2WI alone, +DWI, +DCE, +PSA, and final (i.e., +biopsy information), were 0.62 (95% CI: 0.56-0.69), 0.69 (0.64-0.75), 0.76 (0.71-0.82), 0.79 (0.74-0.84) and 0.82 (0.77-0.86), respectively (Supplementary Material Figure S9 for ROC curve) .

Discussion

Accurate and precise prediction of EPE will result in better surgical outcomes by guiding surgeons to achieve the often-competing surgical goals of minimising PSM (by avoiding EPE) whilst maximising safe NS. Our data on EPE prediction by genitourinary radiologists using a Likert scale to attribute EPE status demonstrates excellent ability of mpMRI to rule out EPE (SE 90.4%, NPV 96%).

Our study is the first to demonstrate improved EPE prediction with higher objectively scored mpMRI scan quality (PI-QUAL). This finding strongly supports the concept that high SE is dependent on good quality mpMRI scans and, we believe, may explain the poor or heterogeneous correlation of mpMRI and EPE status in previous studies.

Increasing SE for the prediction of EPE comes at the cost of reduced SP (52.3%). Arguably, with the primary aim of optimising oncological outcomes by reducing PSM, the interpretation of mpMRI findings should be shifted towards obtaining high SE in order to accurately rule out EPE and thus when a decision for NS is made, this is likely to be appropriate. On the other hand, with low SP and PPV, if a decision not to NS on one side was based solely on mpMRI Likert score (3-5), in this study many men would not get NS in whom it could have safely been performed, thus potentially negatively and unnecessarily affecting functional outcomes.

These results, high SE and lower SP, are at odds with the findings of the systematic review and meta-analysis of MRI for local PCa staging performed by de Rooij et al. in 2016. This review included 75 studies and demonstrated high SP (91%) with poor and heterogeneous SE (51%) (9). Since this review a further 48 studies have been published with significant ongoing variation in diagnostic accuracy reported (14). For instance, Davis et al. reported SE of 13% in their 2016 study of 133 men using scans performed at community radiology centres(15), whereas Alessi et al. reported SE of 99% in 2019 in a study of 301 men where scans were performed at a single academic centre and reported according to European Society of Urogenital Radiology (ESUR) PIRADs EPE score version 2(16). In the UK, to the best of our knowledge, only one other group have published results on the accuracy of MRI to detect EPE prior to RP despite over 98% of trusts now performing mpMRI for men with

suspicion of localised prostate cancer diagnosis(17). In 2004, Allen et al. reported on 56 patients and found SE 50-72% and SP 84-86%(18).

Possible explanations for this broad variation in the literature include differences in study design and clinical practice. In terms of different clinical practice, scans are performed in different settings, on patient populations with different EPE prevalence, before and after biopsy, using different scanners (magnets and manufacturers) and radiologists of differing experience. In terms of study design, there are different (and non-standardised) methods for reporting EPE where clinical information may, or may not be provided to readers and where analysis can be undertaken in a variety of ways. For example, in our study performing analysis 'per prostate lobe' (Table 2) or 'per patient' (Supplementary Material S8) slightly increased SE, but considerably reduced SP and AUC overall (0.82 to 0.61). Such findings are consistent with the pooled sensitivity analysis performed by de Rooij et al who demonstrated that prediction of EPE was more accurate on a 'region only' compared to a 'patient only' level(9). MRI scan quality itself has never been demonstrated as a possible explanation of differing results until the present study, which suggests better mpMRI scan greatly improves the ability to accurately predict EPE.

Thirteen different scanners were used across our referral network. All scans had at least 2 functional sequences available for review, and 103/121 scans had DCE sequences. Our results show that AUC improves with each additional imaging sequence reviewed, including DCE sequences. This finding is supported by the sub-analysis performed by de Rooij et al. within their systematic review, who noted that SE for EPE improved from 53%, to 62%, to 69% for T2WI, to T2WI + one functional technique, to T2WI + two functional techniques, respectively, with no decrease in SP(9). Additionally, similar to our results, incorporation of clinical information is known to improve diagnostic accuracy compared to studies where mpMRI images alone are used(14).

With regards to the additional value of DCE sequences in our study, the administration of contrast in high quality scans appears to improve diagnostic accuracy considerably, but not when the scan is of lesser technical quality (PI-QUAL 1-3) (see Table 3 and Figure S9 A-C). Caglic *et al* showed that mpMRI was no better than biparametirc MRI at detecting EPE, but

mpMRI was better for detecting seminal vesicle invasion, however they did not study the impact of an objective quality assessment of the scan(19). Interestingly in our study, in scans where gadolinium contrast was provided, in the locked sequential analysis AUC after review of DCE images was 0.76 compared to 0.69 before for T2WI and DWI images only (see Figure S6). Results such as these, which suggest the value of DCE images for accurate staging of PCa, raise the question whether men proceeding to RP will require an additional scan including gadolinium contrast in order to best inform the conduct of their surgery if such an MRI scan has not been performed the first instance. Although artefactual changes seen on MRI after biopsy can compromise interpretation, in our study men who had repeat scan following biopsy had excellent levels of diagnostic accuracy (AUC 0.93, Supplementary Material Table S6). Notably, all these scans were a minimum of 63 days since biopsy, all had DCE sequences, and all scans were PI-QUAL score 3 or above.

mpMRI for EPE prediction is improved when radiologists use scores that convey relative likelihood of EPE, rather than relying on binary terms such as 'present' or 'absent'(9). The value of a risk-stratified ordinal scale to predict likelihood of EPE is supported by the findings of this study where detection rates of EPE increased with each increment in the score assigned; 0%, 4.3%, 13.9%, 41.4%, and 73.8% for scores 1, 2, 3, 4, and 5, respectively ($p<0.0001$) (Figure 3 and Supplementary Table S7). There are several other methods of providing EPE predictions scales; EPE grade(20), ESUR(21), curvilinear contact length (CCL)(22), and tumour capsule length (TCL)(23). The EPE Grade system has been externally validated with promisingly similar results(24). Importantly, Park et al. have shown that different methods can perform similarly (25) and there is good evidence to consistently suggest that incorporation of clinical details alongside MRI interpretation (such as in our study) may also improve diagnostic accuracy. In our study we also collected information on the visual features observed in each scan, including tumour capsule abutment, prostate irregularity, NVB thickening, capsule bulge, and 'measurable EPE' in accordance with the 2012 ESUR guidance (21). The frequency of these visual features according to positive scan (Likert ≥3) and positive pathology (EPE) can be viewed in the Supplementary Material (Tables S11 and S12).

Interest in mpMRI has led to its inclusion into multivariable EPE prediction models. A model by Gandaglia et al. has been presented and externally validated(26), but their nomogram does not provide EPE likelihood on a side-specific basis(27), whereas NS decisions are made on a side-by-side basis. SE for pathological EPE according to mpMRI prediction alone in 333 patients analysed in their series was 25% and provided limited improvement in accuracy of their model: AUC 0.67 without mpMRI data vs. 0.7 with. Other nomograms, such as those presented by Soeterik et al. and Nyarangi-Dix et al. that include mpMRI EPE information in a side-specific fashion (as in our study) perform better, with AUC of 0.82 and 0.86, respectively(28, 29).

If the threshold used to classify EPE prediction is modified to allow higher SP with the Likert threshold moved to 4 instead of 3, the SE, SP, PPV and NPV would change to 67.2%, 84.5%, 49.4%, and 92%, respectively (Supplementary Material Table S13). This would potentially facilitate more aggressive NS decision-making, but at the same time more men may incur PSM as a result. Another option when there is concern but uncertainty for EPE, is intra-operative margin assessment such as NeuroSAFE technique or other (30, 31). However, when teams have evaluated their own performance and EPE is highly likely (for instance 73.8% in Likert 5 in this series) aggressive ipsilateral NS may not be warranted.

This work has some limitations. Firstly, our centre benefits from radiologists with high levels of mpMRI expertise. A consideration of paramount importance for any team using mpMRI for EPE prediction to help guide NS decision, is that they must evaluate and understand their own diagnostic performance. Conversely, the MRIs in this study were carried out at a number of community hospitals which improves the external generalisability of the results. Secondly, though blinded to final histology, our radiologists reviewed scans retrospectively. Prospective validation studies with a larger pool of contributing radiologists are planned. Thirdly, our cohort is limited to patients undergoing RP and to those included in the NeuroSAFE PROOF study. Thus, the cohort is biased towards younger patients who had good erectile function at baseline. As such, these findings may not readily transfer to patient cohorts such as undiagnosed men or men undergoing other treatments, though the availability of a good reference test for comparison is not possible in these men. Fourthly, by excluding from our analysis lobes wherein an intra-prostatic positive surgical margin was

noted without EPE elsewhere on the ipsilateral side, we may have introduced some bias in our study population, though the absence of a valid reference standard in these lobes prevented their inclusion.

Conclusion

Likert score can be used very effectively by expert genitourinary radiologists to rule out EPE on a side-specific basis in men undergoing RARP. The diagnostic accuracy of mpMRI for predicting pathological EPE improves with availability of additional MRI sequences, sight of clinical information, and better quality mpMRI scans.

Conflicts of interest: The authors have no personal conflicts of interest to disclose. Within NeuroSAFE PROOF, laparoscopic ports are supplied by Applied Medical. Applied Medical had no role in the design, analysis, or collection of the data; in writing of the manuscript; or in the decision to submit the manuscript for publication.

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Table 1. Patient, radiological, and pathological characteristics of study cohort.

		All (n=121)	***No EPE (n=82)***	***EPE Present (n=39)***
Patient	Mean age, year ± SD (range)	56.9 ± 7 (40-71)	56.6 ± 7.5 (40-71)	57.82 ± 5.6 (48-71)
	Mean PSA, ng/ml ± SD (range)	8.9 ± 6 (1.2-35)	7.1 ± 3.8 (1.2-25)	12.7 ± 7.9 (4.6-35)
	Clinical ISUP, n (%)			
	1	6 (5)	5 (83.3)	1 (16.7)
	2	94 (77)	72 (76.6)	22 (23.4)
	3	14 (11.6)	4 (28.6)	10 (71.4)
	4	6 (5)	1 (16.7)	5 (83.3)
	5	1 (0.8)	0	1 (100)
	EAU Risk, n (%)			
	Low	4 (3.3)	3 (75)	1 (25)
	Int	77 (63.6)	59 (76.6)	18 (23.4)
	High	40 (32.8)	20 (50)	20 (50)
	DRE*, n (%)			
	T1	53 (22.9)	44 (83)	9 (17)
	T2	125 (54.1)	111 (89)	14 (11)
	T3	53 (22.9)	33 (62.3)	20 (37.7)
mpMRI	Mean Time from MRI to operation, days ± SD (range)	108 ± 68.8 (2-355)	114 ± 73.1 (2-355)	98 ± 58.3 (6-292)
	Mean Prostate volume, cc ± (range)	36.6 ± 15.0 (12-86)	36.3 ± 15.1 (13-86)	37.2 ± 14.8 (14-80)
	Tumour side, n (%)			
	Right	35 (28.9)	23 (65.7)	12 (34.3)
	Left	22 (18.2)	16 (72.7)	6 (27.3)
	Both	61 (50.4)	42 (68.9)	19 (31.1)
	No visible lesion	3 (2.5)	1 (33.3)	2 (66.6)
	Tumour position, n (%)			
	Posterior	97 (80.2)	68 (70.1)	29 (29.9)
	Anterior	8 (6.6)	4 (50)	4 (50)
	Both	13 (10.7)	9 (69.2)	4 (31.8)
	No visible lesion	3 (2.5)	1 (33.3)	2 (66.6)

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RP specimen	Mean prostate weight, g ± SD (range)	43.8 ± 13.9 (15-89)	44.6 ± 14.4 (22-89)	42.1 ± 12.7 (15-74)
	Mean Tumour volume, mls ± SD (range)	4.3 ± 3.6 (0.25-22.3)	3.4 ± 2.8 (0.25-12.9)	6.3 ± 4.5 (1.2-22.30
	Pathological ISUP, n (%)			
	1	2 (1.7)	2 (100)	0
	2	92 (75.4)	69 (75)	23 (25)
	3	23 (18.9)	10 (43.5)	13 (56.5)
	4	1 (0.8)	1 (100)	0
	5	3 (2.5)	0	3 (100)
	Pathological stage, n (%)			
	2a-b	7 (5.8)	7	0
	2c	75 (62)	75	0
	3a	32 (26.4)	0	32
	3b	7 (5.8)	0	7

ISUP, international Society Urological Pathologists; PSA, prostate specific antigen; SD, standard deviation; EAU, European Association of Urologists. * Denominator given as lobes included in the study (n= 231)

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Table 2. Per prostate lobe analysis of sensitivity (SE), specificity (SP), positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) by individual radiologist and combined where Likert score 3≥ was positive scan for pathological EPE.

	Reader 1	***Reader 2***	***Reader 3***	***Readers Combined***
SE*	88.4 (74.9-96)	92.5 (79.6-98.4)	90.5 (77.4-97.3)	90.4 (83.8-94.9)
SP*	61.7 (54.4-68.7)	39.5 (32.4-46.9)	55.5 (48-62.9)	52.3 (48-56.5)
PPV*	34.6 (25.7-44.2)	24.8 (18.1-32.6)	31.9 (23.7-41.1)	29.9 (25.3-34.8)
NPV*	95.9 (90.6-98.6)	96.1 (88.9-99.2)	96.2 (90.5-99)	96 (93.2-97.9)
AUC	0.84 (0.77-0.92)	0.77 (0.68-0.86)	0.83 (0.76, 0.9)	0.82 (0.77-0.86)

*95% confidence intervals in parentheses.

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Table 3. Diagnostic performance of MRI for prediction of EPE final Likert score ≥3 for biparametric MRI scans, mpMRI PI-QUAL score 1-3 and 4-5.

	Biparametric scan (n=18)	***PI-QUAL 1-3 (n=63)***	***PI-QUAL 4-5 (n=40)***
SE	80 (59.3 - 93.2)	89.1 (78.8 - 95.5)	100 (90.3 - 100)
SP	48.4 (37.9 - 59)	49.8 (43.7 - 56)	57 (49.7 - 64.1)
NPV	90 (78.2 - 96.7)	95 (90 - 98)	100 (96.7 - 100)
PPV	29.4 (19 - 41.7)	29.8 (23.5 - 36.9)	30.3 (22.2 - 39.4)
AUC	0.76 (0.64 - 0.88)	0.78 (0.72 - 0.84)	0.92 (0.88 - 0.96)

95% confidence intervals in brackets.

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Figures

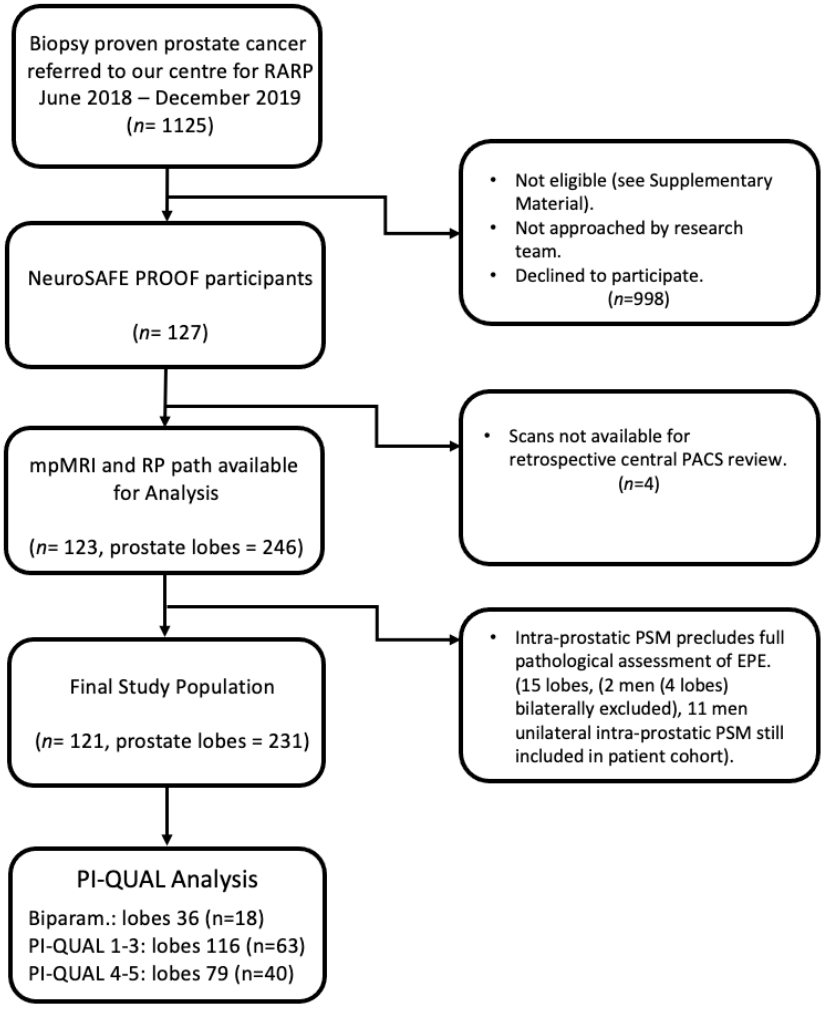

Figure 1. Flow diagram of patient selection for study.

Abbreviations: RARP, robot-assisted radical prostatectomy, PACS, picture archiving and communication system; RP, radical prostatectomy; PSM, positive surgical margin; EPE, extra-prostatic extension, PI-QUAL, prostate imaging quality score; Biparam., bi-parametric MRI scan.

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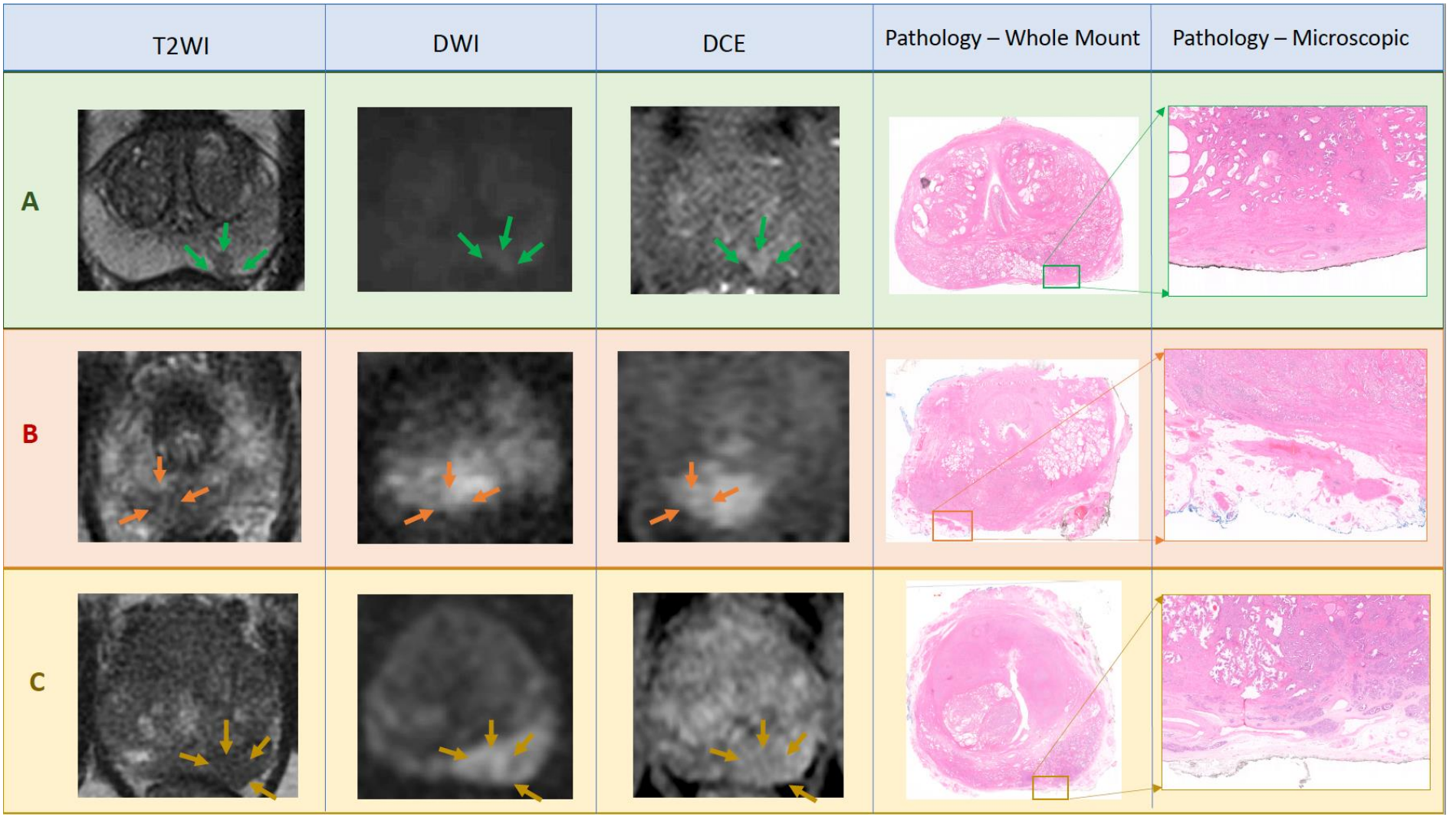

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Figure 2. Panel of example mpMRI scan images with corresponding histological RP whole mount images including areas of interest for EPE displayed in further magnification.

Patient A: Images from mid-gland show Likert score 2 Left - lesion in left peripheral zone posterior medial (green arrows). Corresponding pathology panels shows pT2c including disease confined to the gland, and not extending to the inked margin, in the left posterior medial peripheral zone (x1.5).
Patient B: Images from apex of gland show Likert score 4 Right - lesion in right peripheral zone posterior medial showing irregularity and bulge (orange arrows). Corresponding pathology panels show pT3a including disease extending into the fat for 2mm but clear of the inked margin (x1.42). Patient C: Images from base of gland show Likert score 5 Left - lesion in left peripheral zone posterior medial and posterior lateral demonstrating abutment, irregularity, bulge and 'measurable EPE' (gold arrows). Corresponding pathology panels show pT3a including disease extending circumferentially beyond capsule and into the fat for 8mm but clear of the inked margin (x1.5). All DWI images have b value either b1,400 or b2,000.

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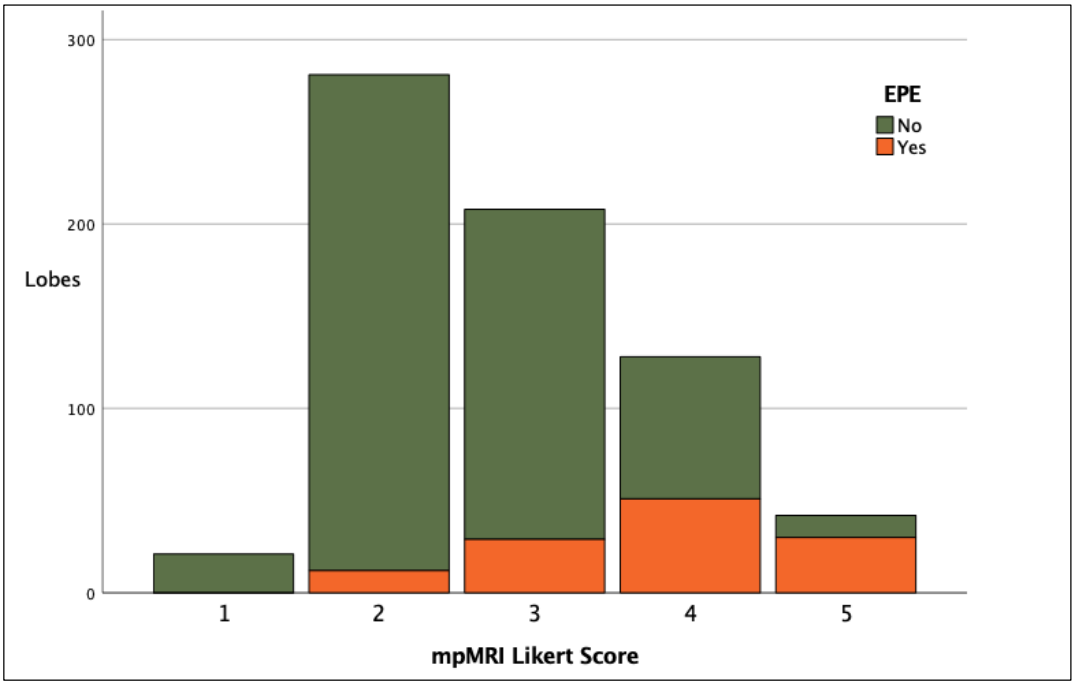

Figure 3. Stacked bar chart showing clinical detection of EPE per lobe according to Final Likert score.

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References

1. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med. 2018;378(19):1767-77.
2. Walz J, Burnett AL, Costello AJ, Eastham JA, Graefen M, Guillonneau B, et al. A critical analysis of the current knowledge of surgical anatomy related to optimization of cancer control and preservation of continence and erection in candidates for radical prostatectomy. Eur Urol. 2010;57(2):179-92.
3. Schiavina R, Bianchi L, Borghesi M, Dababneh H, Chessa F, Pultrone CV, et al. MRI Displays the Prostatic Cancer Anatomy and Improves the Bundles Management Before Robot-Assisted Radical Prostatectomy. J Endourol. 2018;32(4):315-21.
4. Marenco J, Orczyk C, Collins T, Moore C, Emberton M. Role of MRI in planning radical prostatectomy: what is the added value? World J Urol. 2019;37(7):1289-92.
5. Cathcart P, Sridhara A, Ramachandran N, Briggs T, Nathan S, Kelly J. Achieving Quality Assurance of Prostate Cancer Surgery During Reorganisation of Cancer Services. Eur Urol. 2015;68(1):22-9.
6. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2020.
7. Ball MW, Partin AW, Epstein JI. Extent of extraprostatic extension independently influences biochemical recurrence-free survival: evidence for further pT3 subclassification. Urology. 2015;85(1):161-4.
8. Danneman D, Wiklund F, Wiklund NP, Egevad L. Prognostic significance of histopathological features of extraprostatic extension of prostate cancer. Histopathology. 2013;63(4):580-9.
9. de Rooij M, Hamoen EH, Witjes JA, Barentsz JO, Rovers MM. Accuracy of Magnetic Resonance Imaging for Local Staging of Prostate Cancer: A Diagnostic Meta-analysis. Eur Urol. 2016;70(2):233-45.
10. Samaratunga H, Montironi R, True L, Epstein JI, Griffiths DF, Humphrey PA, et al. International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 1: specimen handling. Mod Pathol. 2011;24(1):6-15.
11. Magi-Galluzzi C, Evans AJ, Delahunt B, Epstein JI, Griffiths DF, van der Kwast TH, et al. International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 3: extraprostatic extension, lymphovascular invasion and locally advanced disease. Mod Pathol. 2011;24(1):26-38.
12. Giganti F, Allen C, Emberton M, Moore CM, Kasivisvanathan V, group Ps. Prostate Imaging Quality (PI-QUAL): A New Quality Control Scoring System for Multiparametric Magnetic Resonance Imaging of the Prostate from the PRECISION trial. Eur Urol Oncol. 2020;3(5):615-9.
13. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol. 2016;69(1):16-40.
14. Abrams-Pompe RS, Fanti S, Schoots IG, Moore CM, Turkbey B, Vickers AJ, et al. The Role of Magnetic Resonance Imaging and Positron Emission Tomography/Computed

Tomography in the Primary Staging of Newly Diagnosed Prostate Cancer: A Systematic Review of the Literature. Eur Urol Oncol. 2020.
15. Davis R, Salmasi A, Koprowski C, Kim S, Kwon YS, Faiena I, et al. Accuracy of Multiparametric Magnetic Resonance Imaging for Extracapsular Extension of Prostate Cancer in Community Practice. Clin Genitourin Cancer. 2016;14(6):e617-e22.
16. Alessi S, Pricolo P, Summers P, Femia M, Tagliabue E, Renne G, et al. Low PI-RADS assessment category excludes extraprostatic extension (>/=pT3a) of prostate cancer: a histology-validated study including 301 operated patients. Eur Radiol. 2019;29(10):5478-87.
17. Audit NPC. Annual Report 2019 - Results from the NPCA Prospective Audit in Enhland and Wales. London: Royal College of Surgeons; 2019.
18. Allen DJ, Hindley R, Clovis S, O'Donnell P, Cahill D, Rottenberg G, et al. Does body-coil magnetic-resonance imaging have a role in the preoperative staging of patients with clinically localized prostate cancer? BJU Int. 2004;94(4):534-8.
19. Caglic I, Sushentsev N, Shah N, Warren AY, Lamb BW, Barrett T. Comparison of biparametric versus multiparametric prostate MRI for the detection of extracapsular extension and seminal vesicle invasion in biopsy naive patients. Eur J Radiol. 2021;141:109804.
20. Mehralivand S, Shih JH, Harmon S, Smith C, Bloom J, Czarniecki M, et al. A Grading System for the Assessment of Risk of Extraprostatic Extension of Prostate Cancer at Multiparametric MRI. Radiology. 2019;290(3):709-19.
21. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. Eur Radiol. 2012;22(4):746-57.
22. Kongnyuy M, Sidana A, George AK, Muthigi A, Iyer A, Ho R, et al. Tumor contact with prostate capsule on magnetic resonance imaging: A potential biomarker for staging and prognosis. Urol Oncol. 2017;35(1):30 e1- e8.
23. Bakir B, Onay A, Vural M, Armutlu A, Yildiz SO, Esen T. Can Extraprostatic Extension Be Predicted by Tumor-Capsule Contact Length in Prostate Cancer? Relationship With International Society of Urological Pathology Grade Groups. AJR Am J Roentgenol. 2020;214(3):588-96.
24. Reistaeter LAR HO, Beisland C, Honore A, Gravdal K, Losnegard A, Monssen J, Alslen LA, Biermann M. Assessing Extraprostatic Extension with Multiparametric MRI of the Prostate: Mehralivand Extraprostatic Extension Grade or Extraprostatic Extension Likert Scale? Radiology: Imaging Cancer. 2020;2(1).
25. Park KJ, Kim MH, Kim JK. Extraprostatic Tumor Extension: Comparison of Preoperative Multiparametric MRI Criteria and Histopathologic Correlation after Radical Prostatectomy. Radiology. 2020;296(1):87-95.
26. Diamand R, Ploussard G, Roumiguie M, Oderda M, Benamran D, Fiard G, et al. External Validation of a Multiparametric Magnetic Resonance Imaging-based Nomogram for the Prediction of Extracapsular Extension and Seminal Vesicle Invasion in Prostate Cancer Patients Undergoing Radical Prostatectomy. Eur Urol. 2021;79(2):180-5.
27. Gandaglia G, Ploussard G, Valerio M, Mattei A, Fiori C, Roumiguie M, et al. The Key Combined Value of Multiparametric Magnetic Resonance Imaging, and Magnetic Resonance Imaging-targeted and Concomitant Systematic Biopsies for the Prediction of Adverse Pathological Features in Prostate Cancer Patients Undergoing Radical Prostatectomy. Eur Urol. 2020;77(6):733-41.
28. Soeterik TFW, van Melick HHE, Dijksman LM, Kusters-Vandevelde H, Stomps S, Schoots IG, et al. Development and External Validation of a Novel Nomogram to Predict

 doi:10.20944/preprints202201.0060.v1

Side-specific Extraprostatic Extension in Patients with Prostate Cancer Undergoing Radical Prostatectomy. Eur Urol Oncol. 2020.
29. Nyarangi-Dix J, Wiesenfarth M, Bonekamp D, Hitthaler B, Schutz V, Dieffenbacher S, et al. Combined Clinical Parameters and Multiparametric Magnetic Resonance Imaging for the Prediction of Extraprostatic Disease-A Risk Model for Patient-tailored Risk Stratification When Planning Radical Prostatectomy. Eur Urol Focus. 2020;6(6):1205-12.
30. Dinneen E, Haider A, Grierson J, Freeman A, Oxley J, Briggs T, et al. NeuroSAFE frozen section during robot-assisted radical prostatectomy (RARP): Peri-operative and Histopathological Outcomes from the NeuroSAFE PROOF Feasibility Randomised Controlled Trial. BJU Int. 2020.
31. Petralia G, Musi G, Padhani AR, Summers P, Renne G, Alessi S, et al. Robot-assisted radical prostatectomy: Multiparametric MR imaging-directed intraoperative frozen-section analysis to reduce the rate of positive surgical margins. Radiology. 2015;274(2):434-44.