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Comparison of TRUS-biopsy to Transperineal Template Mapping biopsies stratified by Multi-parametric MRI score within the PROMIS trial

Authors:

C Lovegrove[1] catherinelovegrove1@gmail.com

S Miah[1] Saiful.miah@nhs.net

A El-Shater Bosaily[2] ashater@nhs.net

S Bott[3] simon.bott@nhs.net

L Brown[4] l.brown@ucl.ac.uk

N Burns-Cox[5] nick.burns-cox@tst.nhs.uk

T Dudderidge[6] tim.dudderidge@uhs.nhs.uk

A Freeman[7] alex.freeman2@nhs.net

A Henderson[8] alastairhenderson@nhs.net

R Hindley[9] richard.hindley@nhs.net

R Kaplan[4] r.kaplan@ucl.ac.uk

A Kirkham[10] alexkirkham@nhs.net

R Oldroyd[11] re.oldroyd@btopenworld.com

C Parker[12] chris.parker@rmh.nhs.uk

R Persad[13] raj.persad1@nhs.net

S Punwani[10] shonit.punwani@nhs.net

D Rosario[14] derek.rosario@nhs.net

I Shergill[15] Iqbal.Shergill@wales.nhs.uk

M Winkler[1] mathias.winkler@nhs.net

M Emberton*[2] m.emberton@ucl.ac.uk

H. U. Ahmed*[1,16] hashim.ahmed@imperial.ac.uk

* Joint senior authors

1 Department of Urology, Imperial College Healthcare NHS Trust, London, UK

2 Department of Urology, UCLH NHS Foundation Trust, London, UK

3 Department of Urology, Frimley Park Hospital, NHS Frimley Health Foundation Trust, Frimley, UK

4 MRC Clinical Trials Unit at UCL, London, UK

5 Department of Urology, Musgrove Park Hospital, Taunton and Somerset NHS Foundation Trust, Taunton, UK
6 Department of Urology, University Hospital Southampton NHS Foundation Trust, Southampton, UK
7 Department of Histopathology, UCLH NHS Foundation Trust, London, UK
8 Department of Urology, Maidstone and Tunbridge Wells NHS Trust, Tunbridge Wells, UK
9 Department of Urology, Hampshire Hospitals NHS Foundation Trust, UK
10 Department of Radiology, UCLH NHS Foundation Trust, London, UK
11 Public and patient representative, Nottingham, UK
12 Department of Academic Urology, Royal Marsden Hospital, Sutton, UK
13 Department of Urology, North Bristol NHS Trust, Bristol, UK
14 Department of Urology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
15 Department of Urology, Wrexham Maelor Hospital NHS Trust, Wrexham, UK
16 Imperial Prostate, Division of Surgery, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, UK
Corresponding Author: Catherine Elizabeth Lovegrove, BSc (Hons.), MBBS, Imperial College Healthcare NHS Trust, London, London UNITED KINGDOM, catherinelovegrove1@gmail.com

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Introduction

We evaluated performance of transrectal ultrasound-guided systematic (TRUS) biopsy compared to transperineal template mapping (TPM) with a 5mm sampling frame, stratified by MP-MRI Likert score within the PROMIS study.

Methods

Biopsy-naïve men due prostate biopsy for elevated PSA and/or abnormal digital rectal examination underwent MP-MRI, TPM and TRUS biopsies, conducted and reported blind to other test results. Clinically significant prostate cancer (csPCa) was primarily defined as Gleason >/=4+3 or maximum cancer core length (MCCL) >/=6mm of any grade, and secondarily Gleason >/=3+4 or MCCL >/=4mm of any grade.

Results

In 41 months, 740 men at 11 centres were recruited; 576 underwent all three tests. Of 150 with MRI score 1-2, 8 (5.1%) had any Gleason >/=3+4 disease on TRUS-biopsy. In 75 where TRUS-biopsy showed Gleason 3+3 of any MCCL, 61/75 (81%) had Gleason 3+4, 8/75 (11%) Gleason 4+3 and 0/75 (0%) Gleason >/=4+5. For definition1 csPCa, TRUS-biopsy sensitivity remained stable and low across MP-MRI Likert scores (35%-52%). For definition2 csPCa and any cancer, sensitivity increased with higher MP-MRI score. Negative predictive value varied due to varying disease prevalence but for all cancer thresholds declined with increasing MP-MRI score.

Conclusions

TRUS-biopsy in the setting of MP-MRI Likert scores 1-2 finds Gleason 3+4 disease in only 1 in 20 men. Further, for any csPCa definition, TRUS-biopsy had poor sensitivity and variable but low NPV across MP-MRI scores. Men undergoing TRUS-biopsy without targeting in the setting of MP-MRI score 3 to 5 should be advised to undergo a repeat (targeted) biopsy.

Funding

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Key words: prostate, biopsy, transrectal, template, MRI

Introduction

The PROMIS study assessed the diagnostic accuracy of transrectal ultrasound-guided systematic (TRUS) biopsies and multi-parametric MRI (MP-MRI) compared to transperineal template mapping (TPM) biopsy with a 5mm sampling frame in the detection of clinically significant prostate cancer (csPCa)[1]. Results provided level 1b evidence demonstrating superior sensitivity and negative predictive value for MP-MRI in detecting and ruling-out clinically significant disease, facilitating its use as a triage prior to invasive biopsy sampling in men at risk of harbouring csPCa. The low specificity and positive predictive value of MP-MRI indicated biopsies were still required in those men having a suspicious MP-MRI. The PRECISION randomised controlled trial subsequently

demonstrated the improved utility of MP-MRI triage followed by targeted biopsies in those men with a suspicious lesion scoring 3 or higher[2].

PRECISION did not include systematic sampling of men randomised to the MP-MRI arm with ongoing debate as to the role of systematic TRUS biopsy in men who have undergone a MP-MRI. With this in mind, we aimed to further elaborate on the performance characteristics of systematic TRUS-biopsies alone when compared to TPM-biopsy, stratified by MP-MRI Likert scores[1].

Methods

PROMIS was a prospective, multi-centre, paired-cohort, confirmatory study, which represented level 1b evidence for diagnostic test assessment and reported to the Standards for Reporting Diagnostic Accuracy[3,4]. The full protocol and results have been previously published[1,5,6]. Ethics committee approval was granted by National Research Ethics Service Committee London (reference 11/LO/0185).

Biopsy-naïve men over the age of 18 with a clinical suspicion of prostate cancer were enrolled with the conduct and reporting of each test performed blind to the other test results. Clinical suspicion warranting further investigation included elevated serum PSA (up to 15 ng/mL) within previous 3 months, suspicious digital rectal examination, suspected organ confined stage T2 or lower on rectal examination, or family history. Other inclusion criteria were fitness for spinal anaesthesia, fitness to undergo MP-MRI, TRUS-biopsy and TPM-biopsy and ability to provide informed consent. Exclusion criteria included use of 5-alpha-reductese antagonist medication within the last 6 months, past history or treatment of prostate cancer, presence of a urinary tract infection or prostatitis within the preceding three months, contraindications to MRI (claustrophobia, non-compatible pacemaker, estimated glomerular filtration rate ≤50), past hip-replacement surgery and extensive pelvic orthopaedic metal work.

MP-MRI (index test): Patients received a standardised MP-MRI, compliant with European Society of Uro-Radiology guidelines, with 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. The protocol allowed men to be withdrawn after the MP-MRI scan if there was evidence of T4 disease or prostate volume was greater than 100 mL as TPM-biopsy could not be applied fully to such large prostates. Scans of insufficient quality were repeated before biopsy. MP-

MRI scans were reported by dedicated urologic radiologists with experience of reporting prostate MP-MRI who underwent additional centralised training of two separate whole day courses. Radiologists were provided with clinical details including PSA, digital rectal examination findings, and risk factors including family history. A 5-point Likert radiology reporting scale was used to designate prostates as highly unlikely (1), unlikely (2), equivocal (3), likely (4), and highly likely (5) to harbour clinically significant prostate cancer [1,7-9].

Combined biopsy procedure: Following MP-MRI a combined prostate biopsy procedure was done under general or spinal anaesthesia. Patients and physicians remained blinded to the MP-MRI and reports. TPM-biopsy was done first followed by TRUS-biopsy[10,11]. TPM-biopsy and subsequent TRUS-biopsy were combined under the same procedure to reduce patient visits and minimise dropout between tests. The reference test (TPM-biopsy) sampled at 5mm intervals and was centrally reported by one of two expert uropathologists blinded to all other test findings. In the standard test (TRUS-biopsy), 10–12 core biopsies were taken as per international standard with each core identified and processed separately[12]. TRUS-biopsy samples were reported by expert uropathologists at each site blinded to all other test findings.

Clinically significant prostate cancer: Definitions for clinical significance mirrored those used in our main PROMIS report[1]. The primary definition for clinically significant disease incorporated the presence of Gleason >/=4+3, or a maximum cancer core length (MCCL) involvement >/=6 mm of any grade in any location. Secondary definitions of clinical significance were also considered as the presence of Gleason >/=3+4 or a maximum cancer core length (MCCL) involvement >/=4mm of any grade in any location[13].

Statistical analysis

The original sample size calculations were based on determining the validity of MP-MRI compared to TRUS-biopsy using TPM-biopsy as the reference standard[1]. For the analysis in this paper, there were no a priori sample size calculations. Comparison of the accuracy of TRUS-biopsy compared to TPM-biopsy in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in detection of prostate cancer was performed. These were stratified by using different MP-MRI score thresholds. As there was only one patient with MP-MRI Likert score 1 and clinically significant disease, Likert scores 1 and 2 were combined for statistical analysis to create a cohort of 158 men. Analyses used Stata version 13.0 software (Stata Corporation, College Station, TX, USA). For each comparison, 2 × 2 contingency tables were used to present the results and calculate the

diagnostic accuracy estimates with 95% confidence intervals. The unit of assessment for our 2 × 2 contingency table for assessment of accuracy was one patient (i.e., the whole prostate).

Results

Over 41 months from 17th May 2012 to 9th November 2015, 740 men were recruited across 11 centres and 576 underwent all three investigations[1]. Baseline characteristics have been previously reported and are not repeated here. Gleason scores identified by TPM-biopsy, stratified by MP-MRI Likert score are shown in Table 1.

First, TPM-biopsy identified 230 cases in 576 men (40%) of definition 1 csPCa whereas TRUS-biopsy identified 124/576 (21%) clinically significant cases. Table 2 demonstrates the breakdown of MP-MRI Likert scores for cases identified as being csPCa by TPM-biopsy. On comparison of TRUS-biopsy against TPM-biopsy across MP-MRI Likert scores, sensitivity and specificity remain broadly stable across all Likert scores (35-52%), with PPV and NPV showing greater variability (reflecting their strong correlation to the prevalence of disease at various MP-MRI scores) (Table 3).

Second, in 75 men TRUS-biopsy classified patients as having only Gleason 3+3=6; these men had Gleason 3+4=7 in 61/75 (81%), Gleason 4+3=7 in 8/75 (11%) with none having Gleason score 8 or above on TPM-biopsy (Table 4). Of 158 with MRI score 1-2, 8 (5.1%) had any Gleason >/=3+4 disease on TRUS-biopsy. This is in contrast to the 38 (24%) found on TPM-biopsy (Figure 1).

Third, TPM identified 331 cases in 576 men (57%) of clinically significant prostate cancer by definition 2 csPCa where TRUS biopsy identified 203/576 (35%) definition 2 csPCa cases (Figure 2, Table 5). On comparison of TRUS-biopsy against TPM-biopsy across MP-MRI Likert scores for definition 2 csPCa, sensitivity and specificity are less stable across all MP-MRI Likert scores (Table 6). The sensitivity of TRUS-biopsy appears to increase as MP-MRI score increases (30%-76%). PPV was high and stable where NPV fell with increasing Likert score from 79% to 21%, representative of increasing disease prevalence.

Last, TPM-biopsy identified 408/576 (71%) cases of any grade and length of prostate cancer whereas TRUS-biopsy found 286/576 (50%). TRUS-biopsy found 135/576 men with Gleason 3+3=6 of any MCCL (23.4%) (Table 7). 95/135 (70.4%) patients had a higher Gleason score on TPM. Table 8 demonstrates the breakdown of MRI Likert scores for cases of prostate cancer identified by TPM

biopsy. On comparison of TRUS-biopsy against TPM-biopsy across MP-MRI Likert scores for the presence of any cancer sensitivity appears to increase as MP-MRI significant score increases whilst NPV appears to decrease with increasing MRI score. Specificity and PPV remain high and stable across all scores (Table 9).

Discussion

In summary, TRUS-biopsy applied in men with MP-MRI Likert scores 1 and 2 confers a 1 in 20 chance of yielding Gleason >/=3+4 prostate cancer. Further, for any definition of csPCa, TRUS-biopsy had poor sensitivity and variably low NPV across all MP-MRI score groups reinforcing its inaccuracy if applied in a systematic non-targeted fashion.

Our findings demonstrate that TRUS-biopsy miss-classifies clinically significant disease with 9 in 10 men identified as Gleason 3+3 of any cancer length on TRUS-biopsy, actually having Gleason score >/= 3+4 on TPM-biopsy. Our findings are similar to those of Scott et al who compared TPM-biopsy versus TRUS-biopsy on prostatectomy specimens, concluding that TPM-biopsy more accurately depicted clinical risk and that TRUS-biopsy risked under-diagnosis of occult higher risk disease[14]. Huang et al also discerned 35% upgrading of disease grade on TPM-biopsy for patients with a previously negative TRUS-biopsy, however these were not contemporaneous samples unlike the present study.

Our results have notable practical implications. Reliance on TRUS-biopsy risks inappropriately allocating patients to active surveillance, potentially missing a time-window where curative oncological management could be instigated. In centres utilising a targeted-biopsy strategy, addition of TRUS-biopsy risks the over-treatment of patients through increased detection of insignificant, low-volume, low-grade disease, similar to results from Rouvière et al[15]. The increased sensitivity of TRUS-biopsy that we see with increasing Likert score may be related to the correlation between MRI score and volume of cancer in the index lesion(s) and likelihood of csPCa due to higher probability of multifocality[16].

Whilst the cost-effectiveness of an MRI direct pathway has been shown in the UK and other healthcare systems, results from the current study also have implications for urology departments and patients[17]. The resource and financial burden of TPM-biopsy is not inconsequential. Clinicians

should evaluate findings from the literature in-line with the pathology and biopsy resources available to them and the degree of clinical suspicion of the patient in front of the harbouring csPCa but certainly a TPM-biopsy in all strategy will be prohibitively expensive as well as confer significant side-effects to the patients[18]. Men should be counselled accordingly prior to TRUS-biopsy and made aware of the relative advantages and disadvantages of pre-biopsy mpMRI, TRUS-biopsy and TPM-biopsies[1,2]. Our results also have an impact on many clinicians who wish to carry out a systematic non-targeted TRUS-biopsy in the setting of a non-suspicious MP-MRI**.** PRECISION found 38% clinically significant cancer in the target biopsy arm versus 26% in the standard TRUS-biopsy[2]. Additionally, they showed how MP-MRI triage and subsequent target biopsy reduced the yield of clinically insignificant cancer. With existing evidence and these results, urologists and their patients might conclude that the 5% pick up rate for any Gleason 7 disease or higher is sufficiently low to warrant an avoidance of an immediate TRUS-biopsy. Indeed, van der Leest et al demonstrated the non-inferiority of MP-MRI triage and MRI-targeted biopsy compared to systematic TRUS-biopsy in detecting lesions =/> Gleason 3+4 but superior in reducing the diagnosis of insignificant disease, similar to conclusions from the MRI-FIRST study[15,19]. Gleason 4+3 disease was absent in TPM-biopsy of lesions of Likert 1-2 though there was a 24% prevalence of Gleason 3+4 disease. At present there is insufficient evidence to determine whether the Gleason pattern 4 disease in such patients may be significant long-term. Consequently, clinicians may be deterred from relying on MRI as an indicator to biopsy. However, allocation to active surveillance protocols would facilitate follow-up for these cases and this presents an imperative need to optimise and standardise MRI and active surveillance protocols[20]. The inaccuracy of TRUS-biopsy without targeting continues even when the MP-MRI is suspicious and might question the role of doing systematic biopsies in that setting while the MRI-FIRST study showed the cumulative benefit from targeted and systematic biopsy for suspicious MRI lesions[15]. Miah et al undertook a large, multi-centre series examining the value of targeted fusion biopsy versus non-targeted systematic biopsy in which the latter did not overlap into targeted areas. Non-targeted systematic prostate biopsy cores had only a 9% csPCa yield with a 26.1% prevalence of clinically insignificant prostate cancer. This calls into question the role of systematic biopsy especially in the context of PIRADS >/=3 lesions[21]. Other studies have shown a 1-2 in 20 rate of significant prostate cancer in non-suspicious MP-MRI cases is in-keeping with findings from the PROMIS cohort while showing the rise in insignificant disease detected in using additional non-targeted systematic TRUS-biopsy[19].

There are some limitations. On TPM-biopsy a 5mm interval for sampling the whole prostate was utilised to provide precision for research purposes resulting in the exclusion of men with prostates

greater than 100mL due to technical difficulties in sampling[22]. The exclusion of patients with large prostate glands is likely to have reduced the proportion of men with true negative glands and led to reduced NPV both for MP-MRI and TRUS-biopsy. TPM-biopsy may not be applied routinely to all men in clinical practice owing to the invasive nature of the technique. We have previously reported a 24% rate of urinary retention and significant sustained deterioration in patient reported outcome measures evaluating erectile function and urinary symptoms following TPM-biopsy from the PICTURE trial[23]. This highlights that no test can be equally highly accurate and confer little morbidity and that the application of MP-MRI as a triage and then targeting strategies might offer the optimal balance for men[18]. Third, deployment of TPM- biopsy followed by TRUS-biopsy might have contributed to the reduced accuracy of TRUS-biopsy. This order of sampling was to protect patients from the potential increased risk of disseminating bacteria following TRUS-biopsy and to maintain the reliability of TPM-biopsy as the reference standard within PROMIS. Finally, targeted biopsy techniques were not able to be evaluated as clinicians and patients were blinded to the results of MP-MRI.

Conclusion

TRUS-biopsy in the setting of MP-MRI Likert scores 1-2 finds Gleason 3+4 disease in only 1 in 20 men. Further, for any csPCa definition, TRUS-biopsy had poor sensitivity and variable but low NPV across MP-MRI scores. Men undergoing TRUS-biopsy without MP-MRI or only systematic TRUS-biopsy in the setting of MP-MRI score 3 to 5 should be advised to undergo a repeat targeted biopsy.

Authorship

HUA, CP and ME conceived the study. LB conducted analysis of the data. CL, SM and HUA were responsible for production of the first draft. All authors were involved in data collection, manuscript preparation/drafting and approval of the final draft.

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Declaration of Interests

Ahmed currently receives funding from the Wellcome Trust, Prostate Cancer UK, The Urology Foundation, BMA Foundation, Imperial Healthcare Charity, Sonacare Inc., Trod Medical and Sophiris Biocorp for trials in prostate cancer. Ahmed is a paid medical consultant for Sophiris Biocorp and Sonacare Inc.

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.

Ahmed and Emberton are proctors for HIFU and paid for training other surgeons in this procedure. Ahmed is a proctor for cryotherapy using the Galil/BTG system.

None of the other authors have anything to declare.

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Tables

Legends

Table 1. Gleason score of TPM cores, stratified by MRI findings

Table 2. MRI Likert scores of clinically significant prostate cancer (definition 1) identified on TPM biopsy

Table 3. Diagnostic accuracy of TRUS versus TPM in identifying clinically significant prostate cancer (definition 1) across MRI Likert scores

Table 4. Comparison of TRUS vs. TPM biopsy in men with clinically significant disease (definition 1)

Figures

Legends

Table 1. Gleason score of TPM cores, stratified by MRI findings

MRI Likert score	Gleason score on TPM							
	0	3+3	3+4	3+5	4+3	4+5	5+4	Total
1	12	7	4	0	0	0	0	23
2	72	29	34	0	0	0	0	135
3	65	39	55	0	4	0	0	163
4	13	21	73	1	10	1	1	120
5	6	4	86	0	30	6	3	135
Total	168	100	252	1	44	7	4	576

Table 2. MRI Likert score of clinically significant prostate cancer (definition 1) identified on TPM biopsy

MRI Likert score	TPM biopsy-non-significant disease	TPM biopsy- clinically significant prostate cancer	Total	% identified as prostate cancer
Likert 1	22	1	23	4.35%
Likert 2	119	16	135	11.85%
Likert 3	129	34	163	20.86%
Likert 4	50	70	120	58.34%
Likert 5	26	109	135	80.74%
Total	346	230	576	39.93%

Table 3. Diagnostic accuracy of TRUS versus TPM in identifying clinically significant prostate cancer (definition 1) across MRI Likert scores

MRI Likert score (N)	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
All scores (576)	48% (42-55)	96% (94-98)	90% (83-94)	74% (69-78)
1+2 (158)	35% (14-62)	98% (94-100)	67% (30-93)	93% (87-96)
3 (163)	47% (30-65)	99% (96-100)	94% (71-100)	88% (81-93)
4 (120)	46% (34-58)	90% (78-98)	87% (71-96)	54% (43-65)
5 (135)	52% (43-62)	85% (65-96)	93% (84-98)	30% (20-42)

Table 4. Comparison of TRUS vs. TPM biopsy in men with clinically significant disease (definition 1)

Gleason score TRUS Biopsy	**Gleason Score TPM Biopsy**						
	3+3	3+4	3+5	4+3	4+5	5+4	Total
0	4	25	0	5	0	0	34
3+3	6	61	0	8	0	0	75
3+4	0	69	0	8	3	0	80
3+5	0	0	1	0	0	0	1
4+3	0	7	0	19	1	0	27
4+4	0	1	0	4	1	0	6
4+5	0	1	0	0	2	1	4
5+3	0	0	0	0	0	1	1
5+4	0	0	0	0	0	2	2
Total	10	164	1	44	7	4	230

Table 5. MRI Likert scores of clinically significant prostate cancer (definition 2) identified on TRUS and TPM biopsy

MRI Likert score	Biopsy modality	No significant disease	Clinically significant prostate cancer	Total	% identified as prostate cancer by TPM biopsy
Likert 1	TRUS biopsy	23	0	23	0.00 %
	TPM Biopsy	18	5		21.74 %
Likert 2	TRUS biopsy	122	13	135	2.26 %
	TPM Biopsy	96	39		28.89 %
Likert 3	TRUS biopsy	126	37	163	22.70 %
	TPM Biopsy	94	69		42.33 %
Likert 4	TRUS biopsy	64	56	120	44.80 %
	TPM Biopsy	28	92		76.67 %
Likert 5	TRUS biopsy	38	97	135	71.85 %
	TPM Biopsy	9	126		93.34 %
Total	TRUS biopsy	373	203	576	35.24 %
	TPM Biopsy	245	331		57.47 %

Table 6. Diagnostic accuracy of TRUS versus TPM in identifying clinically significant prostate cancer (definition 2) across MRI Likert scores

MRI Likert score (N)	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
All scores (576)	60% (55-65)	98% (96-100)	98% (95-100)	65% (60-70)
1+2 (158)	30% (17-45)	100% (97-100)	100% (75-100)	79% (71-85)
3 (163)	51% (38-63)	98% (93-100)	95% (82-99)	73% (64-81)
4 (120)	60% (49-70)	96% (82-100)	98% (90-100)	42% (30-55)
5 (135)	76% (68-83)	89% (52-100)	99% (94-100)	21% (10-37)

Table 7. Biopsy findings with any MCCL

Gleason score TRUS biopsy	**Gleason Score TPM Biopsy**							
	0	3+3	3+4	3+5	4+3	4+5	5+4	Total
0	159	67	59	0	5	0	0	290
3+3	9	31	87	0	8	0	0	135
3+4	0	2	90	0	8	0	0	103
3+5	0	0	0	1	0	0	0	1
4+3	0	0	14	0	19	1	0	34
4+4	0	0	1	0	4	1	0	6
4+5	0	0	1	0	0	2	1	4
5+3	0	0	0	0	0	0	1	1
5+4	0	0	0	0	0	0	2	2
Total	168	100	252	1	44	7	4	576

Table 8. MRI Likert scores for prostate cancer identified on TPM biopsy

MRI Likert score	TPM biopsy- no prostate cancer	TPM biopsy- prostate cancer	Total	% identified as prostate cancer
Likert 1	0	2	2	100.00 %
Likert 2	56	45	101	44.55 %
Likert 3	88	109	197	55.33 %
Likert 4	17	115	132	87.12 %
Likert 5	7	137	144	95.14 %
Total	168	408	576	70.83 %

Table 9. Diagnostic accuracy of TRUS relative to TPM across Likert scores for presence of any cancer

MRI Likert score (N)	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
All scores (576)	68% [63-72)	95% (90-98)	97% [94-99)	55% [49-61)
1+2 (103)	40% [26-56)	93% [83-98)	83% [61-95)	65% [54-75)
3 (197)	55% [45-65)	97% [90-99)	95% [87-99)	63% [55-72)
4 (132)	70% [61-79)	94% [71-100)	99% [93-100)	32% [20-47)
5 (144)	85% [78-91)	86% [42-100)	99% [95-100)	23% [9-44)

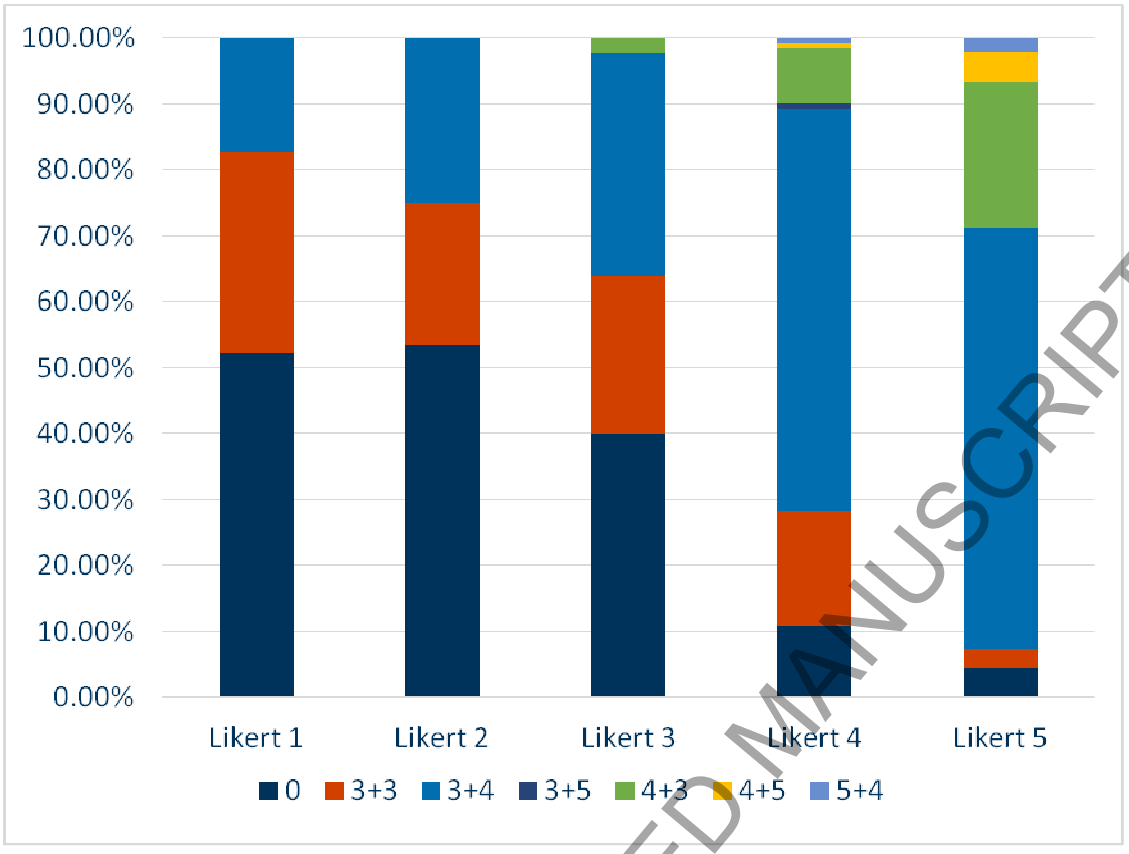

Figure 1. Gleason scores of TPM biopsy cores

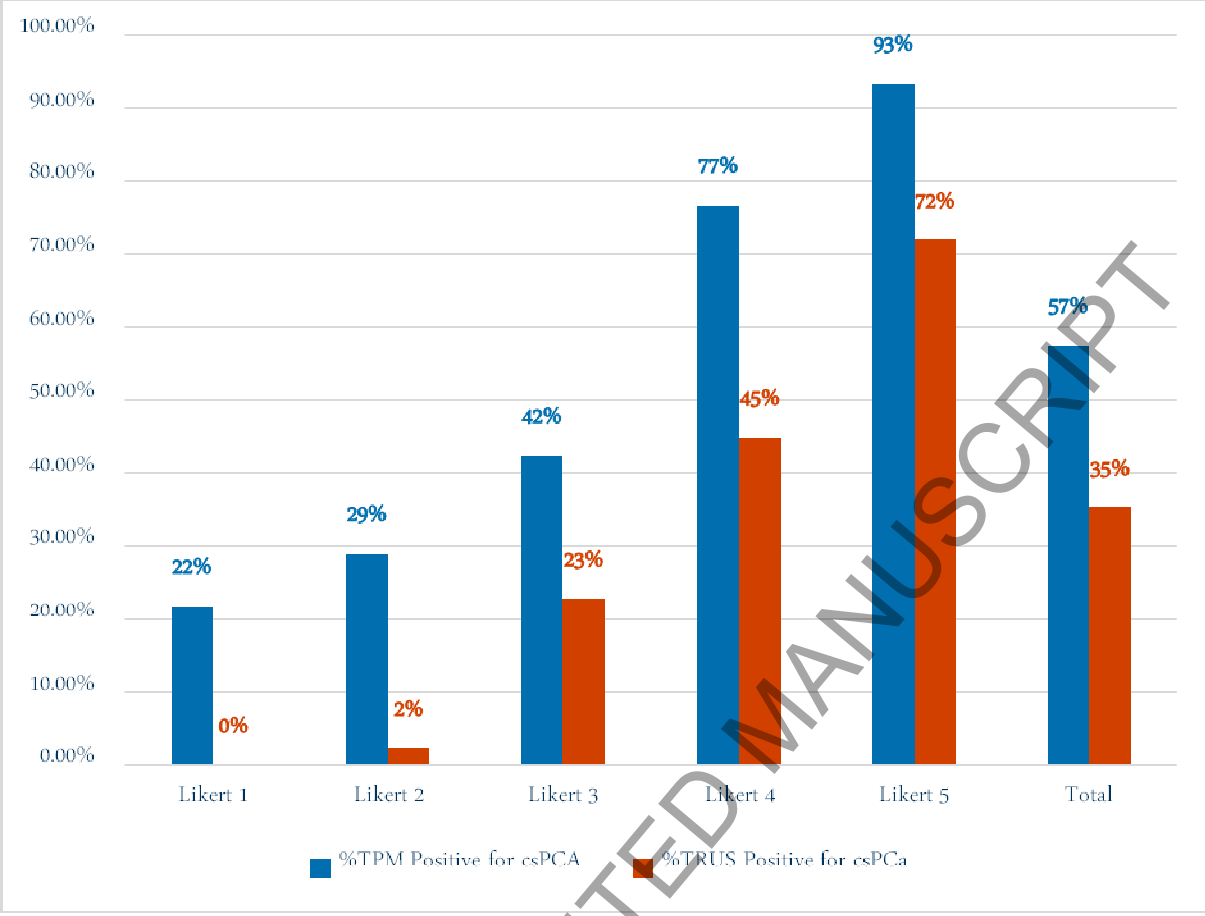

Figure 2. Identification of clinically significant disease (def 2.) TPM vs. TRUS