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Gleason grade accuracy of transperineal and transrectal prostate biopsies in MRI-naïve patients

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Abstract

Purpose Accurate assessment of Gleason grade is essential to guiding prostate cancer management. Not all healthcare systems have universal access to prostate MRI. We investigated whether transperineal (TP) prostate biopsies provide more accurate Gleason grading than transrectal (TR) biopsies in MRI-naïve patients.

Methods Consecutive patients undergoing TP and TR systematic prostate needle biopsies from 2011 to 2018 were analysed. Patients who underwent radical prostatectomy (RP) within 180 days of biopsies were included. Patients undergoing MRI prior to biopsies were excluded. Pathological concordance, incidence of Gleason upgrading, and correlation coefficients among biopsies and RP Gleason grade were compared. A sub-analysis for concordance in anterior prostate tumours was conducted.

Results 262 patients were included (112 TP; 150 TR), the median age was 63 years, and median time from biopsy to RP was 68 days. Concordance with RP histology for TP was 65% compared to 49% for TR ($p=0.011$). Biopsy technique predicted RP concordance independent of the number of cores. Gleason upgrading occurred following 24% of TP versus 33% of TR biopsies. In anterior and apical tumours, upgrading occurred in 19% of TP biopsies and 38% of TR biopsies ($p=0.027$).

Conclusion This study suggests TP approach to prostate biopsies result in improved histological grade accuracy in men whom MRI is not available, even after controlling for number of cores. TP approach also resulted in less upgrading for lesions in the anterior and apical prostate compared to TR.

Keywords Gleason score · Transperineal · Prostate cancer · Template biopsy · Gleason upgrading

Introduction

Approximately 1.1 million men are diagnosed with prostate cancer annually [1]. The accuracy of prostate biopsies is critical for risk stratification and treatment planning. Gleason upgrading after biopsies is common and defined by the radical prostatectomy (RP) specimen harbouring more aggressive Gleason patterns than found by prostate biopsies.

In a review of Gleason upgrading comprising 11,000 cases, the proportion of upgrading was 14–51%, with an average incidence of 35% [2]. The causes of Gleason upgrading are multifactorial and include: anatomical sampling errors during biopsy [3], histological limitations of the small amount of tissue within 18 g needle cores [4], disease progression [5], and inter-observer variability between pathologists [6].

TP biopsies allow comprehensive sampling of the prostate with low risk of sepsis. The apical entry of TP needles allows easy sampling of the apical and anterior prostate, which are common sites of missed tumours with the transrectal (TR) approach [7, 8] (Figs. 1, 2). Anterior prostate tumours account for 5–15% of clinically significant cancers [9].

MRI-guided biopsies have become the gold standard; however, most healthcare systems do not offer universal

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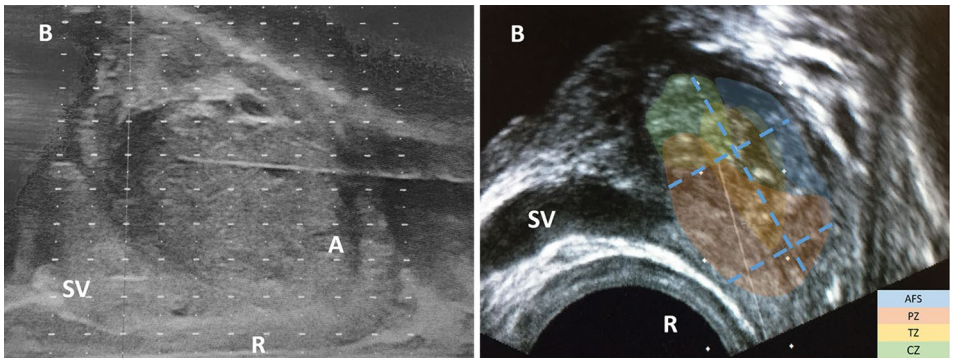

Fig. 1 Comparison of transperineal versus transrectal prostate biopsy approaches. Ultrasound images demonstrating transperineal approach [**a**] versus transrectal [**b**] approach for prostate biopsy. A transperineal approach allows for more convenient sampling of the anterior apical section of the prostate. Regions of the prostate have been highlighted in **b** to illustrate prostate zones and dotted lines are superimposed to delineate the apex, mid, base, and the anterior region. *A* apical region of prostate, *B* bladder, *R* rectum, *SV* seminal vesicle, *AFS* anterior fibromuscular stroma, *PZ* peripheral zone, *TZ* transitional zone, *CZ* central zone

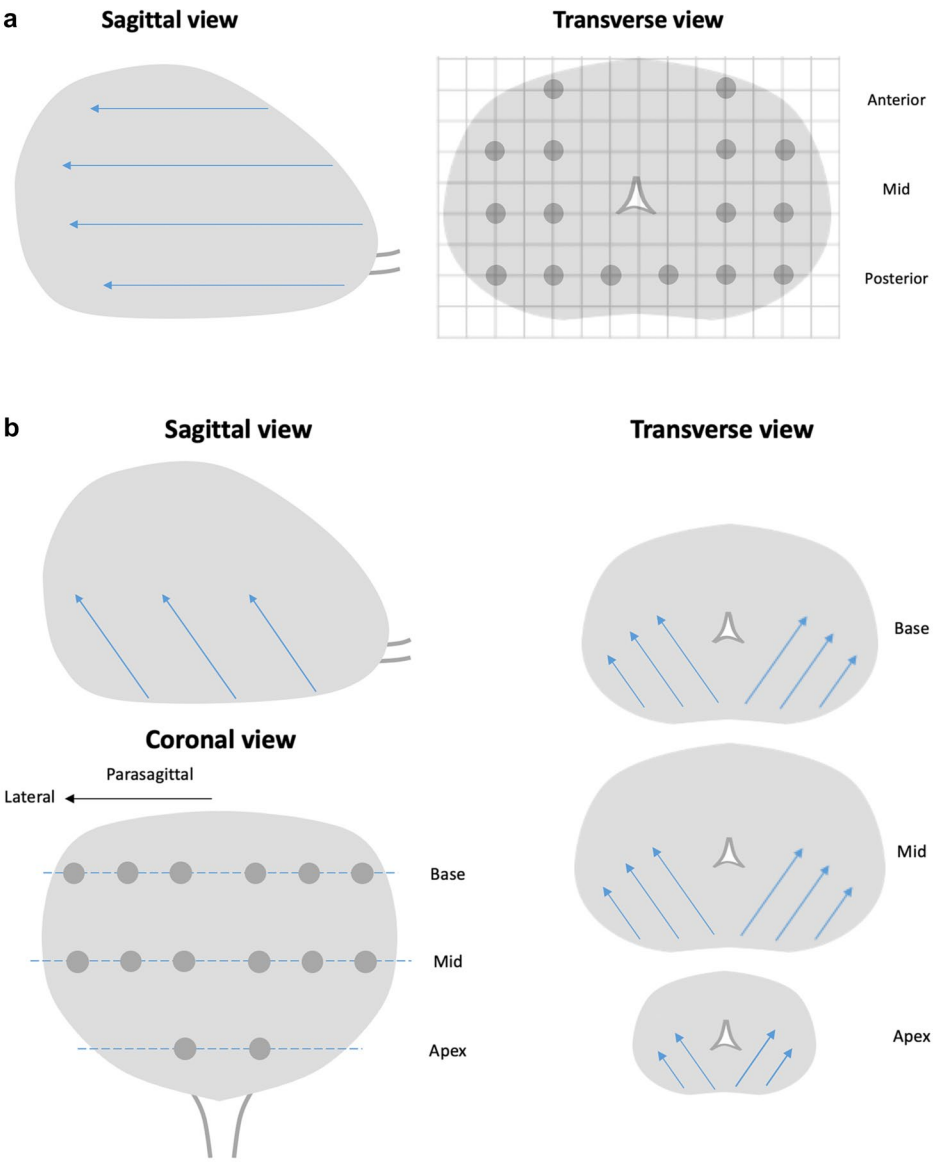

Fig. 2 Prostate biopsy approach template diagrams. Diagrams of the templates used for each biopsy approach are demonstrated. In **a**, the transperineal biopsy is shown with overlaying template grid and sampling of the anterior prostate. In **b**, biopsies of the base, mid and apical regions of the prostate are shown in coronal, transverse and sagittal views

prostate multiparametric MRI (mpMRI) prior to all biopsies. Studies comparing the histological accuracy of TP and TR biopsy techniques are rare in the MRI-naïve population. We aimed to determine if there was a difference between TP and TR histology in a MRI-naïve population of men at our institution.

Materials and methods

Inclusion criteria

We analysed consecutive patients who underwent prostate needle biopsies between 2011 and 2018 at our tertiary-care institution. Inclusion criteria were men with histology available from their biopsy and progression to RP. Patients who underwent prostate mpMRI prior to their biopsies were excluded due to the potential sampling bias that could result from targeting visible lesions. Patients with a delay between biopsy and RP of > 180 days were excluded to account for the higher likelihood of disease progression [10].

Biopsy procedures

The type of biopsy, TP or TR, was determined by our institutional protocols due to an increasing prevalence of TR biopsy sepsis. All patients prior to June 2015 received TR biopsy at our institution, and all patients from June 2015 onwards received TP biopsy. All biopsies were performed in the operating theatre by qualified urologists as per hospital protocol.

Transrectal (TR) prostate biopsy

TR biopsies were performed under intravenous sedation in the lateral foetal position using a 12 mHz TR ultrasound transducer (Flex Focus, BK Medical, Denmark) with an end-fire needle guide and a disposable 18 g × 22 cm biopsy needle (Bard Max Core Needle, Bard, USA), utilising an extended 12–18 core double sextant TR technique progressing from base to apex as previously described [4]. Single-dose gentamicin or imipenem were administered on induction according to hospital protocol.

Transperineal (TP) prostate biopsy

TP biopsies were performed under intravenous sedation or general anaesthesia with the patient in low lithotomy position using bi-planar TR ultrasound (Flex Focus, BK Medical, Denmark), and a disposable 18 g × 22 cm biopsy needle (Bard Max Core Needle, Bard, USA). Prostate mapping was performed in 5–10 mm increments entering through the perineum and apical prostate guided by a disposable brachytherapy template grid (Accucare Template grid, Civco Medical Solutions, UK), as previously described [11, 12]. Twenty-four hours of oral ciprofloxacin prophylaxis and single-dose intravenous gentamicin or imipenem was administered intra-operatively according to hospital protocol.

Patient demographics

Patient demographics including age, PSA, clinical stage, prostate volume, and duration from biopsies to surgery were recorded. Biopsy data including technique, number of cores sampled, and histology were also recorded. For patients undergoing several prostate biopsies over time, the highest Gleason grade obtained over the course the biopsies was analysed. RP histopathological features including tumour location, grade, and stage were recorded.

Histopathological analysis

Histological assessment was performed at our institution by dedicated uropathologists utilising the modified grade group system based on Gleason scores [13]. Reporting of biopsies and RP specimens was conducted according to the outlined structured reporting protocols published by the Royal College of Pathologists of Australasia, in accordance with the International Collaboration on Cancer Reporting. Patients undergoing multiple biopsies were assigned the grade group of the biopsy with the highest Gleason score. Anterior and apical tumours were also recorded according to the histopathological reports and were analysed as a subgroup. Anterior tumours were defined as cancers located anterior to the urethra, typically in the anterior fibromuscular stroma and transition zone (Fig. 1). Apical tumours were defined as those located within the apical horn 1 cm from the urethral margin of the RP specimen (Fig. 1).

Concordance was defined as the biopsy grade group being identical to the RP grade group. Upgrading and downgrading were, respectively, defined as the change of at least one grade group up or down from prostate biopsies to final RP histopathology. Tertiary Gleason grades were not analysed.

Statistical analysis

StataIC v15.1 (College Station, Texas USA) was used for all statistical analyses in this study. Wilcoxon rank-sum tests were used to calculate the differences among characteristics in biopsy modality. Specimens were analysed as proportion of concordant grade groups for each respective biopsy approach and reported with Chi-squared statistics. A p value of < 0.05 was used to determine significance of our findings throughout this study.

Multivariable logistic regression was performed to assess the association between biopsy approach with concordance

while controlling for number of cores. Given the expected influence of cores towards grade concordance, the regression model covariates: biopsy approach and number of cores; were selected a priori and entered simultaneously. In addition, a Cohen kappa coefficient was calculated for each cohort to measure inter-rater agreement between biopsies and final histology, along with 95% confidence intervals (CI).

Sub-analysis of tumours located in the anterior or apical regions of the prostate was conducted. The proportion of these tumours with anterior involvement was reported for both biopsy types. The concordance and rates of upgrading were calculated and compared as described above.

Results

Patient demographics

1106 patients underwent prostate biopsy at our institution from 2011 to 2018. 338 had radical prostatectomy and of these 76 had MRI recorded prior to biopsy and were excluded. In total, 262 men were suitable for final analysis, 112 (43%) had TP and 150 (57%) TR, Baseline characteristics are summarised in Table 1. Patients in the two biopsy modality groups had numerically similar median ages and PSAs, and distribution of pathological stage. The TP cohort had a considerably greater median number of cores per patient than TR, (23 vs 14 cores, respectively, $p < 0.001$). The median number of days between biopsies and RP in the study was slightly longer for TP (72 vs 65 days). Grade group 2 (Gleason Score 3 + 4 = 7) was the commonest histology observed for both modalities (Table 2).

Concordance of histology at radical prostatectomy with biopsy technique

TP biopsies had a significantly greater Gleason grade concordance compared to TR biopsies (65% vs 49% $p = 0.011$). The Kappa coefficient for TP was 0.48 (95% CI 0.35–0.60) indicating moderate agreement, compared to fair agreement for TR biopsies, $\kappa = 0.30$ (95% CI 0.20–0.41).

For patients with biopsy grade group ≤ 4, the incidence of upgrading at RP in the TP cohort was 28%, compared to 38% in the TR cohort ($p = 0.11$). Among patients undergoing TP biopsies, 17.0% ($n = 19$) upgraded by one grade group; 5.4% ($n = 6$) upgraded two grade groups, and 1.8% ($n = 2$) > two grade groups. In patients undergoing TR biopsies, 22.7% ($n = 34$) upgraded one grade group, 8.0% ($n = 12$) by two grade groups, and 2.0% ($n = 3$) by > two grade groups. A significant difference between TP and TR was observed for patients with biopsy grade group ≥ 2 that were downgraded to a lower grade group on RP histopathology (TP 12% vs TR 22%, $p = 0.047$).

Logistic regression was performed to examine the association of biopsy approach with grade concordance, adjusting for number of biopsy cores. Compared to TP biopsies,

Table 1 Basic patient demographics according prostate biopsy approach

	TP biopsy ($n = 112$)	TR biopsy ($n = 150$)	p value
Age, years Median (IQR)	65 (59–68)	63 (57–67)	0.044
PSA, ng/mL Median (IQR)	7.7 (5.7–11.4)	7.0 (5.0–9.7)	0.032
Clinical stage, n (%)*			0.025
T1c	52 (47)	74 (55)	
T2	57 (51)	50 (37)	
T3	2 (1.8)	10 (7.5)	
Previous biopsy			0.14
No	94 (84)	135 (90)	
Yes	18 (16)	15 (10)	
Prostate volume, mL Median (IQR)	36 (28–49)	37 (28–46)	0.93
Cores taken, median (IQR)	23 (20–26)	14 (13–17)	< 0.001
Days from biopsy to RP Median, (IQR)	72 (56–97)	65 (49–87)	0.033
RP T stage, n (%)			0.91
pT2	59 (53)	78 (52)	
pT3/4	53 (47)	72 (48)	

Baseline patient and disease characteristics were compared according to biopsy approach

*17 patients had incomplete DRE

Table 2 Concordance of prostate biopsy grade with final radical prostatectomy histopathological grade

TP biopsy		Radical prostatectomy, *n*					
Grade Group, *n*		Gr 1	Gr 2	Gr 3	Gr 4	Gr 5	Upgraded %
(a)							
Gr 1	9	*3 (33%)*	**4**	**2**	**0**	**0**	66%
Gr 2	56	1	*44 (79%)*	**9**	**0**	**2**	20%
Gr 3	24	0	8	*10 (42%)*	**2**	**4**	25%
Gr 4	7	0	0	1	*2 (29%)*	**4**	57%
Gr 5	16	0	1	1	0	*14 (88%)*	N/A
Total	112	4	57	23	4	24	24%
(b)							
Gr 1	25	*5 (20%)*	**14**	**6**	**0**	**0**	80%
Gr 2	61	4	*38 (62%)*	**16**	**0**	**3**	31%
Gr 3	32	3	6	*16 (50%)*	**1**	**6**	22%
Gr 4	10	0	1	4	*2 (20%)*	**3**	10%
Gr 5	22	0	1	7	1	*13 (59%)*	N/A
Total	150	12	60	49	4	25	33%

Grade group at biopsy (left column) and at RP (right columns) are demonstrated for TP and TR approaches. The italics fields represent biopsy concordance between specimens: histology was concordant in 73 of 112 TP cases (65%); histology was concordant in 74 of 150 TR cases (49%). The bold depicts Gleason upgrading, which is summarised in the right-hand column

undergoing TR biopsies had significantly lower odds of concordance (OR: 0.46, 95% CI 0.23–0.91, $p=0.025$).

Prediction of grade for anterior prostate tumours

Overall, 107 tumours (41%) involved the anterior or apical region of the prostate noted in the RP specimen, TP 49% (54 of 110), TR 36% (53 of 148). Analysis of RP concordance in these tumours demonstrated superior accuracy of TP biopsies compared to TR biopsies (70% vs 42% concordance, $p=0.003$). Significantly less upgrading (19% vs 38%, $p=0.027$) and numerically less downgrading (21% vs 11%, $p=0.17$) was observed with TP biopsies in anterior tumour RP specimens.

Discussion

This study aimed to characterise the difference in upgrading proportion between prostate biopsy approaches, for patients who did not undergo pre-biopsy MRI. Of note, there was significantly greater grade concordance in patients who underwent TP compared to TR biopsy approach, even with number of cores controlled. In addition, a significant difference in upgrading rates of anterior and apical tumours was also demonstrated. This is in the context of increasing evidence for benefits of TP biopsies, where there may be lower infection complications, hospital readmissions, and long-term healthcare costs [14].

It is estimated that one-third of prostate cancer patients experience Gleason upgrading [2, 6, 15]. A medicare-based sample of 34,000 men undergoing RP in 2011 in United States reported 44% were upgraded at RP [15]. A study of 10,089 patients in the US National Cancer database from 2010 to 2012 with Gleason 3 + 4 disease showed 30% were upgraded at RP [16]. Few studies have investigated Gleason upgrading after TP biopsies. Our study demonstrated a significant difference between 24 and 33% incidence of upgrading following TP and TR biopsies, respectively. Our results are in contrast to a similar study of 431 RP specimens from Australia by Scott et al. which demonstrated no difference between TP (30%) and TR biopsy upgrading (33%) [17], but they are similar to those of Marra et al. who reported upgrading occurred in 12.7% of TP versus 19.6% of TR biopsies, although their difference was not significant [7]. Neither of these studies excluded patients with mpMRI prior to biopsy. In a registry of RP outcomes in Victoria, Australia, Evans et al. incidentally found that 28% of TP and 37% of TR biopsies were upgraded at RP (OR 0.6, 95% CI 0.5–0.8) [6], although biopsy technique was not the focus of their study and biopsy details were not reported.

An explanation for our findings is that a TP approach allows superior sampling of the anterior and apical aspects of the prostate due to the apical plane of the biopsy needle passing through the perineum [18]. It is estimated that anterior tumours constitute 20% of prostate cancers; however, anterior tumours are often missed in up to 50% of TR biopsies [3, 9, 12, 19]. In our study, 104 patients (41%) had tumour involvement in the anterior and or apical region of

the prostate at RP, 49% following TP and 36% following TR biopsy. In our sub-analysis of primary anterior tumours, TP biopsy resulted in 19% upgrading, whereas TR biopsy was upgraded in 38% of cases ($p = 0.027$).

Men with mpMRI were intentionally excluded from our study to gain an equal comparison of the biopsy techniques in patients where mpMRI is not available [20]. Prostate mpMRIs play an important role in detecting cancers, particularly small and anterior cancers [21, 22]. MRI-targeted biopsies were superior to 10–12 core TR biopsies at detecting clinically significant cancer in the PROMIS study [3]. Utilising MRI targeting has been shown to decrease the incidence of upgrading with both techniques [23–25]. However, affordable quality prostate mpMRI is not universally accessible to all patients around the globe.

The retrospective design of our study warrants caution when interpreting our findings. A randomised controlled study is ideal; however, it is unethical due to the sepsis risks of TR biopsy. Greater core numbers taken may be associated with greater morbidity; however, this was not examined in this study [3]. This study may also be impacted by the role of biopsies performed by trainees at our tertiary institution. Although all biopsies were overseen by urologists, the role of a learning curve may impact the accuracy and interpretation of biopsy results [26]. Changes in Gleason grade assignment, i.e. grade migration, possibly occurred over the duration of our data collection. To minimise this, our patients underwent RP in an average of 68 days from biopsy, and all biopsy and RP specimens were reviewed internally by our uropathologists. Patients undergoing multiple biopsies were also analysed, as those with negative TR biopsies may have subsequently undergone TP biopsy. However, from our data, of the 18/112 with multiple previous biopsies in the TP group, only three had a prior negative TR biopsy with subsequent biopsy performed due to ongoing suspicion. Prostate tumour volume was also considered for analysis; however, this was excluded due to the varied tumour volume estimation methods utilised amongst histopathology reports—this is a known contentious topic requiring ongoing study [27]. Another possibility for the histological accuracy of TP in this study was the greater number of cores taken with the TP method. Several studies have shown that increasing the number of cores beyond 10 improves cancer detection rate and concordance [28, 29], however, increasing beyond 24 cores leads to no significant improvement in histological grading [30]. We included the number of cores in our multivariable model, and biopsy method, TP versus TR, remained a predictor of upgrading when controlling for number of cores. Other novel techniques that may provide additional accuracy in sampling, such as the PrecisionPoint transperineal biopsy device, were not examined in this study. These novel approaches may be examined in future studies of biopsy technique and diagnostic accuracy [31].

Conclusion

A need for accurate biopsy histology exists in patients who do not have universal access to mpMRI. TP biopsy histology led to significantly more accurate histological grade assessment than TR biopsy in MRI-naïve patients, including those with anterior and apical tumours.

Author contributions LGQ: data collection, data analysis, manuscript writing/editing; MA: data collection; TH: data collection; NP: data analysis, manuscript writing/editing; CP: manuscript writing/editing; BK: manuscript writing/editing; AJME: data analysis, manuscript writing; NL: manuscript writing/editing; DB: manuscript writing/editing; GSJ: Protocol/project development, data analysis, manuscript writing/editing.

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Availability of data and material Data will be provided upon request.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval Ethics approval was obtained from the Austin Health Human Research Ethics Committee. This study was performed in line with the principles of the Declaration of Helsinki.

Informed consent Not applicable.

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