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ORIGINAL ARTICLE

Concordance of Gleason grading with three-dimensional ultrasound systematic biopsy and biopsy core pre-embedding

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Abstract

Purpose To determine the value of a three-dimensional (3D) greyscale transrectal ultrasound (TRUS)-guided prostate biopsy system and biopsy core pre-embedding method on concordance between Gleason scores of needle biopsies and radical prostatectomy (RP) specimens.

Methods Retrospective analysis of prostate biopsies and subsequent RP for PCa in the Jeroen Bosch Hospital, the Netherlands, from 2007 to 2016. Two cohorts were analysed: conventional 2D TRUS-guided biopsies and RP (2007–2013, $n = 266$) versus 3D TRUS-guided biopsies with pre-embedding (2013–2016, $n = 129$). The impact of 3D TRUS-guidance with pre-embedding on Gleason score (GS) concordance between biopsy and RP was evaluated using the κ-coefficient. Predictors of biopsy GS 6 upgrading were assessed using logistic regression models.

Results Gleason concordance was comparable between the two cohorts with a $\kappa = 0.44$ for the 3D cohort, compared to $\kappa = 0.42$ for the 2D cohort. 3D TRUS-guidance with pre-embedding, did not significantly affect the risk of biopsy GS 6 upgrading in univariate and multivariate analysis.

Conclusions 3D TRUS-guidance with biopsy core pre-embedding did not improve Gleason concordance. Improved detection techniques are needed for recognition of low-grade disease upgrading.

Keywords Prostatic neoplasms · Neoplasm grading · Biopsy · Prostatectomy · Three-dimensional imaging · Tissue embedding

Abbreviations

aOR	Adjusted odds ratio
BCR	Biochemical recurrence
bGS	Biopsy Gleason score
CI	Confidence interval

Anouk A. M. A. van der Aa and Christophe K. Mannaerts have contributed equally to this manuscript.

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DRE	Digital rectal examination
GS	Gleason score
IQR	Interquartile range
mpMRI	Multiparametric magnetic resonance imaging
OR	Odds ratio
PCa	Prostate cancer
pGS	Prostatectomy Gleason score
PSA	Prostate-specific antigen
RP	Radical prostatectomy
TRUS	Transrectal ultrasound
3D	Three dimensional
2D	Two dimensional

Introduction

Biopsy Gleason score (bGS) is an important prognostic tool and one of the key factors used to stratify patients with prostate cancer (PCa) into risk groups and direct clinical decision-making [1–3]. The bGS informs treatment decisions in active surveillance (AS) and radiation therapy, including eligibility for brachytherapy, need for pelvic node irradiation and use of androgen deprivation [4, 5]. It is also a key component of preoperative nomograms assessing the risk of disease recurrence and need for extended pelvic lymph node dissection in radical prostatectomy (RP) treatment [6, 7]. Accurate bGS matching the true underlying tumour pathology is, therefore, of utmost importance. Unfortunately, several studies have demonstrated poor concordance between bGS with conventional systematic two-dimensional (2D), greyscale transrectal ultrasound (TRUS)-guided biopsies and radical prostatectomy Gleason score (pGS) with Gleason score (GS) upgrading ranging from 30 to 40% [8–10]. Current data suggest that patients with PCa upgrading from bGS of 6 to a pGS of 7a do not share the same detrimental outcome (PCa death or Biochemical Recurrence) as men without upgrading [11, 12]. As a result, bGS upgrading is concerning and improved diagnostic confidence is needed as significant numbers of clinically significant PCa are not accurately identified using the conventional 2D greyscale TRUS-guided biopsy scheme. Although incorporation of PCa imaging modalities like multiparametric magnetic resonance imaging (mpMRI) and new sonographic modalities with subsequent targeted biopsies have demonstrated improved prediction of final pathology, questions remain whether there are no accessible tools to the community in the large for improved pathology concordance [13–15].

Three-dimensional (3D) TRUS-guided biopsy offers the ability to accurately register the biopsy needle tract location within the prostate allowing for a better biopsy core distribution during TRUS-guided biopsy while biopsy processing with pre-embedding methods lead to significantly larger and non-fragmentized biopsy cores [16–18]. Two studies comparing detection rates of PCa with the systematic 3D TRUS-guided biopsy and conventional 2D TRUS-guided biopsy reported contradictory results while one study demonstrated higher frequencies of PCa diagnosis with a biopsy pre-embedding method [19–21]. Their influence on accurate prediction of final pathology following prostatectomy, however, is still unclear. In the current study, we investigated the value of 3D TRUS-guidance and biopsy core pre-embedding on concordance between bGS and pGS compared to conventional 2D TRUS-guidance in a consecutive cohort of men undergoing systematic prostate biopsies and subsequent RP.

Materials and methods

Study population

Between January 2007 and February 2016, 2171 men underwent prostate biopsy at our institution with 1072 (49%) of these men positive for PCa on biopsy. We performed a retrospective cohort study containing all men ($n = 395$) who underwent both prostate biopsy and subsequent RP. Systematic biopsy with 2D greyscale TRUS-guidance and subsequent RP was performed from January 2007 up to November 2013 (2D TRUS cohort) while systematic biopsy with 3D greyscale TRUS-guidance and biopsy core pre-embedding and subsequent RP was performed from September 2013 up to February 2016 (3D TRUS cohort). Patients eligible for analysis were divided into these two cohorts. Patient files were consulted and collected data included relevant preoperative and postoperative characteristics, biopsy procedure and pathology results with no exclusion of patients. All patients had a biopsy-proven clinical diagnosis of PCa preoperatively.

Biopsy protocols

2D TRUS cohort protocol

A BK medical ultrasound machine (type 2202) and BK medical sidefire probe (type 8808, 6–10 MHz) were used. A 12-core biopsy protocol was performed consisting of 2 biopsies of each base, mid and apex in the peripheral zone on both sides. Biopsy cores were placed in two formalin-filled vials, each vial containing 6 floating free cores of one prostate lobe. Prostate cores were submitted to the hospital pathology lab for processing and examination.

3D TRUS cohort protocol

Protocol-wise the same, the 3D greyscale TRUS system (Navigo™ workstation, UC-care Medical Systems, Yokneam, Israel) was incorporated with 2D ultrasound

images transferred and displayed on the 3D screen. After prostate volume measurements, planimetry was done with the outline of the prostate border manually traced and recorded on a slice-by-slice basis where after a 3D model of the prostate was displayed (as shown in the animation Online Resource 1). The 12-core biopsy protocol was performed with tracking, displaying and recording of biopsy needle trajectory locations in real time using an electromagnetic system. Thus, the 3D system was not used to increase the biopsy core load, i.e. perform a mapping biopsy based on the real-time visual coverage of the different taken biopsy cores in the prostate gland during the biopsy procedure. Biopsy cores were processed using the semi-automated prostate biopsy core pre-embedding method (SmartBx™ device, UC-care Medical Systems, Yokneam, Israel). Biopsy cores of each sampling site (apex, mid and base on both sides) were fixed onto six different cassettes, with a designed membrane to which the cores stay attached throughout pathology lab processing, and placed in two formalin-filled vials (as shown in the animation Online Resource 2). Each vial contained the 3 cassettes with two cores of each different sampling site of one prostate lobe. Each cassette was separately processed and examined at the same hospital pathology lab.

Histopathology

Pathologic analyses of biopsies and prostatectomy specimens were all performed by pathologists at our institution. Haematoxylin–eosin (HE) staining and immunohistochemistry (IHC) with basal cell markers was performed. For biopsies, number of cores per vial, length of biopsy cores, number of positive biopsy cores and tumour volume per lobe were obtained.

All RP specimens were formalin-fixed, paraffin-embedded and cut in 3–5-mm transverse sections.

For RP, prostate weight, pT stage, pN stage and margin status were obtained. GSs were determined according to the International Society of Urological Pathology (ISUP) consensus recommendations [22, 23]. Primary Gleason pattern and highest grade Gleason pattern defined the GS for prostate needle biopsies whereas GS for RP was defined on primary and secondary Gleason patterns with tertiary pattern reported if present. The biopsy and RP specimens were originally reported by multiple pathologists at our institution. Biopsy and RP pathology reports with lacking or insufficient data considering Gleason pattern ($n = 36$) were re-reviewed by one dedicated genito-urinary pathologist (HvdL) for the purpose of this study.

Statistical analysis

Statistical analyses were performed using SPSS Statistics 23.0®. Descriptive statistics were used to summarize patient characteristics. Continuous variables were presented with median and interquartile ranges (IQR) with the Mann–Whitney *U* test used to assess differences. GS (bGS and pGS) were grouped as ≤ 6, 7a ($3 + 4 = 7$), 7b ($4 + 3 = 7$) and 8–10. In cases with multiple, GS different, tumour foci, the highest grade tumour was used for this analysis. Upgrading and downgrading were defined as an increase or decrease, respectively, from one GS group to another. Tertiary pattern on radical prostatectomy did not define a Gleason upgrade or downgrade for statistical analysis. The coefficient of agreement (κ) was used to evaluate the concordance between GS in needle biopsies and RP. The κ coefficient can range from ≤ 0 (no agreement) to 1 (excellent agreement) and measures agreement between discrete variables considering chance agreement. Candidate predictors for bGS 6 upgrading were evaluated in univariate and multivariate logistic regression analyses. A $p < 0.05$ was considered statistically significant.

Results

Between January 2007 and February 2016, 395 patients underwent prostate biopsy and subsequent RP at our institution. 266 of these patients (67.3%) underwent prostate biopsy in the 2D TRUS cohort compared to 129 patients (32.7%) in the 3D TRUS cohort.

Patient and pathological characteristics

Characteristics of both biopsy cohorts are shown in Online Resource 3. Median age at biopsy was higher in the 3D TRUS cohort (64 vs. 62 years, $p = 0.013$). Prebiopsy PSA, clinical T-stage, TRUS prostate volume, hypoechoic lesion on TRUS and EAU risk classification group did not differ significantly between both groups.

The biopsy session type and number of biopsy cores taken per session were comparable between groups, while biopsy sessions in the 3D TRUS cohort were performed more often by an experienced operator (63.6 vs. 50.8%, $p = 0.016$). Fragmentation of cores occurred less often in the 3D TRUS cohort (4.7 vs. 33.8%, $p < 0.001$), while median length of biopsy cores (16.0 vs. 12.5 mm, $p < 0.001$) and the ratio positive cores of total cores taken per session (0.36 vs. 0.33, $p = 0.005$) in the 3D TRUS cohort was higher. Gleason scores from both biopsy and RP specimens were different in both cohorts with less bGS 6 (49.6 vs. 70.7%, $p < 0.001$) and pGS 6 (33.3 vs. 46.2%, $p < 0.005$) in the 3D TRUS cohort. The interval from biopsy to RP, pathologic T-stage and surgical margin status did not differ.

Gleason score concordance

Results of Gleason score concordance in the 2D TRUS cohort and 3D TRUS cohort are illustrated in Fig. 1 and summarized in Table 1. For the 2D TRUS cohort, 64.3% had an equal GS on biopsy and RP, 30.1% had Gleason upgrading on RP and 5.6% had Gleason downgrading on RP. The results in the 3D TRUS cohort were 62.0, 27.1 and 10.9% for equal GS, Gleason upgrading on RP and Gleason downgrading on RP, respectively ($p = 0.170$). The κ for Gleason concordance were comparable between the two cohorts with a $\kappa = 0.44$ (95% CI 0.33–0.56) for the 3D TRUS cohort, compared to $\kappa = 0.42$ (95% CI 0.33–0.50) for the 2D TRUS cohort indicating moderate strength of agreement.

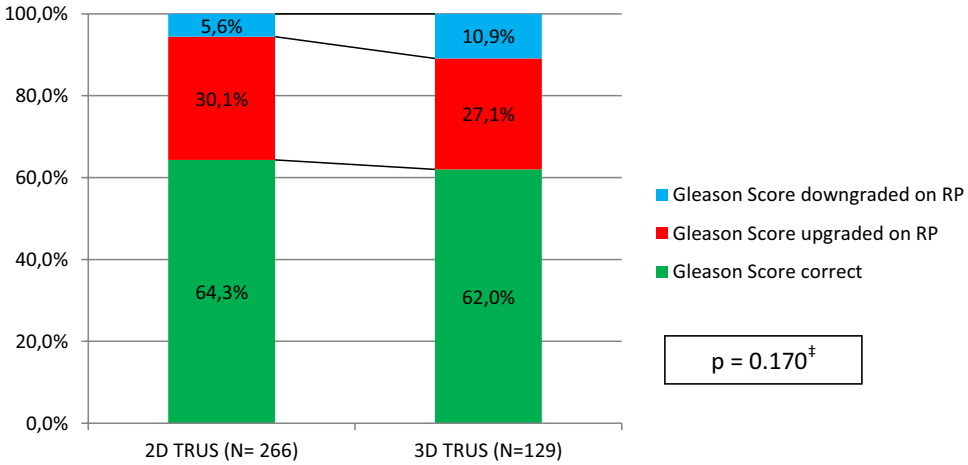

Fig. 1 Gleason score assignment between both study cohorts. Gleason assignment: percentages in the graph present Gleason assignment per category (correct, upgraded on RP, downgraded on RP). *2D* two-dimensional, *3D* three-dimensional, *TRUS* transrectal ultrasound, *RP* radical prostatectomy. Dagger, *p* value: comparison of overall Gleason assignment between both cohorts with a χ^2 test

Table 1 Gleason score concordance between biopsy Gleason score and pathology Gleason score

a. Overall concordance between bGS and pGS for the whole patient cohort					
bGS	pGS				
	6	7a	7b	8-10	Total
6, n (%)	155 (61.5)	64 (25.4)	23 (9.1)	10 (4.0)	252 (100)
7a, n (%)	6 (7.7)	57 (73.1)	12 (15.4)	3 (3.8)	78 (100)
7b, n (%)	3 (12.5)	7 (29.2)	11 (45.8)	3 (12.5)	24 (100)
8-10, n (%)	2 (4.9)	7 (17.1)	4 (9.8)	28 (68.3)	41 (100)
Total	166	135	50	44	395 **(κ = 0.44, 95% CI: 0.37-0.50)**
b. Concordance between bGS and pGS for the 3D TRUS cohort					
bGS	pGS				
	6	7a	7b	8-10	Total
6	38 (59.4)	20 (31.3)	4 (6.3)	2 (3.1)	64 (100)
7a	2 (5.3)	29 (76.3)	7 (18.4)	0	38 (100)
7b	1 (11.1)	3 (33.3)	3 (33.3)	2 (22.2)	9 (100)
8-10	2 (11.1)	5 (27.8)	1 (5.6)	10 (55.6)	18 (100)
Total	43	57	15	14	129 **(κ = 0.44, 95% CI: 0.33-0.56)**
c. Concordance between bGS and pGS for the 2D TRUS cohort					
bGS	pGS				
	6	7a	7b	8-10	Total
6	117 (62.2)	44 (23.4)	19 (10.1)	8 (4.3)	188 (100)
7a	4 (10.0)	28 (70.0)	5 (12.5)	3 (7.5)	40 (100)
7b	2 (13.3)	4 (26.7)	8 (53.3)	1 (6.7)	15 (100)
8-10	0	2 (8.7)	3 (13.0)	18 (78.3)	23 (100)
Total	123	78	35	30	266 **(κ = 0.42 , 95% CI: 0.33-0.50)**

2D two-dimensional, *3D* three-dimensional, *TRUS* transrectal ultrasound, *bGS* biopsy Gleason score, *pGS* pathology Gleason score

Colour indications: Green: GS equal between biopsy and RP, Red: GS upgrading at RP, Blue: GS downgrading at RP

Biopsy Gleason score 6 upgrading

The clinical and pathological characteristics of bGS 6 patients with and without GS upgrading are summarized in Online Resource 4. bGS 6 patients with GS upgrading were significantly older (median age in years; 65 vs. 62, $p = 0.002$), had higher prebiopsy PSA (median PSA in ng/mL; 8.9 vs. 7.4, $p = 0.001$) and more often a palpable tumour on DRE (clinical T-stage; ≥ T2; 44.8% vs. 21.4%, $p < 0.001$). 4 of 23 patients (17.4%) that met PRIAS-study AS criteria had a GS upgrading (all pGS 3 + 4 = 7). bGS 6 patients with upgrading had more positive cores per session (4.0 vs. 3.0, $p < 0.001$) while biopsy method did not differ (2D TRUS cohort: 37.8% vs. 3D TRUS cohort: 40.6%, $p = 0.685$). bGS 6 patients with GS upgrading had higher pathological T-stages (≥ pT3; 25.2 vs. 5.8%, $p < 0.001$), more often positive surgical margins (34.0 vs. 21.9%, $p = 0.035$) and more often biochemical recurrence after RP (24.7 vs. 8.2%, $p < 0.001$).

Online Resource 5 shows the effect of potential preoperative predictors for upgrading from bGS 6 to a higher pGS. On multivariate analysis higher prebiopsy serum PSA level, palpable clinical T-stage and a higher amount of total positive biopsy cores per session were associated with a higher risk of bGS 6 upgrading (PSA; aOD: 1.36 (95% CI 1.02–1.81), $p = 0.039$, clinical T-stage; aOD: 2.10 (95% CI 1.14–3.87), $p = 0.018$ and total positive biopsy cores; aOD: 1.15 (95% CI 1.02–1.29), $p = 0.020$). The biopsy method, 2D TRUS or 3D TRUS with pre-embedding, did not significantly affect the risk of bGS 6 upgrading in univariate and multivariate analyses (aOD: 1.35 (95% CI 0.63–2.92), $p = 0.444$). Further multivariate subanalyses (bGS 6 to GS 7b or higher) were not performed due to limited number of events.

Discussion

The ability to accurately register the biopsy needle tract location using 3D TRUS-guidance with pre-embedding, allowing for a presumably better biopsy core distribution and significantly larger and non-fragmentized biopsy cores did not result in better GS concordance. The κ for Gleason concordance were comparable between the two cohorts and the 3D cohort was not associated with a lower risk of bGS 6 upgrading. The Gleason concordance results of this study, with approximately 29% GS upgrading, are in line with previous published literature on this topic. It demonstrates that systematic prostate biopsy even under optimal imaging guidance and a standardized pathology processing system fails to match the true underlying tumour pathology [8, 9, 24, 25]. Quintana et al. recently demonstrated that their saturation biopsy scheme (median of 20 cores) also did not result in better final pathology prediction compared to a 12-core biopsy scheme. High Gleason grades were often missed because of anatomic locations difficult to biopsy and/or out of the systematic biopsy grid [26]. The intrinsic limitation of 2D TRUS-guided biopsy due to sampling error of common biopsy grid locations, which our 3D TRUS-guidance tends to improve with visually better biopsy core distribution, only occurred in one-third of their patients with GS upgrading. Moreover, Kim et al. demonstrated that besides sampling error, prostate tumour biology also plays an important role in GS upgrading [27]. By including only patients that underwent subsequent RP after their prostate biopsy proved PCa we do not expect that cancer maturation in the presurgical period played a role in the upgrading of bGS. Moreover, there was no significant difference in the interval from biopsy to RP in days between both cohorts. Regardless of the above-mentioned explanations, the significantly larger, non-fragmentized, biopsy core lengths in the 3D cohort neither resulted in higher concordance rates. Öbek et al. demonstrated that higher biopsy core length was associated with an increased PCa detection rate [28]. Their suggested cutoff length of greater than 11.9 mm for quality assurance, although aimed at PCa detection, could explain the absence of GS concordance improvement with our pre-embedding method. After all, the median length in the 2D cohort of 12.5 mm indicates that the majority of the conventional biopsy sessions already met the necessary biopsy length quality insurance.

In line with previous studies, higher prebiopsy serum PSA, palpable clinical T-stages and more biopsy cores with cancer were significantly associated with bGS 6 upgrading [9, 24–26] supporting the use of these variables as selection criteria for AS [5]. There are limitations to the present study. First of all, this is a single-institution, retrospective study with two cohorts that differ in study time period thereby introducing the risk of selection bias and possible time specific factors like Gleason score reclassification potentially influencing GS concordance rates. Second, biopsy and RP GSs were given by multiple pathologists. Interobserver variability and pathologist experience in Gleason grading have been documented and could have influenced GS concordance results [29, 30]. Nonetheless, all Gleason scoring was performed in one institution according to the ISUP recommendations and pathology reports with insufficient data considering Gleason pattern were re-reviewed by one dedicated genito-urinary pathologist [22, 23]. As such, our pathologic data reflect the clinical practice of most practicing urologist. Third, both cohorts differed significantly in biopsy and pathology Gleason scores with the 3D cohort containing substantially less GS 6 disease. Although this paucity of low-risk patients in the 3D cohort undergoing prostatectomy reflects the nationwide shift towards AS, it does limit comparison of both cohorts for Gleason concordance and

generalizability of the results. Fourth, biopsies were performed by operators with different levels of experience potentially influencing PCa detection results. However, for this study we did not find any association between biopsy operator experience and GS upgrading on RP. Last, tertiary pattern was not used to measure GS concordance. The tertiary pattern of the RP was reported with increasing frequency in recent years (2.6% in the 2D cohort vs. 14.7% in the 3D cohort) introducing heterogeneity when incorporating this pattern into statistical analysis. Moreover, there are no specific criteria or definitions for reporting tertiary pattern, although the presence of a higher tertiary pattern is significantly linked to unfavourable tumour features, with recent ISUP consensus paper on Gleason Grading postponing suggestions on the integration of the tertiary pattern [23, 31, 32].

Although our study did not demonstrate a differences in Gleason score concordance using 3D TRUS guidance and pre-embedding there are possible other applications for these techniques. 3D stored biopsy models of previous biopsy sessions in combination with integrated pathology biopsy core results could, for example, be used to define adequate sample sites of interest in prior negative patients and patients in active surveillance.

Our results strengthen the previously published literature on the poor concordance of systematic biopsy GS and RP GS. In view of the fact that patients with bGS 6 upgrading tend to have unfavourable disease outcome, physicians and patients need to be cognizant of these limitations so that well-informed decision-making can be made. Recognition of pre-operative variables associated with Gleason upgrading whether or not incorporated in a nomogram is a first important step [25]. PCa imaging modalities, accurately guiding biopsies to tumour-suspicious lesions, for now combined with systematic biopsy for the best concordance, however, offers greater potential and should be further adopted and refined [13–15].

Conclusion

3D greyscale TRUS-guidance with biopsy core pre-embedding did not allow for prediction of final prostate pathology with greater accuracy than that of conventional 2D TRUS-guidance and biopsy processing. Patients with upgrading of bGS 6 disease are at greater risk of adverse pathologic features and BCR emphasizing the need for recognition of low-grade disease upgrading and supporting the need for improved detection techniques.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interests.

Ethics approval The ethical committee of the Jeroen Bosch Hospital gave ethical approval for this study with a non-WMO declaration.

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