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ORIGINAL ARTICLE

Concordance Between Biopsy and Radical Prostatectomy Gleason Scores: Evaluation of Determinants in a Large-Scale Study of Patients Undergoing RARP in Belgium

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Abstract

To determine whether Gleason scores were concordant between prostate biopsies (bGS) and the definitive resection specimen (pGS) excised with robot-assisted radical prostatectomy (RARP); to identify clinical and pathological factors that might predict upgrading; and to evaluate how upgrading affected outcome. Between 2009 and 2016, 25 Belgian centers participated in collecting prospective data for patients that underwent RARP. We analyzed the concordance rate between the bGS and the pGS in 8021 patients with kappa statistics, and we compared concordance rates from different centers. We assessed the effect of several clinical and pathological factors on the concordance rate with logistic regression analysis. The concordance rate for the entire population was 62.9%. Upgrading from bGS to pGS occurred in 27.3% of patients. The number of biopsies was significantly associated with concordance. Older age (>60 y), a higher clinical T stage (≥cT2), a higher PSA value at the time of biopsy (>10 ng/ml), and more time between the biopsy and the radical prostatectomy were significantly associated with a higher risk of upgrading. Positive margins and PSA relapse occurred more frequently in upgraded patients. Center size did not significantly affect the concordance rate ($p = 0.40$).This prospective, nationwide analysis demonstrated a Gleason score concordance rate of 62.9%. Upgrading was most frequently observed in the non-concordant group. We identified clinical and pathological factors associated with (non)-concordance. Upgrading was associated with a worse oncological outcome. Center volume was not associated with pathological accuracy.

Keywords Prostate cancer · Gleason score · Concordance · Upgrading · Center size

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Introduction

Prostate cancer (Pca) is the most frequent cancer in European men and, due to prostate specific antigen (PSA) screening, it is typically discovered in earlier stages. Currently, the biopsy Gleason score (bGS), together with the clinical stage (cT) and the initial PSA value, is considered an important outcome predictor and a decisive factor for further treatment options.

The Gleason grading system, first described by Donald F Gleason in 1966, correlates with clinical behavior, thus it has prognostic value [1]. Over the years, the Gleason score (GS) has been revised, and grade groups were introduced by the International Society of Urological Pathology (ISUP) [2, 3].

In the past few years, Pca treatments have diversified extensively. Patients with high risk Pca are offered triple modality therapies. In contrast, patients with low risk Pca are typically better served with an active surveillance strategy. Thus, a correct bGS is important in making proper treatment decisions.

However, discordance is often reported between the bGS and the final pathology GS (pGS). Recent studies have reported 53–69% concordance rates [4–6]. There is a contribution of human error such as missing the tumor at biopsy (sampling error) or misreading the Gleason score (grading error) [7]. Nevertheless, upgrading to a higher bGS occurs approximately three times more often than downgrading. This suggest that different factors might play a role [8]. First, the tumor can be multifocal and heterogene [7]. In addition, several other clinical factors are known to influence the likelihood of upgrading including older age, high PSA values, large prostate volumes, high cT stage, and high levels of pathology expertise [4, 5]. A recent analysis demonstrated that a bGS of 6 was associated with elevated risk of Pca-related death in patients with high-risk Pca features [9].

In this prospective population-based study, we investigated clinical and pathological data of patients that underwent robot-assisted radical prostatectomy (RARP). We had four objectives: (*i*) to determine the concordance rate between the GS of prostate needle biopsies and the GS of radical prostatectomy specimens; (*ii*) to assess clinical and pathological factors that might predict upgrading; (*iii*) to identify the effect of upgrading on outcome; and (*iv*) to compare concordance rates of different participating centers and evaluate the effect of center size on outcome.

Methods

In October 2009, the Belgian Cancer Registry and RIZIV/INAMI invited surgeons and centers that performed RARP in Belgium to submit clinical, pathological, and follow-up data for patients that underwent RARP to obtain reimbursement from RIZIV/INAMI for disposable instruments. In response, 25 hospitals (academic, public non-academic, and private) transmitted data to the Belgian Cancer Registry that were electronically encoded by one individual (at each center), in a prospective manner. Data management conformed with strict privacy policies established by Belgian laws, under the supervision of a Cancer Registry professional (N.V.D). Data were collected for 6 years, until February 29, 2016 [10]. Random samples of clinical data were reviewed by the Belgian Cancer Registry, and accuracy was confirmed. Patients that underwent surgery in 2009 and 2016 were included in 2010 and 2015, respectively.

We excluded patients diagnosed with Pca that received a transurethral resection of the prostate or underwent neo-adjuvant therapy (androgen deprivation therapy or radiotherapy). Finally, we included 8922 patients in this study (Fig. 1).

Recorded variables for each patient included age (subdivided into <50 y, 50–60 y, and > 60 y groups), PSA value at the time of diagnosis (subdivided into <10 ng/ml, 10–20 ng/ml, and > 20 ng/ml groups), clinical TNM stage (T1c, T2, T3), date of biopsy, number of biopsies (subdivided into <8 and ≥ 8 groups), percentage of positive biopsies (subdivided into <33%, 33–66%, and > 66% groups), the bGS, date of surgery, the pGS, the pathological TNM stage, section margins, and 24-month PSA follow-up data. For the number of biopsies, we chose 8 as the cut-off value, based on the EAU guideline of 30 ml as a cutoff value for prostate volume; however, prostate volume was not included in our database [11]. Only 12.3% of patients had <8 biopsies and 1.5% had <4 biopsies; therefore, we assumed that most patients underwent systematic biopsies. The analysis of exact numbers of downgrading, concordance and upgrading was done for GS 2 till GS ≥8. For statistical analysis, the bGSs and pGSs were divided into three subgroups, according to risk stratification, as follows: 6, 7, and ≥ 8. Patients with bGS <6 and pGS <6 were included in the GS 6 group. There were no data available of the subgroups of bGS 7 (3 + 4 and 4 + 3). Because the lack of these subgroups and the fact that a major part of the data were collected before ISUP grouping was defined in 2014, we decided not to use the this grouping [3]. A PSA relapse was defined as a PSA >0.2 ng/ml after RARP. Different pathologists conducted pathology reviews of the biopsies and the final specimens.

Among the biopsy specimens, 570 (6.4%) bGS were missing. Furthermore, patients were excluded when data were missing on the year of biopsy, PSA value at the time of biopsy, cT stage, number of biopsies, and/or number of positive cores. Finally, 8021 patients were included in the statistical analyses (Fig. 1). The analyses did not include biopsy length or the percentage of tumor observed in positive biopsies, because these data were available for only 1545 (19.3%) and 3038 (37.9%) patients, respectively.

Concordance between the bGS and the pGS was calculated with the Kappa coefficient, a measure of agreement between

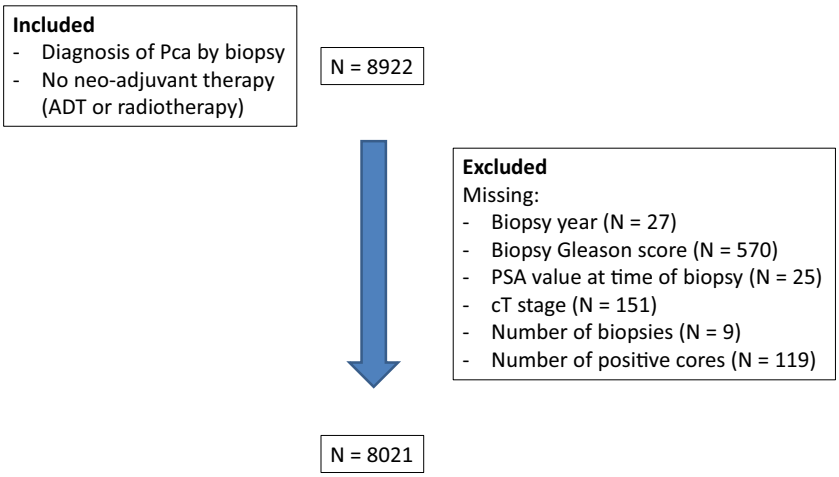

Fig. 1 Prisma flow-chart of inclusion criteria of patients

variables, which corrects for the amount of agreement expected by chance alone. Kappa coefficients were: ≤0, no agreement; 0.01–0.20, none to slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement [12]. Univariate and multivariate logistic regression analyses were performed to analyze predictors of upgrading from bGS 6 to either pGS 7 (low to intermediate grade) or pGS ≥8 (low to high grade).

Furthermore, a regression analysis was performed to assess the effect of upgrading on the risks of PSA relapse and positive margins. We compared concordance rates of the different participating centers anonymously to evaluate the effect of center size on the concordance rate. For this comparison, two centers were excluded, because <10 patients were recruited. Thus, 23 centers were included in the final analysis.

We used SAS 9.3 (SAS Institute Inc., USA) for all statistical analyses.

Results

The mean patient age was 63.3 (± 6.8) years. The mean PSA value at the time of biopsy was 9.2 ng/ml (±7.8). Most patients (74.1%) had PSA <10 ng/ml, and 5.9% had PSA >20 ng/ml. The mean number of biopsies was 11.4 (±4.2). Most patients (87.7%) underwent 8 or more biopsies; of those, 71.8% underwent at least 10 biopsies. The mean number of positive biopsies was 4 (±2.8). The clinical stages were T1c for 3576 patients (44.6%), T2 for 3937 patients (49.1%) and T3 for 503 patients (6.3%). A minority of patients had positive lymph nodes (1.1%) or metastasis (0.1%) at diagnosis. The mean delay between the prostate biopsies and the radical prostatectomy was 79.5 (± 93) days (Table 1).

The most frequent bGS was 6 (46.2%), and the most frequent pGS was 7 (51.8%). The bGS exactly matched the pGS in 5046 cases (concordance rate of 62.9%). The GS was upgraded in 2187 patients (27.3%) and downgraded in 788 patients (9.8%). Percentages of downgrading, concordance and upgrading for each bGS are given in Table 2. The kappa coefficient was 0.44, indicating moderate agreement.

Patients with <8 biopsies had significantly lower concordance rates compared to those with ≥8 biopsies (57.1% vs 61% respectively; $p = 0.020$). When comparing patients with <10 vs ≥10 biopsies, there was a significantly higher concordance rate for the second group (61.6% vs 64.5% respectively; $p = 0.025$). Concordance rates were not significantly different between the subgroup with 10–12 biopsies and the subgroup with >12 biopsies (63.9% vs 66% respectively; $p = 0.13$).

Upgrading from bGS 6 to a higher pGS occurred in 1477 patients (18.4%). Of these, 1378 patients (17.2%) were upgraded to an intermediate-grade tumor and 99 (1.2%) to a high-grade tumor. Among patients with bGS ≥8, 385 (4.8%) had a lower final pGS. Of these, 344 patients (4.3%) were downgraded to an intermediate-grade tumor and 41 (0.5%) to a low-grade tumor. Downgrading from bGS 7 to pGS 6 occurred in 358 patients (4.5%). (Table 2).

In the univariate logistic regression analysis, the risk of upgrading from bGS 6 to pGS 7 was significantly higher in older patients (>60 y), and in patients with a higher cT stage (≥cT2), a higher PSA at the time of biopsy (>10 ng/ml), a proportion of positive biopsies >66% and a longer time between the biopsy and the RARP. A higher number of biopsies (≥8) predicted a significantly higher rate of concordance. In the multivariate analysis, all of the above predictors remained significant except for the number of biopsies and the risk of upgrading when >66% of biopsies were positive (Table 3).

The regression analysis was repeated to analyze upgrading from low grade (bGS 6) to high grade tumors (pGS ≥8). These results were similar to those reported above, except that the proportion of positive biopsies had no significant effect. The number of biopsies was associated with a lower risk of upgrading in both the univariate and multivariate analyses (Table 3).

Section margins were recorded for 6393 patients; of these, 1203 (18.8%) were positive. The risk of positive margins was

Table 1 Clinical and diagnostic characteristics of the 8021patients included in this study

Characteristic	Mean (±SD)	N (%)
Age at time of biopsy (years)	63.3 (±6.8)	
PSA at time of biopsy (ng/ml)	9.2 (±7.8)	
<10		984 (12.3)
10–20		5283 (65.9)
>20		1754 (21.9)
Number of positive biopsycores	4.0 (±2.8)	
Proportion of positive biopsycores (%)		
<33		3930 (49)
33–66		2891 (36)
>66		1200 (15)
Clinical T stage		
T1c		3576 (44.6)
T2		3937 (49.1)
T3		5.3 (6.3)
T4		5 (0.06)
Clinical N stage		
N0		6266 (78.1)
N1		92 (1.1)
Missing		1663 (20.7)
Clinical M stage		
M0		6172 (76.9)
M1		12 (0.1)
Missing		1837 (22.9)
Time between prostate biopsy and RALP (days)	79.5(±93)	

significantly higher when upgrading occurred. When a bGS 6 was upgraded to pGS >7, the odds ratio (OR) for positive margins was 2.08, with a 95% confidence interval (95%CI) of 1.79–2.43 ($p < 0.0001$); and when a bGS 6 was upgraded to pGS ≥8, the OR was 1.89 (95%CI: 1.43–2.5; $p < 0.0001$).

PSA follow-up data were available for 4629 patients. Of these, during follow-up, 549 (11.9%) had a measurable PSA (>0.2 ng/ml), which indicated a relapse. Upgrading was also significantly associated with relapse in both groups: for upgrading bGS 6 to pGS >7 the relapse OR was 1.67 (95%CI: 1.27–2.17; $p = 0.0003$), and for upgrading bGS 6 to pGS ≥8, the relapse OR was 2.04 (95%CI: 1.33–3.13; $p = 0.001$).

The concordance rates of the different hospitals that provided data for this study were compared anonymously. We found that the center size did not significantly affect the

Table 2 Gleason scores from prostate biopsies in relation to Gleason scores from radical prostatectomy specimen from score 2 till ≥8. The three columns on the right side indicate the percentages of downgrading, concordance and upgrading for each bGS

	pGs	2	3	4	5	6	7	≥8	Total	Downgrading (%)	Concordance (%)	Upgrading (%)
bGs	2	0	0	0	1	2	2	0	5	0	0	100
	3	0	1	3	2	38	44	1	89	0	1.1	98.9
	4	0	0	7	5	38	81	19	150	0	4.7	95.3
	5	0	0	0	37	75	82	17	211	0	17.5	82.5
	6	4	1	5	31	2190	1378	99	3708	.1	59.1	39.8
	7	0	0	1	3	358	2220	300	2882	12.6	77	10.4
	≥8	1	0	1	1	38	591	591	976	39.4	60.6	0
	Total	5	2	17	80	2739	4151	1027	8021			

Table 3 Univariate and multivariate logistic regression analysis to evaluate different variables influencing upgrading from low grade to intermediate and high grade GS on RALP specimen

	Upgrading from bGs 6 to pGS 7		Upgrading from bGS 6 to pGS ≥ 8	
	Univariate anaysis Odds ratio (95% confidence interval), *p* value (*N* = 1587)	Multivariate analysis Odds ratio (95% confidence interval), p value	Univariate anaysis Odds ratio (95% confidence interval), p value (*N* = 136)	Multivariate analysis Odds ratio (95% confidence interval), *p* value
Age (years)	p < 0.0001	p < 0.0001	p = 0.0003	*p* = 0.0020
<50	1.0 ref	1.0 ref	1.0 ref	1.0 ref
50–60	1.14 (2.44–0.99); 0.065	1.11 (0.97–1.28); 0.12	1.30 (1.01–1.69); 0.044	1.27 (0.97–1.64);0.087
>60	1.79 (1.45–2.22); <0.001	1.67 (1.35–2.10); <0.0001	2.13 (1.47–3.03); <0.0001	1.96(1.35–2.86);0.0004
Clinical T stage	p < 0.0001	p < 0.0001	p < 0.0001	*p* < 0.0017
T1c	1.0 ref	1.0 ref	1.0 ref	1.0 ref
T2	1.45 (1.27–1.64); <0.0001	1.29 (1.14–1.47); 0.0001	1.59 (1.27–2.00); <0.0001	1.47 (1.15–1.89); 0.0022
T3	2.38 (1.52–3.85); 0.0002	1.82(1.12–2.94);0.02	3.13 (1.54–6.25); 0.002	2.44 (1.18–5.26); 0.017
PSA value at time of biopsy (ng/ml)	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001
<10	1.0 ref	1.0 ref	1.0 ref	1.0 ref
10–20	1.54(1.30–1.82); <0.0001	1.39 (1.18–1.67); 0.0001	1.64(1.20–2.17);0.001	1.45 (1.08–1.96); 0.015
>20	2.86 (1.92–4.00); <0.0001	2.5 (1.67–3.70); <0.0001	2.78(1.52–5.00); 0.0001	2.13 (1.11–4.00); 0.022
Number of biopsies	p < 0.0001	*p* < 0.0051	p < 0.0001	*p* < 0.0061
<8	1.0 ref	1.0 ref	1.0 ref	1.0 ref
≥8	0.64 (1.92–4.00); <0.0001	0.81 (0.67–1.00); 0.051	0.53 (0.38–0.74); 0.0001	0.62 (0.44–0.87); 0.006
Proportion of positive biopsies	p < 0.0001	p < 0.0001	*p* < 0.0019	*p* < 0.17
<33%	1.0 ref	1.0 ref	1.0 ref	1.0 ref
33–66%	0.65 (0.57–0.75); <0.0001	0.69(0.60–0.80);<0.0001	1.08 (0.83–1.41); 0.55	1.08 (0.81–1.43); 0.61
>66%	1.35 (1.06–1.72); <0.015	1.27 (0.98–1.61); 0.073	1.64 (1.06–2.56); 0.025	1.54 (0.98–2.38); 0.060
Time between biopsy and RP	1.49(1.16–1.92); 0.0014	1.67(1.28–2.13); <0.0001	2(1.49–2.78); <0.0001	2.04(1.49–2.78); <0.0001

concordance rate ($p = 0.40$). Interestingly, when the centers were grouped by case volumes, we observed high variability (Fig. 2). In the three volume groups, there were good and poor performers. In the low-volume group, six of 12 centers had a mean concordance rate above average. In the intermediate-volume group, three of nine centers had above average concordance rates. Finally, in the two high-volume centers, one scored below average. Thus, center volumes were not consistently associated with concordance rates.

Discussion

This prospective, nationwide Belgian database study showed moderately matched concordance rates between the bGS and pGS; exact matches were observed in 62.9% of cases (kappa 0.44). These results were similar to those published in other countries. In Europe, Rapiti et al. reported an exact match in 67% (kappa 0.42), and Kvale et al. reported an exact match in 53% of cases (kappa 0.28) [4, 5]. Our exact concordance rate was slightly better than those in similar nationwide studies conducted in the USA (55.4%; kappa 0.36) and Australia (54.5%) [13, 14].

The number of biopsies was a predictor of concordance. We confirmed that at least 10 biopsies was the most accurate cut off showing significantly better concordance with final pathology. Consequently, our results do not encourage extensive needle biopsy protocols. This is in line with the recommendation of the EAU guideline to take at least 10 biopsies in order to reduce the risk of biopsy-related complications (infection and bleeding) [11]. The only exception is prostates with a size of about 30 cc, where the advice is to take at least 8 biopsies. We could not confirm this since we had no data on prostate volume.

We confirmed the known potential predictors of upgrading, including older age, a higher PSA value at the time of biopsy, and a higher clinical stage [4, 5, 9]. Upgrading occurred more frequently, when more time had passed between the biopsy and the radical prostatectomy [4, 15]. Several studies have evaluated the effect of delaying treatment in high risk prostate

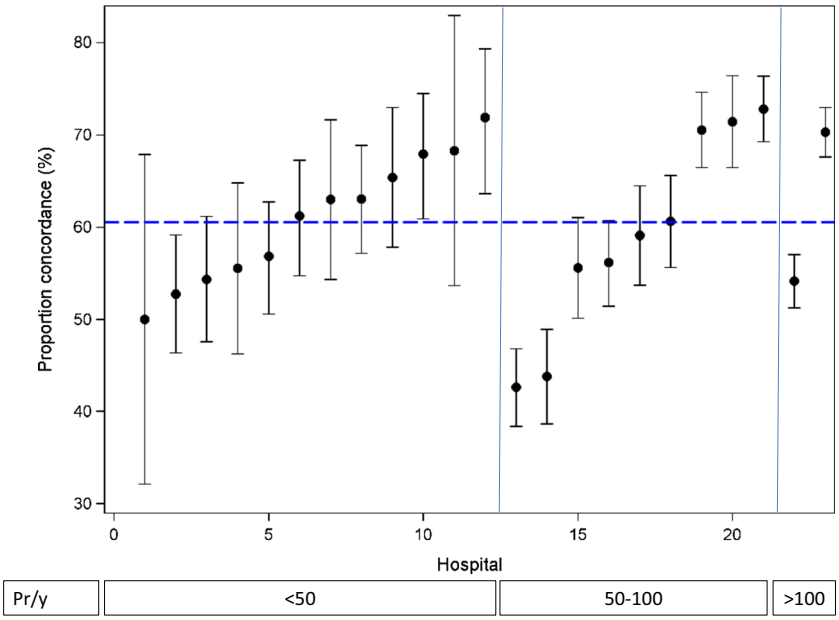

Fig. 2 Anonymous comparison of different participating centres divided by experience: <50 procedures/year, 50–100 procedures/year, >100 procedures/year. Average concordance rate is 60.5%

cancer. In 2017, Fossati et al. evaluated the outcome of 403 patients with high risk prostate cancer and concluded that radical prostatectomy could safely be postponed up till 12 months after diagnosis [16]. In 2018, Gupta et al. evaluated 1059 men with high grade localized prostate cancer who underwent radical prostatectomy at <3 vs 3–6 months after diagnosis. Median follow-up was 3 years for biochemical recurrence free survival and 4 years for metastatic free survival. They found no difference in rates of adjuvant therapy, adverse pathological outcomes (positive section margins, extraprostatic extension, seminal vesicle invasion or lymph node invasion), biochemical recurrence free survival or metastatic free survival [17]. However, there are also data concluding treatment should not be delayed. Meunier et al. stated radical prostatectomy should be performed within 60 days otherwise there was a higher risk of biochemical recurrence [18]. In general, for patients with high risk prostate cancer, delay of treatment of 3 to 6 months appears not to be associated with adverse outcomes [19]. The median time between the biopsy and surgery in our study was only 61 days (mean 79.5) suggesting that, in our population, upgrading most likely occurred because the biopsies missed the most significant tumor.

The innovative part of this study was the evaluation of a new, modifiable factor that might influence concordance: the center size. We hypothesized that center size would correlate with the concordance rate, because larger case volumes are typically associated with higher expertise. However, we observed large variability between good and poor performers; therefore, other unknown factors must have played a role in concordance rates. We think there are two potential explanations for this phenomenon. Firstly, most hospitals likely performed systematic transrectal ultrasound-guided biopsies because only 12.3% of the patients had <8 biopsies taken. Possibly, the hospitals which had higher concordance rates performed a pre-biopsy MRI and conducted cognitive or MRI guided biopsies. However, we have no detailed data on the used biopsy method so this is unknown. Ahmed et al. have proven that mpMRI can be used as a triage test in biopsy naïve patients to distinguish men who need a prostate biopsy and men who might safely avoid biopsy [20]. This was confirmed by Kasivisvanathan et al. who stated that fewer biopsy cores were needed to be obtained compared to standard transrectal ultrasonography-guided biopsy [21]. A systematic review by Van Hove et al. concluded that the combination of systematic and targeted biopsy schemes provided the highest detection rate [22]. Therefore, the EAU guidelines currently advices to perform a mpMRI before prostate biopsies in biopsy naïve men and to combine targeted and systematic biopsies [11]. Kayano et al. showed that the risk of upgrading was lower with MRI/ultrasound fusion-guided biopsies than with systematic random biopsies [23].

Secondly, a parameter for which we could not control was the experience of the pathologist who assessed the biopsies. All 25 centers had an individual pathology laboratory. We expected larger centers to have more exposure leading to higher concordance rates but large variability was seen between small and large centers. As the data analysis was anonymous and we had no ethical approval for centralized revision of the pathology samples, we cannot make conclusions about the reasons for this unexpected variation. To overcome the problem of inter-observer variability, biopsies can be re-evaluated leading to better GS prediction [24]. Pathologists can be encouraged to take continuing medical education

courses and remain informed of current ISUP guidelines. Allsbrook et al. showed that additional learning programs were the most significant demographic factor associated with correct GS interpretations [25].

Finally, upgrading was associated with higher rates of positive margins and PSA relapse. This finding indicated that GS upgrading might reflect a potentially negative influence on the oncological outcome. This hypothesis was previously proposed by Corcoran et al., who showed that, compared to GS concordance, GS upgrading was significantly associated with more aggressive tumors and a higher risk of biochemical recurrence [26].

This study's major strength was the prospective nationwide data collection in 25 centers. Thus, we included a large number of patients with complete data, minimal loss of cases, and no selection bias. Moreover, a quality check of data was conducted at the Cancer Registry with high scores. Additionally, we conducted a novel analysis of the center volume as a predictor of upgrading.

This study also had some limitations. First, the data were gathered by 25 different individuals, and there was no central pathology review of the specimens; this could have led to interobserver variability. Second, our dataset contained no data on prostate volume; therefore, we could not evaluate prostate volume or PSA density. Additionally, the bGS 7 group was not divided into subgroups (3 + 4 and 4 + 3), although they had different potential outcomes.

Conclusions

This prospective nationwide study showed 62.9% GS concordance among individuals with Pca. Patients with non-concordant GSs frequently required upgrading. We support evidence for the European guideline that recommends to take at least 10–12 biopsies rather than extended needle biopsies. We confirmed that GS upgrading was significantly predicted by age > 60 y, clinical stages ≥cT2, PSA >10 ng/ml, and long intervals between the biopsy and RARP. Upgrading increased the risks of positive section margins and PSA relapses. This study also implemented the innovative concept of analyzing center size, but center volume was not associated with pathology accuracy. We suggest that the concordance rate should be adopted as a quality indicator for centers that perform RARP.

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Compliance with Ethical Standards

Conflict of Interest None declared.

Research Involving Human Participants and/or Animals and Informed Consent Yes, involving data of humans. No experiments on humans were performed.Informed consent was obtained.

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