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Non-organ confined stage and upgrading rates in exclusive PSA high-risk prostate cancer patients

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Abstract

Background: The pathological stage of prostate cancer with high-risk prostate-specific antigen (PSA) levels, but otherwise favorable and/or intermediate risk characteristics (clinical T-stage, Gleason Grade group at biopsy [B-GGG]) is unknown. We hypothesized that a considerable proportion of such patients will exhibit clinically meaningful GGG upgrading or non-organ confined (NOC) stage at radical prostatectomy (RP).

Materials and methods: Within the Surveillance, Epidemiology, and End Results database (2010–2015) we identified RP-patients with cT1c-stage and B-GGG1, B-GGG2, or B-GGG3 and PSA 20–50 ng/ml. Rates of GGG4 or GGG5 and/or rates

of NOC stage (≥ pT3 and/or pN1) were analyzed. Subsequently, separate univariable and multivariable logistic regression models tested for predictors of NOC stage and upgrading at RP.

Results: Of 486 assessable patients, 134 (28%) exhibited B-GGG1, 209 (43%) B-GGG2, and 143 (29%) B-GGG3, respectively. The overall upgrading and NOC rates were 11% and 51% for a combined rate of upgrading and/or NOC stage of 53%. In multivariable logistic regression models predicting upgrading, only B-GGG3 was an independent predictor (odds ratio [OR]: 5.29; 95% confidence interval [CI]: 2.21–14.19; $p < 0.001$). Conversely, 33%–66% (OR: 2.36; 95% CI: 1.42–3.95; $p = 0.001$) and >66% of positive biopsy cores (OR: 4.85; 95% CI: 2.84–8.42; $p < 0.001$), as well as B-GGG2 and B-GGG3 were independent predictors for NOC stage (all $p \leq 0.001$).

Conclusions: In cT1c-stage patients with high-risk PSA baseline, but low- to intermediate risk B-GGG, the rate of upgrading to GGG4 or GGG5 is low (11%). However, NOC stage is found in the majority (51%) and can be independently predicted with percentage of positive cores at biopsy and B-GGG.

KEYWORDS

Gleason Grade group, non-organ confined stage, radical prostatectomy, upgrading, upstaging

1 | INTRODUCTION

The D'Amico risk stratification system, initially introduced by D'Amico et al. in 1998, still represents a widely accepted and used risk stratification system for patients with clinically localized prostate cancer (PCa).[1,2] Risk stratification is based on prostate-specific antigen (PSA) level, Gleason score at diagnosis and clinical tumor stage (cT).[1] Among patients that qualify as high-risk patients, some will only harbor high-risk PSA levels (>20 ng/ml) that are accompanied by low-risk clinical stage (cT1c) and low- to intermediate risk Gleason Grade group (GGG) at biopsy (GGG1, GGG2, GGG3). In those specific individuals, dose intensification or treatment assignment according to established high-risk protocols may be questioned based on its excessive intensity, when attempted treatment intensity modifications are based on unknown rates of non-organ confined (NOC) stage and/or of presence high-risk GGG (GGG4/GGG5) at radical prostatectomy (RP) in this specific PCa patient population with an unusual distribution of risk factors.[3–9] For example, in radiation therapy protocols, exemptions may be granted for lower duration of androgen deprivation therapy.[10–12] Similarly, at RP a more limited or no lymph node dissection may be contemplated. We addressed this knowledge gap and examined rates of upgrading to GGG4/GGG5 and NOC stage in this specific PCa population. Additionally, we tested for potential presurgical eligible clinical variables which were associated with upgrading to GGG4/GGG5 or NOC stage. We addressed this void by relying on a contemporary, North-American cohort of patients within the Surveillance, Epidemiology, and End Results (SEER) database (2010–2015).

2 | MATERIALS AND METHODS

2.1 | Study population

The current SEER database samples the United States population and approximates it in demographic composition and cancer incidence.[13] Within SEER database 2010–2015, we identified all patients ≥18 years old with histologically confirmed adenocarcinoma of the prostate, diagnosed at biopsy (International Classification of Disease for Oncology [ICD-O-3] code 8140 site code C61.9), as previously reported.[14] We subsequently focused on cT1c-stage patients (cN0/cM0) and GGG1, GGG2, or GGG3 at biopsy, who underwent RP. Moreover, only patients with PSA >20 and ≤50 ng/ml at diagnosis were included in further analyses. Exclusion criteria consisted of less than 10 or more than 14 biopsy cores, unknown pT-stage and unknown GGG at RP. Furthermore, cases identified only at autopsy or death certificate or with unknown histology were excluded. These selection criteria resulted in a cohort of 486 eligible patients, who represent the population of the current study cohort.

2.2 | Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Means, medians, and interquartile ranges (IQR) were reported for continuously coded variables. The Chi-square tested the statistical significance in proportions'

differences. The *t* test and Kruskal–Wallis test examined the statistical significance of means' and distributions' differences.

Statistical analyses were based on four steps. First, baseline characteristics were tabulated (GGG1 vs. GGG2 vs. GGG3). Second, rates of upgrading and NOC stage were tabulated for each subgroup specifically. Upgrading was defined as presence of GGG4 or GGG5 at RP, irrespective of the initial GGG at biopsy. NOC stage was defined as the presence of extracapsular extension (ECE; pT3a) of the tumor and/or seminal vesicle invasion (SVI; pT3b) and/or pT4 and/or pathological lymph-node invasion (LNI; pN1) at RP. Fourth, two separate multivariable logistic regression models tested for independent predictors of (a) upgrading to GGG4/GGG5 and (b) of presence of NOC stage. Covariates consisted of patient age (per year), baseline PSA (per unit ng/ml), percentage of positive cores for PCa (<33 vs. 33–66 vs. >66%), total numbers of cores obtained at biopsy and GGG at biopsy (GGG1 vs. GGG2 vs. GGG3). Finally, we tested for presence of interaction between GGG at biopsy and percentage of positive cores within each of the two separate logistic regression models.

All tests were two sided with a level of significance set at $p < 0.05$ and R software environment for statistical computing and graphics (version 3.4.3) was used for all analyses.[15]

3 | RESULTS

3.1 | Descriptive characteristics of the study population

Of 486 assessable cT1-stage patients (cN0, cM0) and solely high-risk PSA (>20 ng/ml), 134 (28%), 209 (43%) and 143 (29%) exhibited GGG1, GGG2, and GGG3 at biopsy and median age was 61 (IQR: 56–66), 60 (IQR: 54–65), 63 (IQR: 56–68) years, respectively ($p = 0.007$). Median number of positive biopsy cores was 2 (IQR: 1–5), 5 (IQR: 3–8), 6 (IQR: 4–10) and median percentages of biopsy cores positive for PCa were 17 (IQR: 8–42), 42 (IQR: 29–67), and 50 (IQR: 32–75) % for GGG1, GGG2, and GGG3, respectively (both $p < 0.001$; Table 1 and Figure 1). Stratification according to tertials of percentage of positive cores (<33 vs. 33–66 vs. 66%) resulted in three equally sized groups of 182 (37%), 130 (27%), and 174 (36%) patients, respectively. No statistically significant differences were recorded for median PSA (overall cohort: 26 ng/ml, IQR: 22–32) and total number of cores obtained at biopsy, where 12 cores were obtained in 74% of the population (both $p \geq 0.4$; Table 1). Rates of lymph node dissection were 69%, 88%, and 92% for GGG1, GGG2, and GGG3, respectively ($p < 0.001$; Table 1). Here, number of lymph node removed did not differ according to GGG at biosy. Median number of lymph node removed in the overall cohort was 6 (IQR: 3–11). Figure 2.

3.2 | Rates of upgrading from GGG1/GGG2/GGG3 at biopsy to GGG4/GGG5 at RP

Among 486 patients, rate of upgrading to GGG4 or GGG5 at RP was 11% ($n = 54$) in the overall cohort. Rates of upgrading ranged from 5% to 10% to 19% in, respectively GGG1, GGG2, and GGG3 patients ($p < 0.001$; Table 1). Of 54 patients who exhibited upgrading at RP, 41 (76%) exhibited concomitant NOC stage at RP.

3.3 | Rates of ECE, SVI, and LNI at RP

Rate of ECE was 29% ($n = 140$) in the overall cohort. Rates of ECE ranged from 16 to 33% to 35% in, respectively, GGG1, GGG2, and GGG3 patients ($p < 0.001$; Table 1). Rate of SVI was 21% ($n = 100$) in the overall cohort. Rates of SVI ranged from 9% to 21% to 31%, in respectively, GGG1, GGG2, and GGG3 patients ($p < 0.001$; Table 1). Rate of LNI was 9% ($n = 42$) in the overall cohort. Rates of LNI ranged from 4% to 10% to 12%, in respectively, GGG1, GGG2, and GGG3 patients ($p < 0.001$; Table 1).

3.4 | Rates of NOC stage and combined NOC and/or upgrading at RP

The combined rate of ECE and/or SVI and/or pT4 and/or LNI, defined as NOC stage, was 51% ($n = 247$). Rates of NOC stage ranged from 25% to 55% to 69%, in respectively, GGG1, GGG2, and GGG3 patients ($p < 0.001$; Table 1). The combination of upgrading to GGG4/GGG5 and/or NOC stage was 53% ($n = 260$). Rates of combined upgrading and/or NOC ranged from 28% to 57% to 73%, in respectively, GGG1, GGG2, and GGG3 patients ($p < 0.001$; Table 1).

3.5 | Association between clinical variables and upgrading and NOC stage

In multivariable logistic regression models of upgrading to GGG4 or GGG5, only GGG3 at biopsy was an independent predictor (odds ratio [OR]: 5.29; 95% confidence interval [CI]: 2.21–14.19; $p < 0.001$; Table 2). Conversely, in multivariable logistic regression models of NOC stage, percentage of positive cores and GGG at biopsy represented independent predictors (Table 2). Specifically, GGG2 and GGG3 at biopsy exhibited odds ratios of 2.36 (95% CI: 1.42–3.95; $p = 0.001$) and 3.95 (95% CI: 2.27–6.96; $p = 0.001$). Moreover, individuals with 33%–66% of positive cores exhibited an odds ratio of 2.37 (95% CI: 1.49–3.80; $p < 0.001$) versus 4.85 (95% CI: 2.84–8.42; $p < 0.001$) for >66% of positive cores. All other covariables failed to reach independent predictor status in multivariable logistic regression models (Table 2). Analyses testing for presence of interaction between GGG at biopsy (GGG1 vs. GGG2/GGG3) and percentage of core ratio (<33 vs. 33–66 vs. <66%) revealed insignificant results ($p = 0.8$; data not shown).

TABLE 1 Patient and clinical descriptives characteristics of cT1c-stage prostate cancer patients and GGG1/GGG2/GGG3 at biopsy with PSA >20 and ≤50 ng/ml treated radical prostatectomy within the Surveillance, Epidemiology, and End Results database (2010–2015)

	GGG at biopsy (2010–2015)				
	Overall (*n* = 486)	GGG1 (*n* = 134)	GGG2 (*n* = 209)	GGG3 (*n* = 143)	*p* value
Age in years, median (IQR)	61 (55, 66)	61 (56, 66)	60 (54, 65)	63 (56, 68)	0.007
PSA in ng/ml, median (IQR)	26 (22, 33)	26 (22, 32)	26 (23, 33)	26 (22, 33)	>0.9
Total number of cores at biopsy, *n* (%)					0.4
10	28 (5.8%)	9 (6.7%)	11 (5.3%)	8 (5.6%)	
11	11 (2.3%)	4 (3.0%)	3 (1.4%)	4 (2.8%)	
12	359 (74%)	93 (69%)	163 (78%)	103 (72%)	
13	37 (7.6%)	10 (7.5%)	16 (7.7%)	11 (7.7%)	
14	51 (10%)	18 (13%)	16 (7.7%)	17 (12%)	
Number of positive cores, median (IQR)	5.0 (2.0, 8.0)	2.0 (1.0, 5.0)	5.0 (3.0, 8.0)	6.0 (4.0, 10.0)	<0.001
Percentage of positive cores, median (IQR)	0.42 (0.17, 0.67)	0.17 (0.08, 0.42)	0.42 (0.29, 0.67)	0.50 (0.32, 0.75)	<0.001
Race/ethnicity, *n* (%)					0.008
Caucasian	292 (60%)	82 (61%)	116 (56%)	94 (66%)	
African-American	107 (22%)	22 (16%)	62 (30%)	23 (16%)	
Hispanic/Latino	57 (12%)	23 (17%)	17 (8.1%)	17 (12%)	
Asian	30 (6.2%)	7 (5.2%)	14 (6.7%)	9 (6.3%)	
Lymph node dissection, *n* (%)					<0.001
No	77 (16%)	41 (31%)	25 (12%)	11 (7.7%)	
Yes	409 (84%)	93 (69%)	184 (88%)	132 (92%)	
Number of lymph nodes removed, median (IQR)	6 (3, 11)	6 (3, 10)	6 (3, 11)	6 (3, 12)	0.6
pT-stage, *n* (%)					<0.001
pT2	244 (50%)	101 (75%)	94 (45%)	49 (34%)	
pT3a	140 (29%)	21 (16%)	69 (33%)	50 (35%)	
pT3b	100 (21%)	12 (9.0%)	44 (21%)	44 (31%)	
pT4	2 (0.4%)	0 (0%)	2 (1.0%)	0 (0%)	
pN-stage, *n* (%)					<0.001
pN0	367 (76%)	88 (66%)	164 (78%)	115 (80%)	
pN1	42 (8.6%)	5 (3.7%)	20 (9.6%)	17 (12%)	
pNx	77 (16%)	41 (31%)	25 (12%)	11 (7.7%)	
GGG at radical prostatectomy, *n* (%)					<0.001
1	70 (14%)	60 (45%)	9 (4.3%)	1 (0.7%)	
2	220 (45%)	49 (37%)	123 (59%)	48 (34%)	
3	142 (29%)	18 (13%)	57 (27%)	67 (47%)	
4	28 (5.8%)	3 (2.2%)	13 (6.2%)	12 (8.5%)	
5	26 (5.3%)	4 (3.0%)	7 (3.3%)	15 (10%)	

TABLE 1 (Continued)

	GGG at biopsy (2010–2015)				
	Overall (n = 486)	GGG1 (n = 134)	GGG2 (n = 209)	GGG3 (n = 143)	p value
Upgrading to GGG4/GGG5, n (%)	54 (11%)	7 (5.2%)	20 (9.5%)	27 (19%)	<0.001
Extracapsular extension, n (%)	140 (29%)	21 (16%)	69 (33%)	50 (35%)	<0.001
Seminal vesicles invasion, n (%)	100 (21%)	12 (9.0%)	44 (21%)	44 (31%)	<0.001
Non-organ confined (NOC) stage, n (%)	247 (51%)	34 (25%)	115 (55%)	98 (69%)	<0.001
Upgrading and/or NOC stage, n (%)	260 (53%)	37 (28%)	119 (57%)	104 (73%)	<0.001

Note: All values are medians (IQR) or frequencies (%).

Abbreviations: GGG, Gleason grade group; IQR, interquartile range; PSA, prostate-specific antigen.

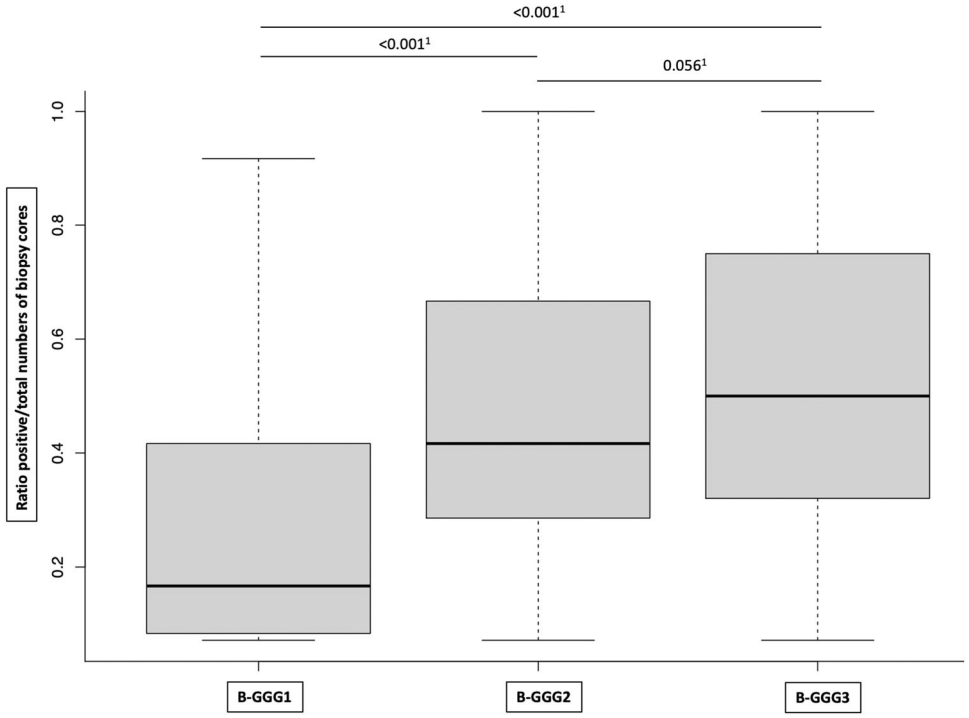

FIGURE 1 Boxplot depicting the ratio of positive cores and total numbers of cores harbored at biopsy, stratified by Gleason Grade group at biopsy (GGG1 vs. GGG2 vs. GGG3) of prostate cancer patients with cT1c-stage and PSA >20 and ≤50 ng/ml, subsequently treated with radical prostatectomy within the Surveillance, Epidemiology, and End Results database (2010–2015). GGG, Gleason grade group; PSA, prostate-specific antigen

4 | DISCUSSION

We hypothesized that a considerable proportion of PCa patients with high-risk PSA levels, but otherwise favorable stage (cT1c) and/or favorable to intermediate risk GGG at biopsy, will harbor clinical meaningful upgrading (GGG4/GGG5) or NOC stage at radical RP. Additionally, we tested for predictors of upgrading or NOC stage. We relied on a contemporary, North-American cohort of RP-patients from within the SEER database (2010–2015) and made several noteworthy findings.

First, within the current RP-PCa population, two clinical assessable variables, namely GGG1, GGG2, or GGG3 at biopsy and percentage of positive cores, emerged as potentially promising indicators of either GGG4/GGG5 or NOC stage at RP. Patients who harbored GGG4 or GGG5 instead of biopsy detected GGG1, GGG2, or GGG3, and patients with unsuspected NOC stage at original diagnosis, represent a different disease spectrum and require different treatment considerations. Regarding rates of GGG1, GGG2 and GGG3 at biopsy, relatively equal proportions within the current study population were identified, respectively, 28%, 43% and 29%, with similarly equally

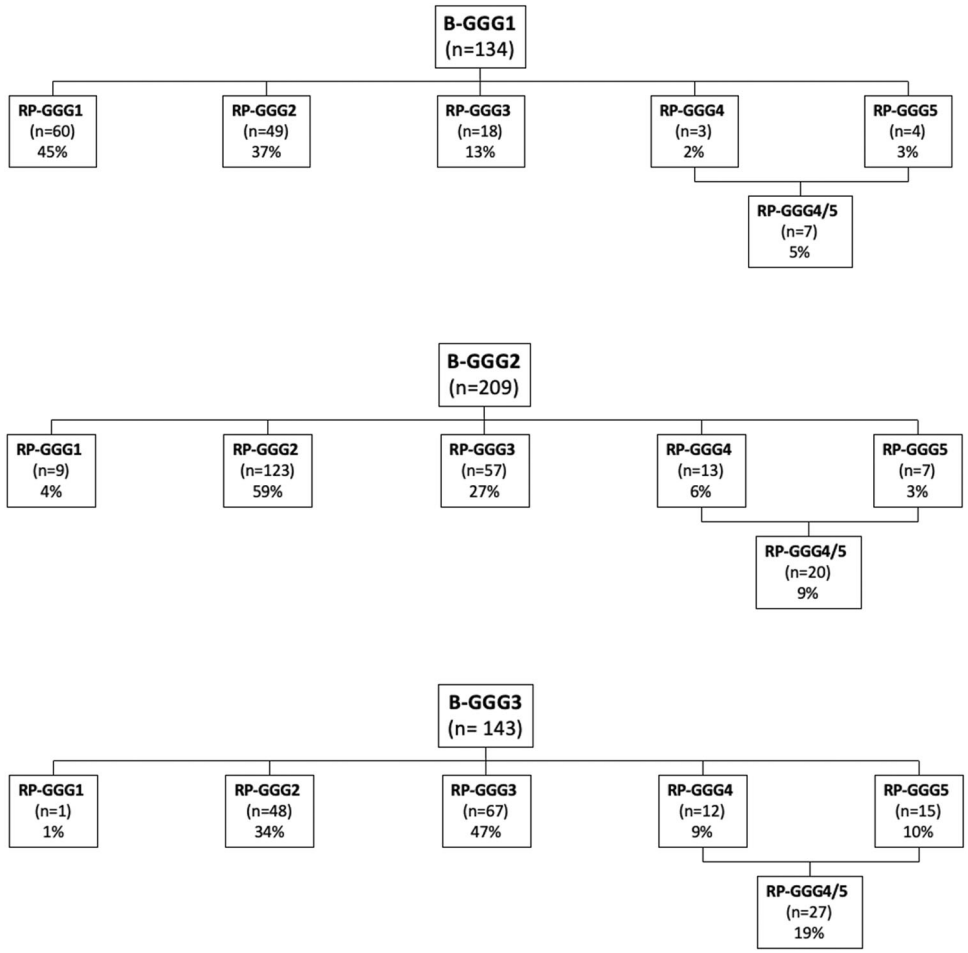

FIGURE 2 Diagrams depicting concordance and discordance rates between biopsy Gleason grade group (B-GGG) and radical prostatectomy GGG (RP-GGG), stratified by the initial B-GGG of prostate cancer patients with cT1c-stage and PSA >20 and ≤50 ng/ml, subsequently treated with radical prostatectomy within the Surveillance, Epidemiology, and End Results database (2010–2015); All values are frequencies (%). GGG, Gleason grade group; PSA, prostate-specific antigen

distributed PSA values. Besides GGG rates at biopsy, stratification of the study population according to tertials of percentage of positive cores (<33 vs. 33–66 vs. 66%), resulted in equally sized groups (37 vs. 27 vs. 26%). In consequence, observations which relied on those clinical variables, are unlikely to be biased by an unequal distribution of aforementioned variables.

Second, we identified an unexpectantly high rate of NOC stage (51%). Conversely, a minority exhibited upgrading to GGG4 or GGG5 (11%). Of patients upgraded to GGG4 or GGG5, a vast majority (76%) also exhibited a NOC stage. In consequence, it may be postulated that exclusive upgrading to GGG4 or GGG5 represents a rare event. Contrary to this, NOC affects the majority (51%). Therefore, it may be generalized that NOC stage should be considered as the endpoint of interest within the patient cohort with high-risk PSA, but favorable clinical stage and favorable to intermediate GGG at biopsy.

Third, we attempted to identify predictors of NOC stage based on GGG at biopsy and/or percentage of positive cores (Table 2). In multivariable logistic regression models, GGG2 and GGG3 as well as 33–66 and <66% of cores positive for PCa emerged as independent predictors. In consequence, patients with GGG2 and/or 33%–66% of cores positive for PCa should be considered at intermediate risk NOC stage.

These observations including rates and odds ratios may represent a useful indicator of risk stratification within this special population of interest with high-risk PSA, but favorable clinical stage and favorable to intermediate GGG at biopsy. To the best of our knowledge, this special patient population with discordant baseline risk characteristics has not been previously addressed.

Finally, rates of lymph node dissection differed significantly within the study population. Specifically, rates of lymph node dissection were 69%, 88%, and 92% for, respectively, patients with GGG1, GGG2, and GGG3 at biopsy ($p < 0.001$; Table 1). Despite the fact that the lymph node yield, defined as the number of lymph nodes resected during lymph node dissection, did not differ between GGG1, GGG2, and GGG3 patients ($p = 0.6$), it may be postulated that GGG at biopsy most likely has influenced the rate of lymph node dissections performed within the current study population. It is of interest that the extent of lymph node removal recorded (Median: 6; IQR: 3–11) in

TABLE 2 Separate multivariable logistic regression models testing for independent predictor for (a) upgrading to GGG4/GGG5 and (b) non-organ confined stage in clinical T1c-stage prostate cancer patients with PSA >20 and ≤50 ng/ml, treated radical prostatectomy within the Surveillance, Epidemiology, and End Results database (2010–2015)

	Logistic regression model predicting upgrading to GGG4/GGG5 Multivariable				Logistic regression model predicting non-organ confined stage Multivariable			
	Odds ratio	2.5%	97.5%	*p* value	Odds ratio	2.5%	97.5%	*p* value
Percentage of positive cores								
<33%	*Ref.*				*Ref.*			
33%–66%	0.82	0.41	1.64	0.58	2.37	1.49	3.80	<0.001
>66%	0.48	0.21	1.06	0.08	4.85	2.84	8.42	<0.001
GGG at biopsy								
GGG1	*Ref.*				*Ref*			
GGG2	2.34	0.97	6.31	0.07	2.36	1.42	3.95	0.001
GGG3	5.29	2.21	14.19	<0.001	3.95	2.27	6.96	0.001
Age in years	1.01	0.97	1.05	0.61	1.01	0.98	1.04	0.39
PSA in ng/ml	1.02	0.98	1.06	0.31	1.00	0.98	1.03	0.79

Abbreviations: GGG, Gleason Grade group; PSA, prostate-specific antigen.

the current study is in line with previously reports investigating the extent of lymph node dissection in intermediate and high-risk PCa patients.[16]

Taken together, patients with high-risk PSA at baseline, despite favorable clinical stage, favorable or intermediate GGG at biopsy should be expected to harbor NOC stage in the majority of scenarios. Conversely, only a small proportion of such individuals will independently harbor GGG4 or GGG5 in absence of concomitant NOC stage. In consequence from a practical perspective, NOC stage represents the rate-limiting entity in those individuals as well as the rate determining consideration in treatment planning. Furthermore, the study indicates that presence of favorable clinical stage, favorable or intermediate GGG at biopsy that is associated with high-risk baseline PSA, should not be interpreted as an overestimation of risk due to baseline PSA that is "inconsistent" with clinical stage and/or GGG at biopsy. Instead, clinicians should consider the 51% rate of NOC stage that clearly put such patients within a risk category where treatment intensifications according to D'Amico risk criteria, are required at RP, as well as radiotherapy, such as dose intensifications and/or treatment type adjustments.[3–7]

The current study is not devoid limitations. First, even though relying on a large-scaled population-based data source, namely the SEER, the current study should be interpreted under the light of a limited sample size. However, it is of note that population-based approaches, such as the current design, represent the most promising approach for addressing these hypotheses due to available data magnitude. Second, potential important differences in baseline characteristics which were not assessable within SEER, may have confounded our findings, such as imaging findings (e.g., magnetic resonance imaging), prostate-associated features (prostate volume, chronic inflammation), and potential bias arising from methodological differences in the process of specimen procurement, fixation and histopathological analyses.[17–21] Moreover, lack of central pathology review may impose a bias that could not be accounted for in the current manuscript. It is of note that this limitation is inherent to all population-based analyses.[22,23] Additionally, the SEER database does not allow to account for the percentage of tumor infiltration within a specific biopsy core. However, since this lack of information is attributable to all subgroups equally and can be seen as a non-differential bias, it is unlikely that the results between those groups were biased in a substantial manner. Finally, exact data regarding potential differences in biopsy mapping templates are not available and might demonstrate a potential bias. To minimize potential biases which are likely to arise from different biopsy templates and consequently different numbers of biopsy cores taken, we included only patients with 10–14 cores harbored at biopsy. By relying on this very strict inclusion criteria, confounding due to a heterogeneity in number of cores was reduced in the best possible approach.

5 | CONCLUSIONS

In cT1c-stage patients with high-risk PSA baseline, but low- to intermediate risk biopsy-GGG, the rate of upgrading to GGG4 or GGG5 is low (11%). However, NOC stage is found in the majority (51%) and can be independently predicted with percentage of positive cores at biopsy and GGG at biopsy.

ACKNOWLEGMENTS

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

All analyses and their reporting followed the SEER reporting guidelines. Due to the anonymously coded design of the SEER database, study-specific Institutional Review Board ethics approval was not required.

DATA AVAILABILITY STATEMENT

All data generated for this analysis were from the SEER database. The code for the analyses will be made available upon request.

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