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Research Article

Up- and downgrading in single intermediate-risk positive biopsy core prostate cancer

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ABSTRACT

Background: Up- and/or downgrading rates in single intermediate-risk positive biopsy core are unknown.
Methods: We identified single intermediate-risk (Gleason grade group (GGG) 2/GGG3) positive biopsy core prostate cancer patients ($\leq$ cT2c and PSA $\leq$ 20 ng/mL) within the Surveillance, Epidemiology, and End Results (SEER) database (2010–2015). Subsequently, separate uni- and multivariable logistic regression models tested for independent predictors of up- and downgrading.
Results: Of 1,328 assessable patients with single core positive intermediate-risk prostate cancer at biopsy, 972 (73%) harbored GGG2 versus 356 (27%) harbored GGG3. Median PSA (5.5 vs 5.7; $p = 0.3$), median age (62 vs 63 years; $p = 0.07$) and cT1-stage (77 vs 75%; $p = 0.3$) did not differ between GGG2 and GGG3 patients. Of individuals with single GGG2 positive biopsy core, 191 (20%) showed downgrading to GGG1 versus 35 (4%) upgrading to GGG4 or GGG5 at RP. Of individuals with single GGG3 positive biopsy core, 36 (10%) showed downgrading to GGG1 versus 42 (12%) significant upgrading to GGG4 or GGG5 at RP. In multivariable logistic regression models, elevated PSA (10–20 ng/mL) was an independent predictor of upgrading to GGG4/GGG5 in single GGG3 positive biopsy core patients (OR:2.89; 95%-CI: 1.31–6.11; $p = 0.007$).
Conclusion: In single GGG2 positive biopsy core patients, downgrading was four times more often recorded compared to upgrading. Conversely, in single GGG3 positive biopsy core patients, up- and downgrading rates were comparable and should be expected in one out of ten patients.
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1. Introduction

Prostate cancer (PCa) patients with single intermediate-risk positive biopsy core and without other high-risk features pose a therapeutic dilemma, since the rates of high-risk grading features at definite therapy are unknown.[1–4] More precisely, the rates of

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Gleason grade group (GGG) agreement and more or less favorable GGG at radical prostatectomy (RP) are virtually unknown in the subgroup of single GGG2 or GGG3 positive biopsy core. Exception consists of three methodologically limited and small-scaled studies that provided a potentially biased perspective of upgrading rates in single core positive patients.[5–7] To fill this current knowledge gap, we addressed this void and hypothesized that virtually all single intermediate-risk positive biopsy core patients will not harbor high-risk GGG features at RP. We tested this hypothesis in the Surveillance, Epidemiology, and End Results (SEER) database (2010–2015) and specifically tested for rates in grade agreement, up- and downgrading between biopsy versus radical prostatectomy pathology.

2. Material and methods

2.1. Study population

The current SEER database samples 34.6% of the United States population and approximates it in demographic composition and cancer incidence.[8] 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). We included all patients with a single positive core at biopsy harboring GGG2 or GGG3 who underwent RP . Exclusion criteria consisted of less than 10 or more than 14 biopsy cores, unknown prostate-specific antigen (PSA)/clinical T-stage or presence of high-risk PSA (> 20 ng/mL) or clinical T-stage features according to the National Comprehensive Cancer Network (NCCN) prostate cancer guidelines.[3] Furthermore, cases identified only at autopsy or death certificate or with unknown histology were excluded. These selection criteria resulted in a cohort of 1,328 assessable NCCN intermediate-risk PCa patients.

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 three steps. First, baseline characteristics were tabulated according to GGG2 versus GGG3 at biopsy. Second, rates of GGG agreement, up- and downgrading were tabulated. Finally, separate univariable and multivariable logistic regression models tested for independent predictors (PSA [< 10 ng/mL vs 10–20 ng/mL]; clinical T-stage [cT1 vs cT2]) for upgrading and downgrading in GGG2 versus GGG3 single core positive patients, respectively. Hereby, upgrading was defined as an increase of GGG at RP relative to GGG at biopsy and downgrading as decrease of GGG at RP relative to GGG at biopsy. Additional covariates consisted of age (per year), numbers of cores at biopsy (continuously coded) and year of diagnosis (continuously coded). 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.[9]

Table 1
Descriptive characteristics of single GGG2 or GGG3 positive biopsy core prostate cancer patients treated with radical prostatectomy within the Surveillance, Epidemiology, and End Results database (2010–2015)

	Overall, n = 1,328	GGG2, n = 972 (73.3%)	GGG3, n = 356 (26.8%)	P-value
Age in years, median (IQR)	62 (57, 66)	62 (57, 66)	63 (58, 67)	0.071
PSA in ng/mL, median (IQR)	5.6 (4.4, 7.6)	5.5 (4.4, 7.6)	5.7 (4.6, 7.4)	0.2
PSA (grouped) in ng/mL, median (IQR)				0.3
< 10	1,163 (88%)	857 (88%)	306 (86%)	
10–20	165 (12%)	115 (12%)	50 (14%)	
Year of diagnosis, n (%)				0.13
2010	226 (17%)	180 (19%)	46 (13%)	
2011	217 (16%)	162 (17%)	55 (15%)	
2012	231 (17%)	161 (17%)	70 (20%)	
2013	233 (18%)	162 (17%)	71 (20%)	
2014	203 (15%)	151 (16%)	52 (15%)	
2015	218 (16%)	156 (16%)	62 (17%)	
cT-stage, n (%)				0.4
cT1c	1,019 (77%)	753 (77%)	266 (75%)	
cT2a	105 (7.9%)	71 (7.3%)	34 (9.6%)	
cT2b	3 (0.2%)	2 (0.2%)	1 (0.3%)	
cT2c	32 (2.4%)	22 (2.3%)	10 (2.8%)	
cT2x	169 (13%)	124 (13%)	45 (13%)	
cT-stage combined, n (%)				0.3
cT1	1,019 (77%)	753 (77%)	266 (75%)	
cT2	309 (23%)	219 (23%)	90 (25%)	
Number of biopsy cores, n (%)				0.2
10	72 (5.4%)	50 (5.1%)	22 (6.2%)	
11	21 (1.6%)	13 (1.3%)	8 (2.2%)	
12	1025 (77%)	765 (79%)	260 (73%)	
13	79 (5.9%)	57 (5.9%)	22 (6.2%)	
14	131 (9.9%)	87 (9.0%)	44 (12%)	
GGG RP-specimen, n (%)				<0.001
1	227 (17%)	191 (20%)	36 (10%)	
2	744 (56%)	616 (63%)	128 (36%)	
3	280 (21%)	130 (13%)	150 (42%)	
4	52 (3.9%)	27 (2.8%)	25 (7.0%)	
5	25 (1.9%)	8 (0.8%)	17 (4.8%)	

Abbreviations: GGG = Gleason Grade Group; PSA= Prostate-specific antigen; RP = Radical prostatectomy; IQR= Interquartile range

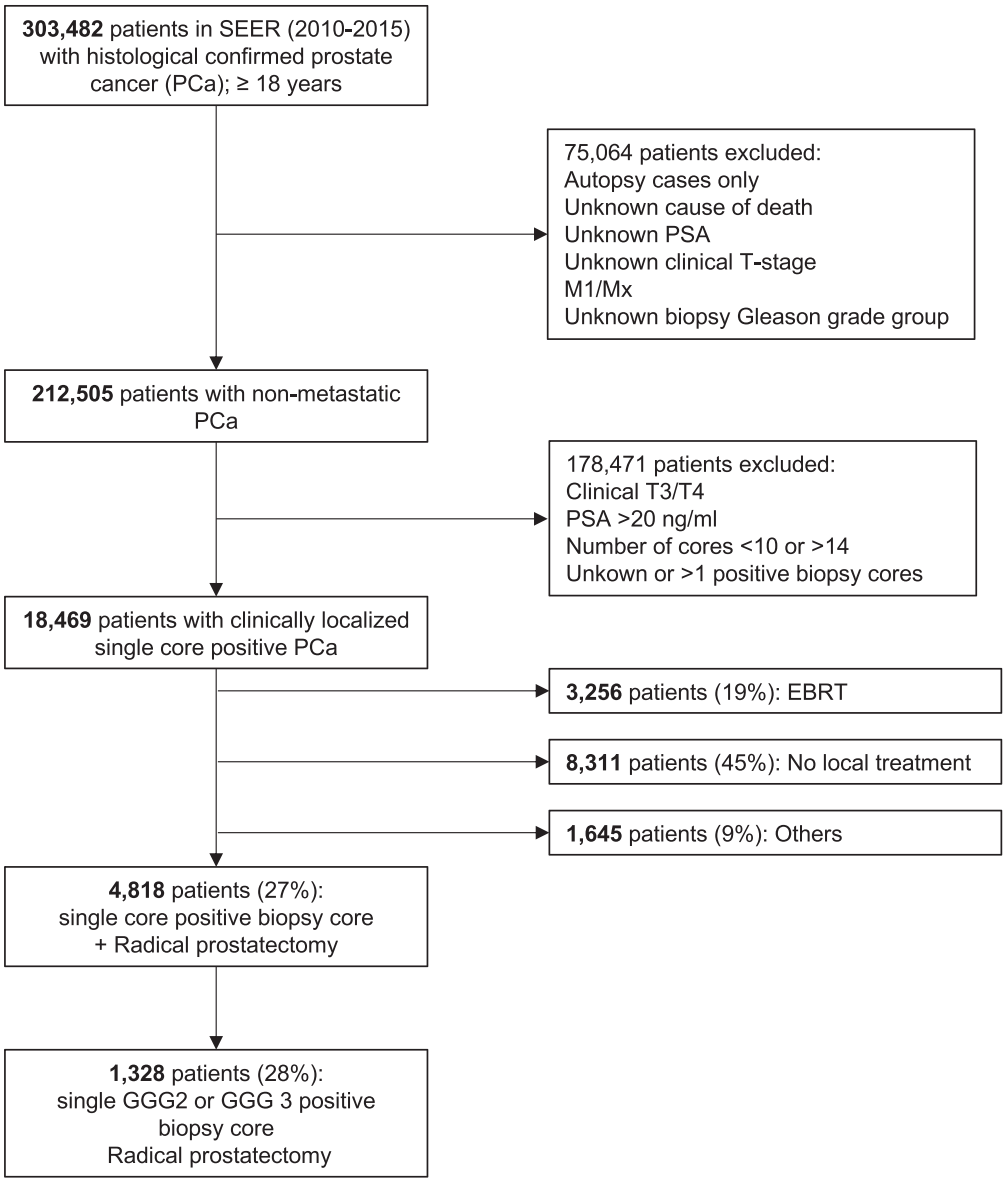

Fig. 1. Consort diagram depicting patients' selection criteria within the Surveillance, Epidemiology, and End Results database (2010–2015). Abbreviations: EBRT = External beam radiotherapy; PCa = Prostate cancer; RP = Radical prostatectomy; GGG = Gleason grade group; SEER = Surveillance, epidemiology, and end results; PSA = Prostate-specific antigen

3. Results

3.1. Descriptive characteristics of the study population

Between 2010 -2015, we identified 1328 assessable NCCN intermediate-risk PCa patients with a single positive core of GGG2 or GGG3 at biopsy (Table 1 and Fig. 1). Of those, 972 (73.3%) harbored GGG2 at biopsy, whereas 356 (26.8%) GGG3, respectively. Median age was 62 (IQR: 57–66) versus 63 years (IQR: 58–67) and median PSA was 5.5 (IQR: 4.4–7.6) versus 5.7 ng/mL (IQR: 4.6–7.4) for GGG2 versus GGG3 patients, respectively (both $p > 0.05$). Median number of cores was 12 (IQR: 12–12) and did not differ between both groups. At RP-specimen, GGG1 was 20 versus 10%, GGG2 63 versus 36%, GGG3 13 versus 42%, GGG4 3 versus 7% and GGG5 1 versus 5% for GGG2 versus GGG3 at biopsy, respectively ($p < 0.001$).

3.2. Rates of up- and downgrading in single GGG2 positive biopsy core PCa patients

Of 972 patients with single GGG2 positive core at biopsy, 616 patients (63%) also exhibited GGG2 versus 191 (20%) GGG1 at RP. Of GGG2 patients, 165 (17%) exhibited higher GGG at RP: 130 GGG3 (13%) versus 27 GGG4 (3%) versus 8 GGG5 (1%) patients at RP, respectively (Fig. 2a).

3.3. Rates of up- and downgrading in single GGG3 positive biopsy core PCa patients

Of 356 patients with single GGG3 positive core at biopsy, 150 patients (42%) also exhibited GGG3 versus 128 GGG2 (36%) versus 36 GGG1 (10%) at RP. Of GGG3 patients, 42 (12%) exhibited higher GGG at RP: 25 GGG4 (7%) versus 17 GGG5 (5%) patients at RP, respectively (Fig. 2b).

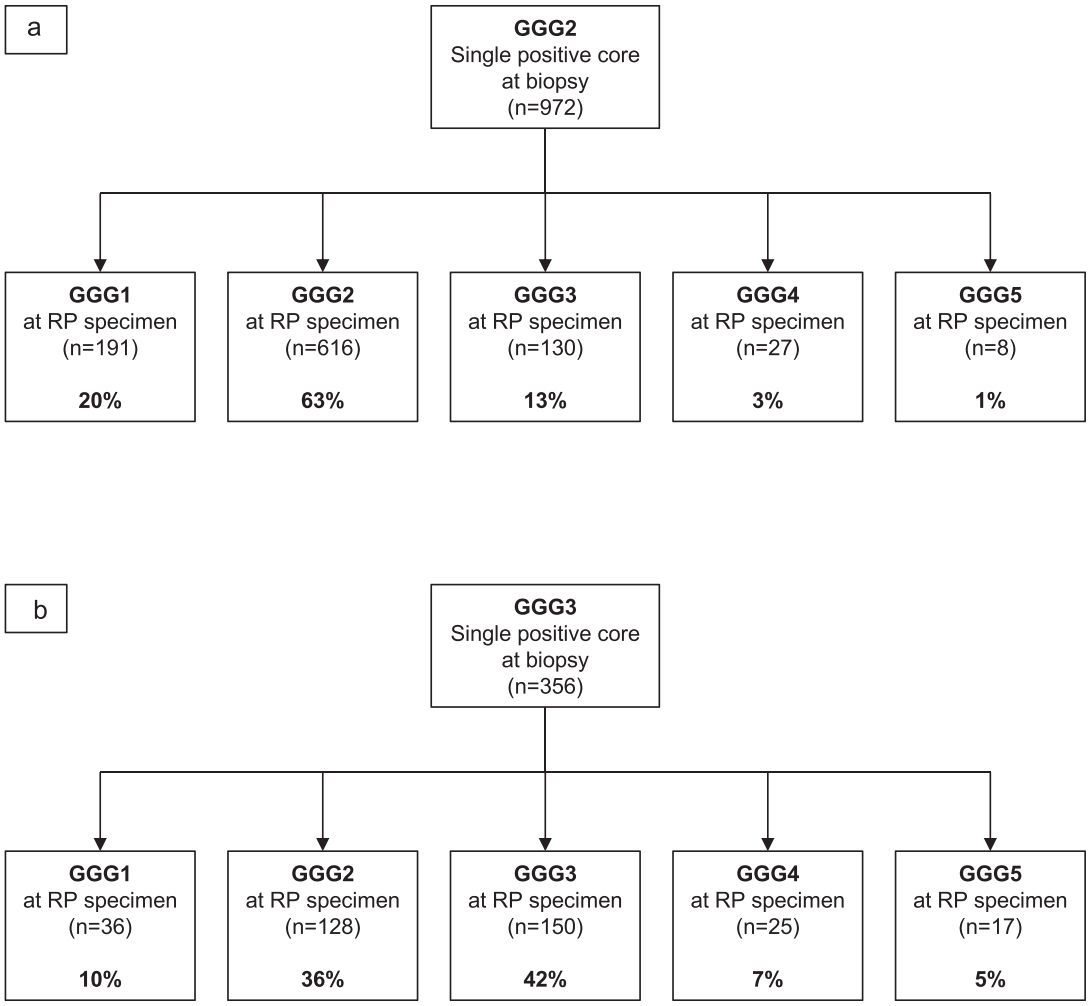

Fig. 2. Flow-diagram depicting Gleason grade group agreement and disagreement in intermediate-risk prostate cancer patients (≤ cT2 and PSA ≤ 20 ng/mL) treated with radical prostatectomy following (a) single GGG2 positive core at biopsy and (b) single GGG3 positive core at biopsy. Abbreviations: GGG = Gleason grade group; RP = Radical prostatectomy

3.4. Effect of clinical variables on changes in GGG pattern in RP-specimen

In uni- and multivariable logistic regression models predicting downgrading in GGG2 patients, age was a modest, independent predictor of downgrading (multivariable OR:0.94; 95%-CI: 0.93–0.97; $p < 0.001$). Other covariates failed to reach independent predictor status for up- or downgrading in GGG2 (Table 2).

Conversely, in uni- and multivariable logistic regression models predicting upgrading in GGG3, PSA of 10-20 ng/mL was an independent, strong risk factor for upgrading in GGG RP-specimen in both uni- and multivariable logistic regression models (multivariable OR:2.89; 95%-CI: 1.31–6.11; $p = 0.007$). Furthermore, year of diagnosis was an independent predictor for downgrading in GGG3 in both univariable and multivariable logistic regression models (multivariable OR: 0.78; 95%-CI: 0.62–0.97; $p = 0.03$). Other covariates failed to reach independent predictor status for up- or downgrading in GGG3 (Table 3).

4. Discussion

The rates of upgrading, grade agreement and downgrading between Gleason Grade groups at biopsy versus RP in PCa patients with a single intermediate-risk (GGG2 or GGG3) positive biopsy core are unknown. We hypothesized that virtually all such patients will harbor the same or lower GGG at RP. We tested this hypothesis in two specific cohorts, namely single GGG2 positive core versus single GGG3 positive core at biopsy, respectively. We relied on SEER database (2010–2015) and made some noteworthy findings.

First, the overall number of individuals with clinically localized, intermediate-risk prostate cancer (≤ cT2c and PSA ≤ 20 ng/mL) and single positive core at biopsy was substantial ($n = 18{,}469$) in the study population between 2010 and 2015. Of those, 4,818 (27%) patients underwent RP as active treatment choice. Interestingly, among those patients who underwent RP, GGG2 or GGG3 was present as a single positive core at biopsy in 28% of the cases (Fig. 1). In consequence, the combination of a single intermediate-risk positive core at biopsy with lack of further high-risk features in PCa patients does not represent a rare entity and is of high importance, since the appropriate treatment choice among those specific patient group is still an ongoing debate.[10–12]

Second, we did not identify either statistically significant or clinically meaningful differences in baseline prostate cancer characteristics between single GGG2 positive biopsy core and GGG3 in intermediate-risk patients, respectively. In consequence, other prostate cancer characteristics are not helpful in distinguishing between these two specific patients' groups.

Table 2
Separate univariable and multivariable logistic regression models testing for independent predictors for down and upgrading in single GGG2 positive core at biopsy in prostate cancer patients treated with radical prostatectomy within the surveillance, epidemiology, and end results (SEER) database (2010–2015)

	Downgrading to GGG1								Upgrading to GGG4/GGG5							
	Univariable				Multivariable				Univariable				Multivariable			
	Odds Ratio	2.5%	97.5%	*P*-value	Odds Ratio	2.5%	97.5%	*P*-value	Odds Ratio	2.5%	97.5%	*P*-value	Odds Ratio	2.5%	97.5%	*P*-value
PSA < 10 ng/mL	*Ref.*				*Ref.*				*Ref.*				*Ref.*			
PSA 10–20 ng/mL	0.49	0.26	0.86	0.02	0.60	0.31	1.08	0.11	2.30	0.95	4.97	0.045	2.12	0.86	4.72	0.08
Numbers of biopsy cores	0.89	0.72	1.09	0.25	0.90	0.73	1.11	0.33	1.19	0.78	1.79	0.41	1.16	0.76	1.74	0.49
cT1c-stage	*Ref.*				*Ref.*				*Ref.*				*Ref.*			
cT2-stage	1.16	0.79	1.66	0.44	1.23	0.84	1.79	0.28	1.39	0.63	2.86	0.39	1.40	0.63	2.91	0.38
Age	0.95	0.92	0.97	< 0.001	0.94	0.93	0.97	< 0.001	1.03	0.98	1.09	0.22	1.02	0.97	1.08	0.44
Year of diagnosis	0.91	0.83	0.99	0.04	0.92	0.84	1.01	0.08	1.10	0.90	1.34	0.36	1.08	0.88	1.32	0.47

Abbreviations: PSA= Prostate-specific antigen

Table 3
Separate univariable and multivariable logistic regression models testing for independent predictors for down and upgrading in single GGG3 positive core at biopsy in prostate cancer patients treated with radical prostatectomy within the surveillance, epidemiology, and end results (SEER) database (2010–2015)

	Downgrading to GGG1								Upgrading to GGG4/GGG5							
	Univariable				Multivariable				Univariable				Multivariable			
	Odds Ratio	2.5%	97.5%	*P*-value	Odds Ratio	2.5%	97.5%	*P*-value	Odds Ratio	2.5%	97.5%	*P*-value	Odds Ratio	2.5%	97.5%	*P*-value
PSA < 10 ng/mL	*Ref.*				*Ref.*				*Ref.*				*Ref.*			
PSA 10–20 ng/mL	0.33	0.05	1.15	0.14	0.39	0.06	1.36	0.21	3.36	1.57	6.93	0.001	2.89	1.31	6.11	0.007
Numbers of biopsy cores	0.83	0.56	1.22	0.34	0.86	0.58	1.28	0.47	0.94	0.65	1.35	0.73	0.94	0.64	1.36	0.74
cT1c-stage	*Ref.*				*Ref.*				*Ref.*				*Ref.*			
cT2-stage	0.98	0.42	2.11	0.97	1.05	0.44	2.31	0.90	0.67	0.28	1.43	0.33	0.64	0.26	1.44	0.31
Age	0.99	0.94	1.04	0.55	0.99	0.94	1.05	0.77	1.06	1.01	1.11	0.03	1.04	0.99	1.10	0.10
Year of diagnosis	0.76	0.61	0.95	0.02	0.78	0.62	0.97	0.03	1.25	1.03	1.55	0.03	1.21	0.99	1.51	0.07

Abbreviations: PSA= Prostate-specific antigen

Third, in single GGG2 positive biopsy core patients, only 4% harbored high-risk GGG features at RP (GGG4: 3% vs GGG5: 1%). In those patients, the presence of GGG4 or GGG5 at RP would virtually invariably imply treatment modifications. In EBRT candidates, administration of ADT of long duration would be recommended, in RP candidates, an extended lymphadenectomy should invariably be considered.[13,14] Additionally, a small proportion harbored GGG3 at RP (13%). In those individuals, fewer treatment applications would be applicable. Nonetheless, ADT treatment of short duration and extended pelvic lymph node dissection might also be required.[13,15–19] Moreover, the vast majority (63%) of GGG2 patients exhibited a GGG agreement at RP. Interestingly, an intermediate sized-group (20%) exhibited GGG1 at RP, where conservative management could have been applied in regards to GGG risk factor.[20–22] Taken together, in single GGG2 positive biopsy core patients, very few individuals with significantly more aggressive GGG were identified. Nonetheless, an intermediate proportion of individuals with favorable grade were identified. In consequence, it may be argued that definite treatment in single GGG2 positive biopsy core patients will at least overtreat 20% of such individuals based on GGG1 features.

Fourth, trends in single GGG3 positive biopsy core patients significantly differed from those in GGG2 patients. In 12% of GGG3 patients, final RP pathology revealed the presence of GGG4 (7%) or GGG5 (5%), demonstrating a clinically meaningful upgrading to high-risk grade features. Changes in treatment modalities which were previously extrapolated for upgrading in GGG2 patients, account equally for GGG3 patients. It is of note that elevated PSA at diagnosis (> 10 ng/mL) was a strong risk factor in multivariable logistic regression models predicting upgrading in single GGG3 positive biopsy core patients (OR: 2.89). As a consequence, preoperative PSA independently predicted upgrading in GGG3 and should be considered of utmost importance in treatment decision making, within this specific subgroup of single GGG3 positive biopsy core patients. Furthermore, grade agreement in GGG3 patients was present in 42% patients. Interestingly in single GGG3 positive biopsy core, a smaller, yet considerably sized group of 36% patients exhibited GGG2 features in RP pathology. Moreover, a fairly small proportion (10%) of GGG3 patients exhibited GGG1 at final RP pathology. Consequently, overtreatment in single GGG3 positive biopsy core patients may have occurred based on grade downgrading in at least one out of ten patients.

The current study is not devoid of limitations. First, it reflects the selection bias inherent in a surgical cohort. Second, despite extensive multivariable adjustments, we were unable to adjust for potential important baseline characteristics not recorded in SEER, such as imaging findings (e.g., MRI), PSA density, family history, and potential bias arising from methodological differences in the process of specimen procurement, fixation, and histopathological analyses.[23–26] These limitations apply to both the biopsy and RP specimen equally. It is of note that this limitation is inherent to other population-based databases.[27] Finally, exact data regarding potential differences in biopsy mapping templates are not available and might demonstrate a bias. To minimize potential biases that are likely to arise from different biopsy templates and consequently different numbers of biopsy cores taken, we included only patients with ten to fourteen 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 single core positive GGG2 patients, a marginal fraction will exhibit high-risk GGG at RP. The vast majority will exhibit the same GGG and a minority will harbor GGG1 at RP. Conversely, in single core positive GGG3 patients, the majority will harbor lower GGG at RP. An equally sized group will harbor the same GGG and a minority will harbor high-risk GGG4 and GGG5 at RP. In the future, large-scale studies are needed to confirm these findings in the context of MRI-guided single intermediate-risk positive biopsy core.

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.

Ethics consent 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's ethics approval was not required.

Funding statement

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Patient consent statement, permission to reproduce material from other sources and clinical trial registration

Not applicable

Conflicts of interest

The authors declare that there is no conflict of interests.

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