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Grade and stage misclassification in intermediate unfavorable-risk prostate cancer radiotherapy candidates

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Abstract

Background: We tested for upgrading (Gleason grade group [GGG] ≥ 4) and/or upstaging to non-organ-confined stage ([NOC] ≥ pT3/pN1) in intermediate unfavorable-risk (IU) prostate cancer (PCa) patients treated with radical prostatectomy, since both change the considerations for dose and/or type of radiotherapy (RT) and duration of androgen deprivation therapy (ADT).

Methods: We relied on Surveillance, Epidemiology, and End Results (2010–2015). Proportions of (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging were tabulated and tested in multivariable logistic regression models.

Results: We identified 7269 IU PCa patients. Upgrading was recorded in 479 (6.6%) and upstaging in 2398 (33.0%), for a total of 2616 (36.0%) upgraded and/or upstaged patients, who no longer fulfilled the IU grade and stage definition. Prostate-specific antigen, clinical stage, biopsy GGG, and percentage of positive cores, neither individually nor in multivariable logistic regression models, discriminated between upgraded and/or upstaged patients versus others.

Conclusions: IU PCa patients showed very high (36%) upgrading and/or upstaging proportion. Interestingly, the overwhelming majority of those were upstaged to NOC. Conversely, very few were upgraded to GGG ≥ 4. In consequence, more than one-third of IU PCa patients treated with RT may be exposed to suboptimal dose and/or type of RT and to insufficient duration of ADT, since their true grade and stage corresponded to high-risk PCa definition, instead of IU PCa. Data about magnetic resonance imaging were not available but may potentially help with better stage discrimination.

KEYWORDS
MRI, pathology, prostate biopsy, prostatectomy, PSA, risk stratification

1 | INTRODUCTION

Approximately 50% of patients with clinical intermediate unfavorable-risk (IU) prostate cancer (PCa) undergo radiotherapy (RT).[1,2] IU-risk PCa patients represent a broad category with heterogeneous combination of tumor characteristics. Among those, some invariably will harbor higher pathological grade and/or stage than identified at initial diagnosis, as reported within a historical and smaller cohort by Zumsteg et al.[3] Such patients may be exposed to suboptimal dose and/or type of RT and insufficient duration of androgen deprivation therapy (ADT), since their true grade and stage correspond to high-risk PCa definition, instead of IU PCa. This undertreatment may subsequently affect negatively oncological outcome of IU PCa. In that regard, Keane et al. reported a cancer-specific mortality in IU which was very similar to that of high-risk PCa patients, that may be attributed to those who harbored occult higher grade and/or stage.[4] Some studies reported on upgrading and/or upstaging, but mostly for active surveillance consideration in low and favorable intermediate-risk PCa.[5–8] Conversely, Martin et al. in a smaller and historical cohort of IU PCa tested for upgrading but omitted upstaging.[9] To address this void, we tested the proportion of (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging within a large contemporary population-based cohort. We hypothesized that contemporary IU PCa patients may exhibit very low upgrading and/or upstaging proportions. To address this hypothesis, we relied on Surveillance, Epidemiology, and End Results (SEER) database (2010–2015) and made several noteworthy observations.

2 | MATERIALS AND METHODS

2.1 | Study population

Within SEER database (2010–2015), we identified patients from 40 to 80 years old with histologically confirmed and clinically localized adenocarcinoma of the prostate diagnosed at biopsy (International Classification of Disease for Oncology [ICD-O-3] code 8140 site code C61.9) who fulfill IU-risk criteria, according to National Comprehensive Cancer Network (NCCN) stratification, treated with radical prostatectomy (RP). Patients with IU-risk PCa were defined according to the presence of GGG3 or percentage of positive cores >50% or multiple intermediate-risk factors (cT2b-c, prostate-specific antigen [PSA] 10–20 ng/ml, GGG 2 or 3) with no high-risk features (cT3, PSA > 20.0 ng/ml, GGG > 3). Exclusion criteria consisted of cases identified only at autopsy or death certificate, less than 10 or more than 14 biopsy cores, unknown PSA or clinical or pathological T stage or Gleason grade group (GGG), or unknown total number of cores or number of positive cores. These selection criteria resulted in a cohort of 7269 assessable patients (Figure 1).

2.2 | Statistical analyses

Statistical analyses consisted of two steps. First, we tabulated proportions of (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging. Hereby, upgrading was defined as GGG ≥ 4 at RP. Upstaging was defined as presence of non-organ-confined stage (NOC) (≥pT3/pN1) stage at RP. Second, multivariable logistic regression models (MVA) were fitted to test for independent predictors of (a) upgrading, (b) upstaging, or (c) upgrading

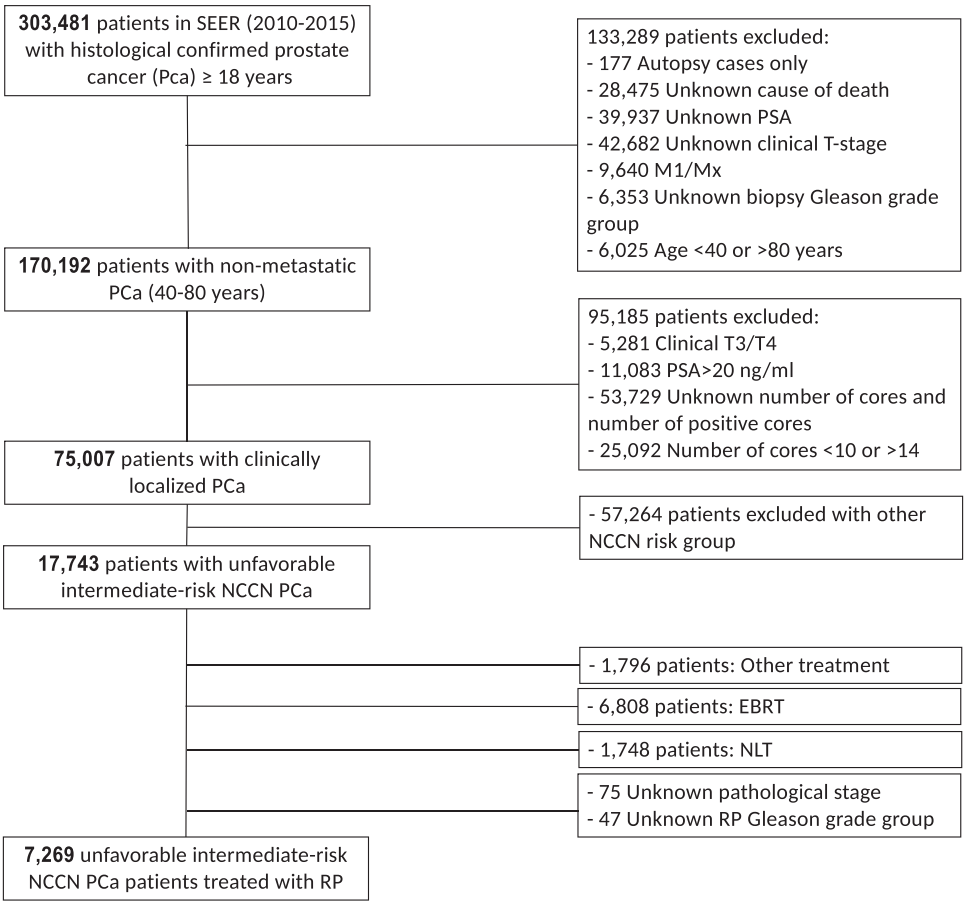

FIGURE 1 Patient selection flowchart. NCCN, National Comprehensive Cancer Network; RP, radical prostatectomy

and/or upstaging. MVA variables consisted of GGG at biopsy (GGG1 vs. GGG2 vs. GGG3), clinical T stage (T1c vs. T2), percentage of positive cores (<25 vs. 25.1–50 vs. >50%), PSA (≤5 vs. 5.1–10 vs. 10.1–20 ng/ml) and patient age (years). The ability of the MVA to predict (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging was quantified using the area under receiver operating characteristics (ROCs)-derived area under the curve (AUC). 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 4.1.1) was used for all analyses.

3 | RESULTS

3.1 | Descriptive characteristics of the study population

Between 2010 and 2015, we identified 7269 assessable NCCN IU PCa patients treated with RP (Figure 1). Median age was 62 (interquartile range [IQR]: 57–66), and median PSA was 6.3 (IQR: 4.9–8.8). At biopsy, 411 (5.7%), 3347 (46.0%), and 3511 (48.3%) harbored respectively, GGG1, GGG2, and GGG3. Median percentage of positive cores was 50% (IQR: 42–67) and 5502 (75.7%) had clinical T1c stage (Table 1).

3.1.1 | Proportions of (a) upgrading to GGG ≥ 4, (b) upstaging to NOC disease, or (c) upgrading and/or upstaging at RP

Of 7269 IU PCa patients, 479 (6.6%) exhibited upgrading at RP (Figure 2). Of those, 296 (4.1%) harbored GGG4 and 183 (2.5%) harbored GGG5. Of 7269 IU PCa patients, 2398 (33.0%) independently harbored NOC disease. Specifically, 2351 (32.3%) exhibited higher pathological stage at RP: pT3a 1746 (24.0%), pT3b 589 (8.1%), pT4 16 (0.2%). Furthermore, among those with NOC 204 (2.8%) harbored pN1 stage. In the entire cohort of 7269, combined proportion of upgrading and/or upstaging was identified in 2616 (36.0%).

3.1.2 | Proportions of (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging according to PSA categories, clinical T stage, GGG, and percentage of positive cores

Stratification of (a) upgrading according to clinical characteristics, showed increased proportions with higher PSA categories, higher clinical T stage, and higher GGG, but not with higher percentage of positive cores. Stratification of (b) upstaging according to clinical

TABLE 1 Clinical characteristics of 7269 assessable intermediate unfavorable-risk prostate cancer patients treated with radical prostatectomy

Variables	Intermediate unfavorable-risk, *N* = 7269
Age at diagnosis	62 (57, 66)
Positive cores	6.0 (5.0, 8.0)
Percentage of positive cores	50 (42, 67)
PSA (ng/ml)	6.3 (4.9, 8.8)
PSA range (ng/ml)	
0–5	2038 (28.0%)
5.1–10	3872 (53.3%)
10.1–20	1359 (18.7%)
GGG at Bx	
GGG1	411 (5.7%)
GGG2	3347 (46.0%)
GGG3	3511 (48.3%)
Clinical T stage	
T1c	5502 (75.7%)
T2	1767 (24.3%)
GGG at RP	
GGG1	603 (8.3%)
GGG2	4123 (56.7%)
GGG3	2064 (28.4%)
GGG4	296 (4.1%)
GGG5	183 (2.5%)
pT stage	
pT2	4918 (67.7%)
pT3a	1746 (24.0%)
pT3b	589 (8.1%)
pT4	16 (0.2%)
pN stage	
pN0	4955 (68.2%)
pN1	204 (2.8%)
pNX	2110 (29.0%)

Note: Median (interquartile range); *n* (%).

Abbreviations: Bx, biopsy; GGG, Gleason grade group; PSA, prostate-specific antigen; RP, radical prostatectomy.

characteristics, showed increased proportions with higher PSA categories, higher clinical T stage, higher GGG, and higher percentage of positive cores. Stratification of (c) upgrading and/or upstaging according to clinical characteristics, also showed increased proportions with higher PSA categories, higher clinical T stage, higher GGG, and higher percentage of positive cores (Table 2).

3.1.3 | Proportions of (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging according to combined effect of PSA categories and GGG, percentage of positive cores and PSA categories, GGG, and percentage of positive cores

The same relationship persisted when further stratification according to PSA categories versus GGG, percentage of positive cores versus PSA categories, and GGG versus percentage of positive cores was applied to (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging (Table 3).

3.1.4 | Clinical characteristics associated with absence versus presence of (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging at RP

Relative to patients without upgrading, patients with (a) upgrading exhibited higher PSA, higher clinical T stage, and higher GGG, but not higher percentage of positive cores. Relative to patients without upstaging, patients with (b) upstaging exhibited higher PSA, higher percentage of positive cores, higher clinical T stage, and higher GGG. Relative to patients without upgrading and/or upstaging, patients with (c) upgrading and/or upstaging exhibited also higher PSA, higher percentage of positive cores, higher clinical T stage, and higher GGG. However, the distribution of each variable overlapped, according to presence versus absence of (a) upgrading, (b) upstaging, (c) upgrading and/or upstaging (Figure 3).

In MVA predicting (a) upgrading, (b) upstaging, (c) upgrading and/or upstaging, several variables reached the independent predictors status. In (a) models, age, PSA above than 10 ng/ml, clinical T2 stage, and GGG3 emerged as independent predictors. In (b) and (c) models, age, PSA, clinical T stage, GGG, and percentage of positive cores emerged as independent predictors. The combined contribution of all variables underlying logistic regression models resulted in an accuracy according to the ROC-derived AUC of 0.69 (95% confidence interval [CI]: 0.67–0.71) for (a) upgrading versus 0.63 (CI: 0.63–0.65) for (b) upstaging versus 0.63 (CI: 0.62–0.65) for (c) upgrading and/or upstaging (Table 4).

4 | DISCUSSION

We tested the proportion of (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging within a large contemporary population-based cohort. We hypothesized that contemporary IU PCa patients may exhibited very low upgrading and/or upstaging proportion. To address this hypothesis, we relied on SEER database (2010–2015) and made several noteworthy observations.

First, in 7269 IU PCa patients (Figure 2), the proportions of (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging were respectively, 6.6 ($n = 479$) versus 33.0 ($n = 2398$) versus 36.0% ($n = 2616$). PCa patients with (a) upgrading, (b) upstaging, or (c)

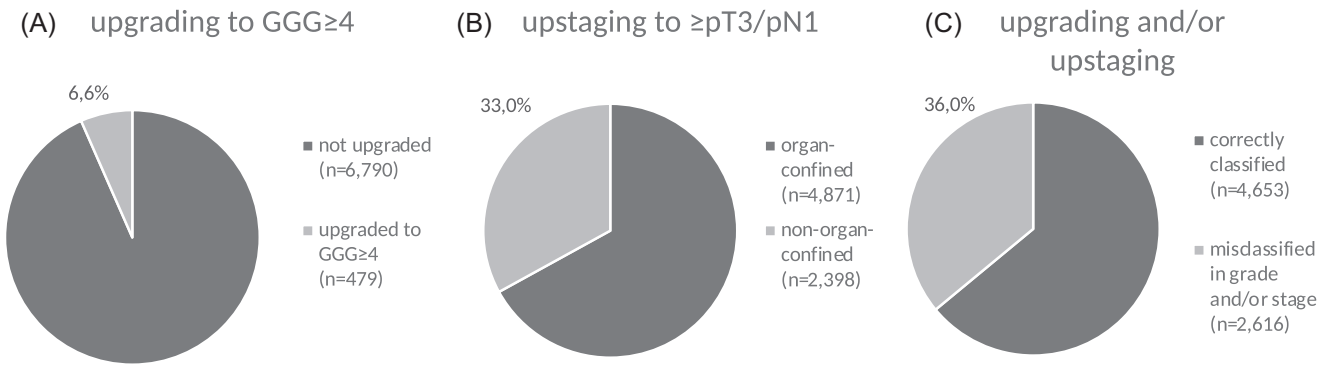

FIGURE 2 Pie charts depicting (A) upgrading to Gleason grade group (GGG) ≥ 4, (B) upstaging to non-organ-confined stage (≥pT3/pN1), or (C) upgrading and/or upstaging among 7269 intermediate unfavorable-risk prostate cancer patients treated with radical prostatectomy

TABLE 2 Clinical characteristics of 7269 intermediate unfavorable-risk prostate cancer patients treated with radical prostatectomy according to (a) upgrading to GGG ≥ 4, (b) upstaging to non-organ-confined pathological stage (≥pT3/pN1), and (c) upgrading and/or upstaging

Characteristic	Overall, *N* = 7269	Upgrading to pathological GGG ≥ 4, *N* = 479 (6.6%)	Upstaging to pathological non-organ-confined, *N* = 2398 (33.0%)	Upgrading and/or upstaging, *N* = 2616 (36.0%)
PSA (ng/ml)				
0–5	2038 (28.0%)	111 (5.4%)	550 (27.0%)	598 (29.3%)
5.1–10	3872 (53.3%)	239 (6.2%)	1257 (32.5%)	1378 (35.6%)
10.1–20	1359 (18.7%)	129 (9.5%)	591 (43.5%)	640 (47.1%)
Clinical T stage				
T1c	5502 (75.7%)	345 (6.3%)	1751 (31.8%)	1914 (34.8%)
T2	1767 (24.3%)	134 (7.6%)	647 (36.6%)	702 (39.7%)
GGG				
GGG1	411 (5.7%)	16 (3.9%)	88 (21.4%)	95 (23.1%)
GGG2	3347 (46.0%)	102 (3.0%)	1109 (33.1%)	1154 (34.5%)
GGG3	3511 (48.3%)	361 (10.3%)	1201 (34.2%)	1367 (38.9%)
% positive cores				
<25%	1215 (16.7%)	121 (10.0%)	256 (21.1%)	331 (27.2%)
25.1%–50%	2565 (35.3%)	171 (6.7%)	834 (32.5%)	916 (35.7%)
>50%	3489 (48.0%)	187 (5.4%)	1308 (37.5%)	1369 (39.2%)

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

upgrading and/or upstaging, no longer fulfill the characteristics of IU, but instead should be considered as high-risk PCa patients. According to this argument, patients with (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging require RT dose and/or type, as well as ADT duration that are clearly different than those recommended for IU patients, without evidence of (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging. Although distinction between upgraded versus upstaged patients is of academic importance, it does not change the RT and ADT considerations, since both patient groups invariably require higher RT dose and longer ADT duration. Specifically, in high-risk PCa patients, long-term adjuvant ADT represents the standard of care, according to results of pivotal trials.[10–12] Similarly, RT dose intensification such as seminal vesicle or whole-pelvis radiation are often considered in high-risk patients.[13–15] Moreover, in surgical candidates, stage and/or grade misclassification could also have consequences. These may apply to nerve-sparing considerations, extent of primary tumor technique, and extend of primary tumor resection and lymphadenectomy considerations.[12,16,17] Moreover, accurate prediction of NOC is of critical importance in estimating prognosis in RT patients, in whom primary tumor is not removed and surgical pathology specimen is unavailable for accurate staging.[18]

TABLE 3 Proportions of intermediate unfavorable-risk prostate cancer patients treated with radical prostatectomy that exhibited upgrading to GGG ≥ 4, upstaging to non-organ-confined stage (≥pT3/pN1) or upgrading and/or upstaging according to (a) PSA categories (≤5, 5–10, >10) versus GGG (1-2-3), (b) percentage of positive cores (≤25, 25.1–50, >50%) versus PSA categories (≤5, 5–10, >10), and (c) GGG (1-2-3) versus percentage of positive cores (≤25, 25.1–50, >50%)

	Upgrading = 479 (7%)			**Upstaging = 2398 (33%)**			**Upgrading and/or upstaging = 2616 (36%)**		
(a) PSA (ng/ml)									
Gleason grade group	≤5	5.1–10	>10	≤5	5.1–10	>10	≤5	5.1–10	>10
GGG1	1/64 (1.6%)	4/106 (3.8%)	11/241 (4.6%)	7/64 (10.9%)	12/106 (11.3%)	69/241 (28.6%)	8/64 (12.5%)	14/106 (13.2%)	73/241 (30.3%)
n = 411 (5.7%)									
GGG2	23/978 (2.4%)	57/1822 (3.1%)	22/547 (4.0%)	277/978 (28.3%)	577/1822 (31.7%)	255/547 (46.6%)	285/978 (29.1%)	607/1822 (33.3%)	262/547 (47.9%)
n = 3347 (46.0%)									
GGG3	87/996 (8.7%)	178/1994 (9.2%)	96/571 (16.8%)	266/996 (26.7%)	668/1944 (34.4%)	267/571 (46.8%)	305/996 (30.6%)	757/1944 (38.9%)	305/571 (53.4%)
n = 3551 (48.3%)									
(b) % positive cores									
PSA (ng/ml)	≤25%	25.1%–50%	>50%	≤25%	25.1%–50%	>50%	≤25%	25.1%–50%	>50%
≤5	22/374 (5.9%)	50/747 (6.7%)	39/917 (4.6%)	54/374 (14.4%)	208/747 (27.8%)	288/917 (31.4%)	70/374 (18.7%)	229/747 (30.7%)	299/917 (32.6%)
n = 2038 (28.0%)									
5–10	64/627 (10.2%)	81/1398 (5.8%)	94/1847 (5.1%)	151/627 (24.1%)	452/1398 (32.3%)	654/1847 (35.4%)	191/627 (30.5%)	495/1398 (35.4%)	692/1847 (37.5%)
n = 3872 (53.3%)									
>10	35/214 (16.4%)	40/420 (9.5%)	54/725 (7.4%)	51/214 (23.8%)	174/420 (41.4%)	366/725 (50.5%)	70/214 (32.7%)	192/420 (45.7%)	378/725 (52.1%)
n = 1359 (18.7%)									
(c) Gleason grade group									
% positive cores	GGG1	GGG2	GGG3	GGG1	GGG2	GGG3	GGG1	GGG2	GGG3
≤25%	2/33 (6.1%)	4/28 (14.3%)	115/1154 (10.0%)	3/33 (9.1%)	6/28 (21.4%)	247/1154 (21.4%)	3/33 (9.1%)	9/28 (32.1%)	319/1154 (27.6%)
n = 1215 (16.7%)									
25.1%–50%	5/123 (4.1%)	28/1046 (2.7%)	138/1396 (9.9%)	26/123 (21.1%)	328/1046 (31.4%)	480/1396 (34.4%)	29/123 (23.6%)	341/1046 (32.6%)	546/1396 (39.1%)
n = 2565 (35.3%)									
>50%	9/255 (3.5%)	70/2273 (3.1%)	108/961 (11.2%)	59/255 (23.1%)	775/2273 (34.1%)	474/961 (49.3%)	63/255 (24.7%)	804/2273 (35.4%)	502/961 (52.2%)
n = 3489 (48.3%)									

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

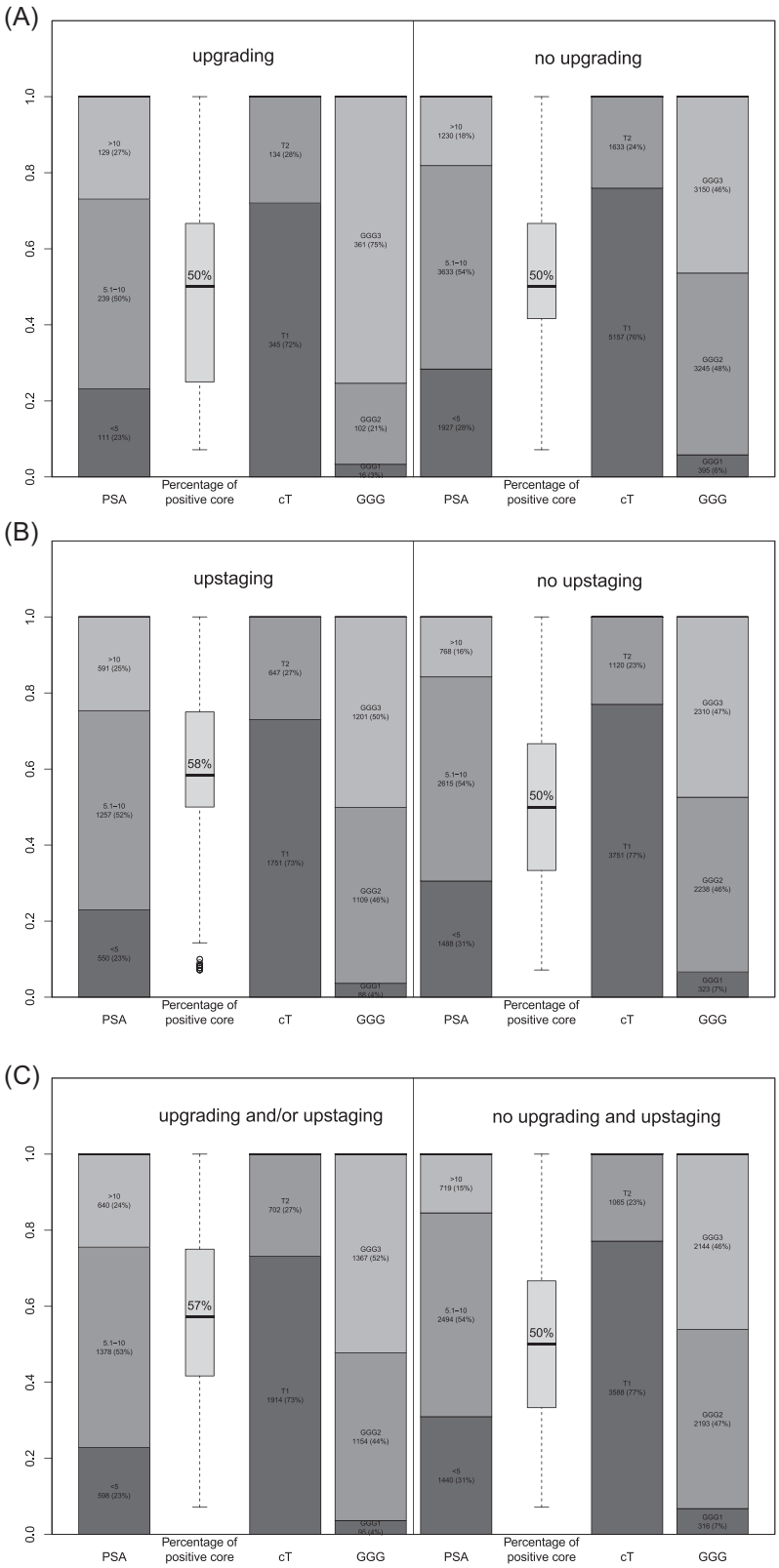

FIGURE 3 Clinical characteristics of 7269 intermediate unfavorable-risk prostate cancer patients treated with radical prostatectomy with (A) upgrading to Gleason grade group (GGG) ≥ 4 versus no upgrading, (B) upstaging to non-organ-confined stage (≥pT3/pN1) versus no upstaging, or (C) upgrading and/or upstaging versus no upgrading and no upstaging

Second, we observed an increase in proportions of (b) upstaging, as well as (c) in upgrading and/or upstaging, with increasing PSA, increasing GGG, and increasing percentage of positive cores. Conversely, we observed an increase in proportion of (a) upgrading, with increasing PSA and increasing GGG, but not with increasing percentage of positive cores. Additional stratifications according to the combined effects of increasing PSA and GGG, as well as to the combined effects of increasing percentage of positive cores and PSA, as well as to the combined effects of increasing GGG and percentage of positive cores, also demonstrated a gradual increase in proportions

TABLE 4 Multivariable logistic regression testing for (a) upgrading to GGG ≥ 4 or (b) non-organ-confined stage (≥pT3/pN1) or (c) upgrading and/or upstaging in 7269 intermediate unfavorable-risk prostate cancer patients treated with radical prostatectomy

Multivariable logistic regression models									
	Model predicting upgrading			Model predicting upstaging			Model predicting upgrading and/or upstaging		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age (years)	1.02	1.00, 1.03	**0.006**	1.03	1.02, 1.04	**<0.001**	1.03	1.02, 1.04	**<0.001**
Versus PSA ≤5 (ng/ml)	Ref.			Ref.			Ref.		
5.1–10	1.12	0.89, 1.43	0.314	1.25	1.11, 1.42	**<0.001**	1.29	1.14, 1.45	**<0.001**
10.1–20	2.01	1.53, 2.64	**<0.001**	2.32	2.00, 2.71	**<0.001**	2.43	2.09, 2.82	**<0.001**
Versus clinical T1c	Ref.						Ref.		
cT2	1.32	1.07, 1.64	**0.009**	1.31	1.17, 1.48	**<0.001**	1.33	1.18, 1.49	**<0.001**
Versus GGG1	Ref.								
GGG2	1.09	0.64, 1.96	0.746	2.49	1.93, 3.25	**<0.001**	2.46	1.91, 3.18	**<0.001**
GGG3	3.97	2.41, 7.01	**<0.001**	3.56	2.74, 4.65	**<0.001**	3.86	3.00, 5.02	**<0.001**
Versus ≤25% of positive cores	Ref.			Ref.			Ref.		
25.1%–50%	0.92	0.72, 1.19	0.557	2.15	1.82, 2.55	**<0.001**	1.83	1.56, 2.15	**<0.001**
>50%	1.00	0.77, 1.31	0.948	3.01	2.53, 3.58	**<0.001**	2.44	2.08, 2.88	**<0.001**
	C index: 0.69 (0.67–0.71)			**C index: 0.63** (CI: 0.63–0.65)			**C index: 0.63** (CI: 0.62–0.65)		

Abbreviations: CI, confidence interval; GGG, Gleason grade group; OR, odds ratio; PSA, prostate-specific antigen.

of (b) upstaging or (c) upgrading and/or upstaging. Conversely, a gradual increase in (a) upgrading proportion was recorded with combined effects of increasing PSA and GGG, less importantly with the combined effects of increasing GGG and percentage of positive cores, but not with the combined effects of increasing percentage of positive cores and PSA. Taken together, these observations indicate that individual and combined effect of risk factors on proportions of (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging represent a continuum which is consistent with a dose-response effect, that gradually arises from the input of these three risk variables according to their intensity level. These observations imply that risk category assignment is not an all versus none phenomenon, but instead represents a gradual transition between neighboring risk categories. In consequence, categorical stratification of risk at initial diagnosis, as assigned by various categorical risk-stratification tools that include NCCN criteria, will invariably result in misclassification of patients whose, true grade and/or stage exceed the risk-category, unless high-risk definition is applied. Similarly, a proportion of patients with high-risk features at initial diagnosis will be misclassified with categorical risk stratification tools, since some may harbor lower grade and/or stage.

Third, we attempted to identify predictors of (a) upgrading, (b) upstaging, and (c) upgrading and/or upstaging. Graphical display of PSA, percentage of positive cores, clinical T stage, and GGG between those with (a) upgrading versus no upgrading, (b) upstaging versus no upstaging, or (c) upgrading and/or upstaging versus no upgrading and/or upstaging, exhibited a very high degree of overlap in PSA, percentage of positive cores, clinical T stage and GGG (Figure 3). Unfortunately, attempts to predict (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging using MVA modeling, were not successful based on accuracy that ranged from 0.63 to 0.69 (Table 4). These accuracy figures are suboptimal and are due to the inherited heterogenicity of clinical characteristics within IU-risk category. When more complex logistic regression modeling was performed, did not result in a better accuracy compared with our simpler proposed model. Therefore, other characteristics are required to predict absence of upgrading and/or upstaging that is of utmost importance, especially for PCa patients considered for definitive RT. Luzzago et al. and Lantz et al. used this premise to test whether magnetic resonance imaging (MRI) findings may help better predicting NOC and/or GGG ≥ 3, and both groups of investigators identified an added benefit.[19,20] However, the latters were not yet externally validated within an independent cohort. Conversely, Diamand et al. failed to identify added benefit from MRI findings regarding prediction of extracapsular extension and seminal vesicle invasion, according to results recorded in an external validation cohort.[21,22] Furthermore, other studies reported an underestimation of MRI regarding the true size and extend of PCa tumor.[23,24] Since the ability of MRI to improve prediction of upgrading and/or upstaging is still under debate, other clinical tools, such as PSMA PET/CT scans or biomarkers (the prostate health index, urine PCA3, 4Kscore, TMPRSS2–ERG, and ConfirmMDX) may prove of value.[25,26] Moreover, despite novel findings, these tools still have to prove their efficacy and are not currently available in the clinical practice.

Other studies reported proportions of upgrading and upstaging, mostly for active surveillance consideration in low and favorable intermediate-risk PCa.[5–8] For example, Yang et al. in a large cohort of GGG2 intermediate favorable-risk PCa patients, identified the same predictors of upgrading and/or upstaging, despite in a more favorable population. However, clinical variables were not able to provide adequate discrimination for predicting more advanced disease in clinical practice, as observed also in the current study.[5] Two historical and smaller studies reported proportion of upgrading and/or upstaging in IU PCa patients virtually comparable with the current one.[3,6] Specifically, Zumsteg et al. ($n = 961$, 1988–2013) observed 31% proportion of upgrading and/or upstaging in IU PCa patients, while Dinh et al. ($n = 4008$, 2010–2011) observed 34%. However, both studies did not test for clinical independent predictors of upgrading and/or upstaging in IU PCa patients. By contrast, the current proportion of upgrading (6%) is lower than that reported (14%, $n = 19/136$) within a smaller single-center historical cohort of IU PCa patients (2005–2008) by Martin et al.[9] However, the sample size limitation of that report, critically limits its generalizability and the value of comparisons with larger studies such as the current one. Moreover, Martin et al. exclusively focused on upgrading, but omitted upstaging.[9] We demonstrated that upgrading affects a relatively small proportion of misclassified patients. Conversely, upstaging represented the overwhelming majority of misclassification. In consequence, both phenomena required a contemporary reassessment which was completed in the current study.

The current study is not devoid of limitations. First, our findings are derived from a surgical cohort. Unfortunately, pathological stage and grade information that would quantify upgrading and/or upstaging in RT patients can not be obtained. In consequence previous investigators, who examined the same concept relied on the same methodology.[9] Second, the retrospective information of the SEER database limits the amount of detail regarding certain clinical and/or pathological characteristics that may be more detailed within prospectively recorded institutional series.[23,27] For example, the SEER database does not offer information about MRI imaging. Similarly, the SEER does not offer information on percentage of cancer within individual biopsy core.[28,29] However, this makes our findings generalizable to routine clinical practice, where central pathology is not available. However, the substantially larger sample size that can be identified within the SEER database, at least partially corrected for these limitations.

5 | CONCLUSIONS

IU PCa patients showed very high (36%) upgrading and/or upstaging proportion. Interestingly, the overwhelming majority of those were upstaged to NOC. Conversely, very few were upgraded to GGG ≥ 4. In consequence, more than one-third of IU PCa patients treated with RT may be exposed to suboptimal dose and/or type of RT and to insufficient duration of ADT, since their true grade and stage corresponded to high-risk PCa definition, instead of IU PCa. Data about MRI were not available, but may potentially help with better stage discrimination.

AUTHOR CONTRIBUTIONS

Gabriele Sorce: conception and design, acquisition of data, analysis and interpretation of data, statistical analysis, drafting of the manuscript and critical revision of the manuscript for important intellectual content. **Rocco Simone Flammia**: acquisition of data, analysis and interpretation of the data and critical revision of the manuscript for important intellectual content. **Benedikt Hoeh**: acquisition of data, analysis and interpretation of the data and critical revision of the manuscript for important intellectual content. **Francesco Chierigo**: acquisition of data, analysis and interpretation of the data and critical revision of the manuscript for important intellectual content. **Lukas Hohenhorst**: acquisition of data, analysis and interpretation of the data and critical revision of the manuscript for important intellectual content. **Andrea Panunzio**: acquisition of data, analysis and interpretation of the data and critical revision of the manuscript for important intellectual content. **Armando Stabile**: analysis and interpretation of the data and critical revision of the manuscript for important intellectual content. **Giorgio Gandaglia**: analysis and interpretation of the data and critical revision of the manuscript for important intellectual content. **Zhe Tian**: statistical analysis and critical revision of the manuscript for important intellectual content. **Derya Tilki**: supervision, critical revision of the manuscript for important intellectual content. **Carlo Terrone**: supervision, critical revision of the manuscript for important intellectual content. **Michele Gallucci**: supervision, critical revision of the manuscript for important intellectual content. **Felix K. H. Chun**: supervision, critical revision of the manuscript for important intellectual content. **Alessandro Antonelli**: supervision, critical revision of the manuscript for important intellectual content. **Fred Saad**: supervision, critical revision of the manuscript for important intellectual content. **Shahrokh F. Shariat**: supervision, critical revision of the manuscript for important intellectual content. **Francesco Montorsi**: supervision, critical revision of the manuscript for important intellectual content. **Alberto Briganti**: supervision, critical revision of the manuscript for important intellectual content. **Pierre I. Karakiewicz**: conception and design, analysis and interpretation of data, drafting of the manuscript, supervision and critical revision of the manuscript for important intellectual content.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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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