Increasing rate of pathologic upgrading in low risk prostate cancer patients in the active surveillance era

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Introduction: *Management of prostate cancer has seen an increasing predilection for active surveillance in low risk (LR) patients. We aimed to evaluate the rate of pathologic upgrading in patients with very low (VLR) or LR prostate cancer after prostatectomy.*
Materials and methods: *The National Cancer Database (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) Database were queried for patients diagnosed with Gleason 6 prostate cancer and prostate specific antigen (PSA) < 10 ng/mL from 2010 to 2016. All patients underwent 12-core biopsy and a subsequent prostatectomy for final pathologic staging. Our primary outcome was rate of pathologic upgrading over the study period.*
Results: *A total of 35,332 patients from the NCDB and 7,186 patients from the SEER database were collected. Patient population had an average age of about 59 years old and was over 80% white. Mean pre-biopsy PSA was higher for the upgraded cohorts in the NCDB and SEER populations (5.3 versus 4.9 and 5.5 versus 5.1 respectively, $p < 0.001$). Upgraded cohorts were more likely to have a higher percentage of positive cores at biopsy ($p < 0.001$). Multivariable analysis demonstrated that increasing age, increasing PSA and year of diagnosis were all predictors of upgrading ($p < 0.05$) in both databases. African American race was significantly associated with upgrading in the NCDB database only ($p = 0.001$). Over the studied time period, the rate of upgrading at prostatectomy increased from 41.2% to 56.7% in the NCDB population and from 41.9% to 45.4% in the SEER population.*
Conclusions: *The rate of pathologic upgrading of VLR and LR prostate cancer at prostatectomy has been increasing in recent years. Increasing age, pre-biopsy PSA and an increasing percentage of positive cores at biopsy are predictors of this outcome. This may relate to improved patient selection for active surveillance and definitive treatment.*

Key Words: cancer staging, prostatic cancer, prostatectomy

Introduction

Prostate cancer is the most common malignancy in men, with over 248,530 new cases estimated for 2021 alone.[1] Options for treatment of localized disease include active surveillance (AS), prostatectomy, and radiation therapy. For men with low or very low risk disease, AS is encouraged as an initial treatment strategy.[2]

Discordant pathology between prostate biopsy and definitive prostatectomy specimen is a known risk and a significant percentage of men with initial low risk disease may be upgraded at the time of prostatectomy.[3] Prostate specific antigen (PSA) and number of positive biopsy cores are considered predictors for upstaging

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and may influence care decisions.[4] The risk of upgrading remains unknown in the modern era with the increased utilization of AS for low risk disease. In this analysis, we reviewed the National Cancer Database (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) Database from 2010 to 2016 to collect data on patients with low risk disease. We aimed to evaluate the rate in upgrading patients with low risk prostate cancer after prostatectomy and identify variables predicting upgrading.

Materials and methods

Data source

Data for a portion of this analysis was derived from the Commission on Cancer's NCDB Participant User File for prostate cancer from 2010 to 2016. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB is a national cancer outcomes dataset that includes input from over 1,500 Commission on Cancer-accredited centers in the United States. This data includes all cancer patients treated at participating Commission on Cancer-accredited institutions and is estimated to capture over 70% of new cancer cases in the United States. Standardized coding definitions are utilized, and the data is freely available to participating institutions after application for projects are accepted by the NCDB. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

The second analysis undertaken was from data gathered from the National Cancer Institute's SEER Database from 2010-2016. SEER registries chosen encompass 27.8% of the US population across 18 regions and codes demographics, tumor stage, Gleason score (GS), number of biopsies, PSA, treatment type, follow up and mortality.[5]

Study population

The NCDB and SEER datasets were queried for patients with GS 3+3 prostate adenocarcinoma diagnosed on prostate biopsy. Patients had undergone a 12-core biopsy with a pre-prostatectomy PSA < 10 ng/mL, ultimately classifying them as having very low risk (VLR) or low risk (LR) disease as per National Comprehensive Cancer Network's guidelines (NCCN).[2] All patients underwent a prostatectomy for a final pathologic diagnosis and appropriate grading. Patients with a previously diagnosed malignancy were excluded. Notably, SEER database tracks cancer-specific mortality, which was included in our analysis, while NCDB only tracks overall survival. We identified 7,186 patients in the SEER database and 35,532 patients in the NCDB database. Patients aged less than 18 years old were excluded.

Patient demographic variables are different between databases. Variables included in the NCDB analysis were as follows: age, race, sex, Charlson comorbidity index, income status, treatment facility volume, and insurance status. Treatment facilities that accumulated 500 or more newly diagnosed cancer cases per year were considered to be high volume, while facilities with less than 500 were labeled low volume. The SEER database included race, insurance status, and marital status but no information on comorbidities. Year of diagnosis was also retrieved from both datasets so as to trend rate of upgrading throughout the studied time period.

Statistical analysis and outcomes measures

Primary outcome was rate of upgrading from 2010-2016. Our secondary outcome was predictors of pathologic upgrading. Pathologic upgrading was defined as final pathology at prostatectomy with a GS of 7 or higher. Student's T-test was performed for continuous variables. Fischer's exact or Pearson chi-square test was used for categorical variables. Using factors that were significant on univariate analysis, we performed multivariable logistic regression to identify risk factors associated with pathologic upgrading. We utilized SPSS v25 (NY, USA) for all analyses, with p value of < 0.05 denoting statistical significance.

Results

Table 1 highlights the patient demographics and clinical tumor characteristics of patients from our NCDB population. The 35,532 patients amassed were predominantly white (84%) with a mean age of 59.4 years old. Those upgraded at prostatectomy where more likely to be older (60.0 versus 58.8 years old, $p < 0.001$) and African American (12.8% versus 11.8%, $p = 0.005$). On average, the upgraded cohort had a higher PSA (5.3 ng/mL versus 4.9 ng/mL, $p < 0.001$) and number of cores positive with 13.4% of patients having > 6 cores positive. Of those upgraded, 2.8% were upgraded to a Gleason score sum of 8-10.

Table 2 illustrates the patient demographics and clinical tumor characteristics of our SEER cohort. We accumulated 7,186 patients who were also predominantly white (81.3%) with a mean age of 59.1

TABLE 1. **NCDB - Patient demographics and clinical tumor characteristics**

Variable	All (n = 35,532)	Gleason 6 (n = 18,434)	Gleason 7+ (n = 17,098)	sig
Mean age	59.4 ± 6.9	58.8 ± 6.9	60.0 ± 6.8	< 0.001
Race				0.005
White	29,842 (84.0%)	15,588 (84.6%)	14,254 (83.4%)	
Black	4,363 (12.3%)	2,166 (11.8%)	2,197 (12.8%)	
Other	1,327 (3.7%)	680 (3.7%)	647 (3.8%)	
Charlson				0.023
0	29,717 (83.6%)	15,504 (84.1%)	14,213 (83.1%)	
1	4,993 (14.1%)	2,525 (13.7%)	2,468 (14.4%)	
2	637 (1.8%)	324 (1.8%)	313 (1.8%)	
3+	185 (0.5%)	81 (0.4%)	104 (0.6%)	
Income status				0.006
< $38,000	4,537 (12.8%)	2,336 (12.7%)	2,201 (12.9%)	
$38,000-47,999	6,916 (19.5%)	3,482 (18.9%)	3,434 (20.1%)	
$48,000-62,999	9,473 (26.7%)	4,891 (26.6%)	4,582 (26.8%)	
$63,000+	14,542 (41.0%)	7,686 (41.8%)	6,856 (40.2%)	
Uninsured	401 (1.1%)	197 (1.1%)	204 (1.2%)	0.290
Mean PSA	5.1 ± 1.9	4.9 ± 1.9	5.3 ± 1.9	< 0.001
cT2	6044 (17.0%)	3130 (17.0%)	2914 (17.0%)	0.885
# cores positive				< 0.001
1-3	21,680 (61.0%)	12,504 (67.8%)	9,176 (53.7%)	
4-6	10,038 (28.3%)	4,397 (23.9%)	5,641 (33.0%)	
7-9	2,951 (8.3%)	1,197 (6.5%)	1,754 (10.3%)	
10-12	863 (2.4%)	336 (1.8%)	527 (3.1%)	
Prostatectomy Gleason 8-10	-	-	484 (2.8%)	-

NCDB = National Cancer Database; PSA = Prostate specific antigen

years old. The upgraded cohort was once again, more likely to be older (59.8 versus 58.5 years old, p < 0.001). No significant difference in race was seen (p = 0.36). Mean PSA was significantly higher (5.5 ng/mL) in the upgraded group compared to the non-upgraded group (5.1 ng/mL). Also, patients who were upgraded tended to have a higher number of cores positive with 13.5% of upgraded patients having > 6 cores positive. Of those upgraded, 2.7% were upgraded to a Gleason score sum of 8-10. Cancer-specific survival was not significantly different between groups (p = 0.4).

Logistic regression for upgrading in the NCDB and SEER population is depicted in Table 3. Increasing age and advancing year of diagnosis were both independently associated with upgrading patients at prostatectomy (p < 0.001). African American race demonstrated an increased risk of upgrading in the NCDB (OR 1.12, p = 0.001) but not in the SEER (1.102, p = 0.175) database. Also, as number of cores positive increased, a corresponding increase in OR was noted (1.685-2.022, p < 0.001) for the NCDB cohort and SEER cohort (1.584-2.118, p < 0.001). Income and Charlson comorbidity index were not significantly associated with upgrading in the NCDB cohort (p > 0.05) and cT2 disease was not associated with upgrading in either cohort.

Figure 1 illustrates the trend in upgrading patients with VLR and LR prostate cancer at prostatectomy to grade group 2 or higher for the NCDB population. In 2010, 42.1% of patients were upgraded at prostatectomy, increasing to 56.8% by 2016 (p < 0.001). Figure 2 illustrates the trend in upgrading patients with VLR and LR prostate cancer at prostatectomy to grade group 2 or higher for the SEER population. In 2010, 41.9% of patients were upgraded at prostatectomy, increasing to 45.4% by 2016 (p < 0.001).

TABLE 2. **SEER - Patient demographics and clinical tumor characteristics**

Variable	All (n = 7,186)	Gleason 6 (n = 3,926)	Gleason 7+ (n = 3,260)	sig
Mean age	59.1 ± 6.9	58.5 ± 6.9	59.8 ± 6.9	< 0.001
Race				0.360
White	5,845 (81.3%)	3,214 (81.9%)	2,631 (80.7%)	
Black	970 (13.5%)	517 (13.2%)	453 (13.9%)	
Other	291 (4.0%)	148 (3.8%)	143 (4.4%)	
Unknown	80 (1.1%)	47 (1.2%)	33 (1.0%)	
Uninsured	56 (0.8%)	25 (0.6%)	31 (1.0%)	0.138
Mean PSA	5.3 ± 1.8	5.1 ± 1.8	5.5 ± 1.7	< 0.001
cT2	498 (6.9%)	300 (7.6%)	198 (6.1%)	0.010
# cores positive				< 0.001
1-3	4,472 (62.2%)	2,680 (68.3%)	1,792 (55.0%)	
4-6	1,963 (27.3%)	938 (23.9%)	1,025 (31.4%)	
7-9	580 (8.1%)	233 (5.9%)	347 (10.6%)	
10-12	171 (2.4%)	75 (1.9%)	96 (2.9%)	
Prostatectomy Gleason 8-10	-	-	88 (2.7%)	-
Death	126 (1.8%)	67 (1.7%)	59 (1.8%)	0.787
Cancer-specific	12 (0.2%)	5 (0.1%)	7 (0.2%)	0.400

SEER = Surveillance, Epidemiology, and End Results; PSA = prostate specific antigen

TABLE 3. **Logistic regression for upgrading (NCDB and SEER)**

	NCDB				SEER			
Variable	**OR**	**95% CI**	**95% CI**	**p value**	**OR**	**95% CI**	**95% CI**	**p value**
Age	1.023	1.020	1.026	< 0.001	1.025	1.017	1.032	< 0.001
Race (white ref)								
Black	1.120	1.047	1.198	0.001	1.102	.958	1.269	0.175
Other	1.048	.936	1.173	0.414	1.161	.913	1.476	0.224
Charlson (0 ref)								
1	1.034	.972	1.100	0.287	-	-	-	-
2	.960	.818	1.128	0.622	-	-	-	-
3+	1.122	.833	1.512	0.449	-	-	-	-
Income (63,000+ ref)								
<$38,000	.983	.917	1.055	0.638	-	-	-	-
$38,000-47,999	1.039	.980	1.103	0.199	-	-	-	-
$48,000-62,999	1.018	.965	1.074	0.510	-	-	-	-
PSA	1.009	1.008	1.010	< 0.001	1.010	1.007	1.012	< 0.001
cT2	1.024	.967	1.085	0.421	.847	.698	1.027	0.091
# cores positive (1-3 ref)								
4-6	1.685	1.605	1.768	< 0.001	1.584	1.421	1.766	< 0.001
7-9	1.882	1.739	2.038	< 0.001	2.118	1.769	2.534	< 0.001
10-12	2.022	1.756	2.330	< 0.001	1.860	1.357	2.548	< 0.001
Year of diagnosis	1.093	1.081	1.105	< 0.001	1.058	1.028	1.089	< 0.001

NCDB = National Cancer Database; SEER = Surveillance, Epidemiology, and End Results; PSA = prostate specific antigen

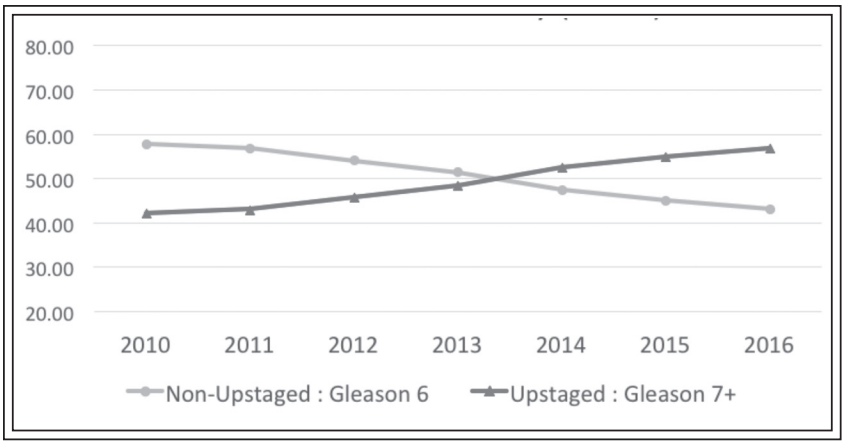

Figure 1. Rate of upstaging for low risk prostate cancer at prostatectomy (NCDB).

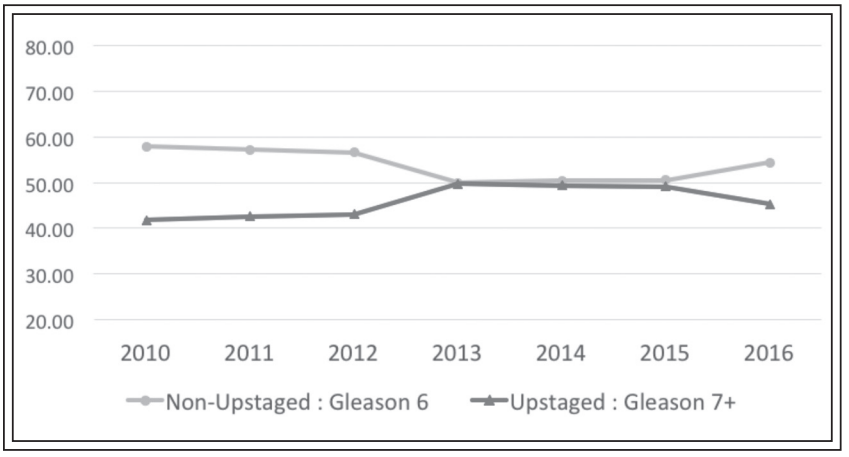

Figure 2. Rate of upstaging for low risk prostate cancer at prostatectomy (SEER).

Discussion

Our analysis reveals an increasing trend in the upgrading of VLR and LR prostate cancer at prostatectomy from 2010-2016. Advancing year of diagnosis was an independently associated variable suggestive of upgrading. In 2010, 41.2%-41.9% of patients with LR disease were upgraded at prostatectomy, while in 2016, this number increased to 45.4%-56.8% ($p < 0.001$). Meanwhile, previously reported risk factors for pathologic upgrading such as increasing age, preoperative PSA and percentage of positive cores at prostate biopsy were also seen in this study.[6-8] This analysis, of two of the largest cancer databases across the United States, reveals a thought-provoking trend which could impact the long term oncologic outcomes of prostate cancer patients.

Over the last decade there has developed an increased proclivity to enlist LR patients into AS protocols in an effort to reduce the harms of over treatment.[9,10] This trend is noteworthy, as enrolling patients in AS for a prolonged period of time increases the risk of disease progression simply due to the passage of time.[11] For LR patients, the NCCN recommends that AS include PSA monitoring every 6 months, digital rectal exams every 12 months and confirmatory biopsies at a rate no more frequent than yearly.[2] Such a protocol can be considered inconvenient and/or invasive by patients and therefore lead to non-adherence. Studies have found that only 65%-81% of LR prostate cancer patients choosing AS, undergo their scheduled confirmatory biopsy 12-months later.[12,13] In a systematic review of the literature, Kinsella et al identified a variety of patient and disease characteristics that may influence compliance in AS protocols.[14] Taking this data one step further, Bokhorst et al prospectively followed 4,547 men with LR prostate cancer on AS across multiple international sites and examined the effects of compliance on oncological outcomes. In their study, at 1-year, only 81% of patients underwent their scheduled confirmatory biopsy, and the rate of compliance would decrease further in subsequent years. By year 4, 25% of patients who had failed to comply with their scheduled repeat biopsy were upgraded and/or had an increased number of positive cores compared to only 16% of patients who were compliant ($p = 0.028$).[13] Importantly, Bokhorst et al defined LR patients as those with less than or equal to two positive cores of grade group 1 disease, which is no longer standard.[13] Within our own analysis, we found the rate of upgrading to increase over time, which may relate to patient compliance, similar to these studies. We were unable to measure patient compliance within these national datasets; however, the increased rate of upgrading with time may relate to this phenomenon.

Currently, the NCCN considers LR patients as those with PSA < 10 ng/mL, T1-T2a disease and grade group 1 histology, regardless of number of cores positive.[2] Percentage of positive cores relative to total cores samples has been demonstrated to prognosticate cancer-specific outcomes such as biochemical recurrence free survival, disease free survival and cancer-specific survival.[8,15,16] Our study coincides with previous reports that an increasing number of cores positive at biopsy exhibits an increasing propensity for upgrading. This suggests that patients who fall under the current LR umbrella, such as in this contemporary review, may experience higher rates of upgrading relative to the aforementioned Bokhorst et al study, regardless of compliance, due to the increased number of positive cores at diagnosis.

In patients who avoid AS and proceed straight to prostatectomy after biopsy, there is still a known risk of discordant pathology between specimens. An institutional review at the Lahey Clinic Medical Center highlighted the shortfalls in the standard template 12-core biopsy. They evaluated 2,890 patients with biopsy and prostatectomy data who were grouped into low (2-6), moderate (7), and high (8-10) Gleason scores. Analysis was undertaken to establish a percentage of patients who were upgraded, downgraded or remained the same for each cohort. Patients classified as having low grade disease were upgraded 46% of the time while the kappa statistic for biopsy and prostatectomy indicated only "fair agreement" (kappa=0.33). Furthermore, a meta-analysis with over 14,000 patients revealed 38% rate of upgrading for those with GS 2-6 and an associated kappa of 0.37.[17] Our own analysis is congruent with these previous findings but additionally notes an increasing rate of pathologic upgrading with time. The underlying cause of this effect is unknown but several hypotheses can be generated. The increased utilization of multiparametric magnetic resonance imaging (mpMRI) and genomic markers may improve proper selection for AS versus definitive treatment. On the contrary, changes in the use of PSA screening for prostate cancer may have continued effects on diagnosis and disease staging which is only now emerging.[18,19] Importantly, this trend of upgrading does not confer a change in cancer-specific outcomes and can be viewed in a positive light as men are being more accurately selected for definitive therapy.

It is possible with the numerous diagnostic tools at our disposal, including mpMRI and genomic testing, we are improving our selection of patients fit for AS. However, the changes in PSA screening recommendations by the United States Preventative Services Task Force in 2012 may have also played a role in this increasing trend of upgrading. Repercussions from this statement have yielded a relative decreased incidence of prostate cancer, due to under-screening, but a stage migration towards more aggressive disease.[19-21] Although likely multifactorial, the demonstrated increased trend of upgrading in our study, may be in part due to delayed diagnosis and requires close follow up on future analyses.

Demographic predictors of upgrading disease such as age and race were also noted within this study. African American race, within the NCDB, portended upgrading disease (1.120, p = 0.001). This finding has been demonstrated before by Sundi et al who retrospectively reviewed their institutional database at Johns Hopkins University for patients meeting NCCN criteria for VLR prostate cancer who underwent radical prostatectomy. When comparing 101 African American patients to a cohort of 258 predominantly white patients, they found an adjusted 2.26 OR (p = 0.03) of upgrading African American patients and an OR of 3.23 (p = 0.03) of unveiling adverse pathologic features.[22] Meanwhile, previously published analyses of LR patients in the NCDB and SEER database demonstrated conflicting results affirming and rejecting the role of race as a predictor of upgrading, respectively.[23,24] Examining a more contemporary cohort, the inconsistencies between the NCDB and SEER database persist, and the etiology of these inconsistencies are not clear. In regards to the association between age and upgrading disease, our analysis exhibited an OR of 1.023-1.025 (p < 0.001) with increasing age. Multiple studies have reproduced similar associations with age and upgrading, postulating that the incorporation of mpMRI earlier in a patient's work up may prove most beneficial in this population or age-related pathologic factors may be involved.[25-27]

As a review of large national databases, certain information is lacking including PSA density and percent of an individual core positive for disease. These are salient variables as they are necessary to properly stratify patients between the VLR and LR categories.[2] This limitation highlights our inability to confidently classify patients with 1-3 cores positive, as either VLR or LR. Therefore, conclusions pertaining to the VLR population should be made with caution. Moreover, the International Society of Urological Pathology consensus conference in 2014 concluded that various histological findings previously reported as Gleason score 3, should be reclassified as Gleason score 4 due to their adverse prognostic significance. This ruling implies that, prior to 2014, certain patient's

pathologic grade would have been underestimated in the modern grading system.[28] The NCDB and SEER do not provide with ability to track AS protocol and it unclear which patients may have undergone mpMRI, genomic testing, repeated PSA, or DRE findings. This limits the extrapolation of these results into the future as mpMRI becomes increasingly supported in the evaluation of biopsy naïve patients.[29] Furthermore, when determining to undergo prostatectomy for LR disease, certain unmeasured psychologic variables are discussed between physician and patient and are unable to be captured in a large dataset. Lastly, we chose only to include patients undergoing surgery for definitive management, thus patients choosing radiation therapy are not included.

Despite these limitations, our modern review of two of the largest cancer databases within the United States, offers a glimpse into the evolution of prostate cancer and the increasing tendency to upgrade disease at prostatectomy. At risk patients, with increasing age, PSA and number of positive cores, warrant earlier consideration for intervention given the increased threat of upgrading. Perhaps our advancing technology (mpMRI), the addition of genomic sequencing and simply an improved understanding of the natural history of patients opting for AS has allowed us to better select patients for intervention as evidence by the increasing rate of upgrading. This trend is likely due to all of the aforementioned factors in this manuscript and ensuring that we continue to improve our patient selection is paramount.

Conclusions

In a large database review, we expose a growing proclivity for pathologic upgrading of VLR and LR prostate cancer at prostatectomy. Increasing age, PSA and an increasing number of positive cores at biopsy are suggestive of this outcome. Changes to AS protocols, mpMRI, genomic testing, and PSA screening habits may affect this trend, and further follow up is necessary to determine the metastatic and survival effects. □

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