Upgrading on radical prostatectomy specimens of very low- and low-risk prostate cancer patients on active surveillance: A population-level analysis

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Abstract

Introduction: A proportion of prostate cancer (PCa) patients initially managed with active surveillance (AS) are upgraded to a higher Gleason score (GS) at the time of radical prostatectomy (RP). Our objective was to determine predictors of upgrading on RP specimens using a national database.

Methods: The Surveillance, Epidemiology, and End Results Prostate with Watchful Waiting database was used to identify AS patients diagnosed with very low- or low-risk PCa who underwent delayed RP between 2010 and 2015. The primary outcome was upgrading to GS 7 disease or worse. Logistic regression analyses were used to evaluate demographic and oncological predictors of upgrading on final specimen.

Results: A total of 3775 men underwent RP after a period of AS, 3541 (93.8%) of whom were cT2a; 792 (21.0%) patients were upgraded on RP specimen, with 85.4%, 10.6%, and 3.4% upgraded to GS 7(3+4), 7(4+3), and 8 diseases, respectively. On multivariable analysis, higher prostate-specific antigen (PSA) at diagnosis (5–10 vs. 0–2 ng/ml, odd ratio [OR] 2.59, p<0.001) and percent core involvement (80–100% vs. 0–20%, OR 2.52, p=0.003) were significant predictors of upgrading on final RP specimen, whereas higher socioeconomic status predicted lower odds of upgrading (highest vs. lowest quartile OR 0.75, p=0.013).

Conclusions: Higher baseline PSA and percent positive cores involvement are associated with significantly increased risk of upgrading on RP after AS, whereas higher socioeconomic status predicts lower odds of such events. These results may help identify patients at increased risk of adverse pathology on final specimen who may benefit from earlier definitive treatment.

Introduction

Active surveillance (AS) has emerged as the preferred management option for patients with favorable-risk, localized prostate cancer (PCa).[1] While AS reduces the risk of overtreatment of clinically insignificant PCa, at least a third of such patients will undergo definitive treatment within 10 years of diagnosis.[2] Among patients undergoing radical prostatectomy (RP), a significant number are diagnosed with more histologically aggressive forms of PCa,[3-5] which is likely due to a combination of disease progression and/or fallibility of initial risk stratification approaches. As higher-grade disease portends worse oncological outcomes,[6] identifying patients at increased risk of worse pathological disease becomes critical, as such patients may be considered for earlier definitive treatment. Our objective was thus to identify predictors of upgrading on RP specimens in men with very low- and low-risk PCa initially opting for AS using a nationally representative cohort.

Methods

Study design, setting, and participants

We used the Surveillance, Epidemiology, and End Results (SEER) Prostate with Watchful Waiting database, which is a

nationally representative database supported by the National Cancer Institute. This database captures men with incident PCa from 18 population-based registries between 2010 and 2015, and covers approximately 30% of the U.S. population.[7] We included men younger than 80 years old with National Comprehensive Cancer Network very low- or low-risk PCa,[8] who opted initially for AS and ultimately underwent an RP. No institutional review board approval was required for this study.

Study outcome

The primary study outcome was upgrading to Gleason score (GS) 7 (3+4) or worse on final pathological specimen. Other pathological information, such as stage, extraprostatic extension, or percent tumor involvement was not available from this database.

Study variables

The following patient-level variables were abstracted: year of diagnosis, age at diagnosis, race, insurance status, marital status, SEER registry region, first cancer diagnosis (i.e., whether PCa was the first cancer diagnosis the patient received or whether he had previously been diagnosed with a different, unrelated malignancy), cT stage (cT1a-b, cT1c, or cT2a), prostate-specific antigen (PSA) level at diagnosis (0–2, 2–5, or 5–10 ng/ml), GS on prostate biopsy or transurethral resection of prostate (TURP), and number of positive and examined prostate cores/specimens. County-level socioeconomic status (SES) (first [lowest], second, third, or fourth highest]) was derived from: percentage of individuals 1) with less than a high school education; 2) below the poverty line; 3) unemployed; 4) foreign-born; and 5) median household income.[9] Percent positive cores variable was derived from number of cores/specimen positive and examined.

Statistical methods

Continuous variables were reported using medians and interquartile ranges (IQR), with categorical variables described using frequencies and proportions. Univariable and multivariable logistic regression analyses were performed to evaluate for predictors of upgrading on RP specimen. All predictors were operationalized as categorical variables in the regression models. The overall statistical significance of categorical variables was assessed using the likelihood ratio test. Due to their clinical relevance, decision was made a priori to include all the study variables in both the univariable and multivariable models. Variable collinearity was evaluated using the variance inflation factor test. Statistical significance was set at $p<0.05$. All statistical analyses were performed using R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Fig. 1 demonstrates the derivation of the study cohort. Among 32 874 men with very low- or low-risk PCa, 3775 (11.5%) underwent RP during the study period. Median patient age was 60.0 years (IQR 55.0–65.0), 2774 (73.5%) patients were Caucasian, 2981 (79.0%) married, 3548 (94.0%) were insured, and 110 (2.9%) were covered by Medicaid (Table 1). A total of 3765 (99.7%) were GS 6 on biopsy/TURP specimen, with the remaining 10 (0.3%) were GS 5 or lower, and 3541 (93.8%) were clinical stage cT2a. Median PSA and percent positive cores were 4.9 ng/ml (IQR 3.7–6.3) and 15.4% (IQR 8.3–25.0), respectively. PCa was the first cancer diagnosis in 3590 (95.1%) patients.

In terms of upgrading, 792 (21.0%) patients were upgraded on final RP specimen; 676 (85.4%) were upgraded to GS 7 (3+4), 84 (10.6%) to GS 7 (4+3), and 27 (3.4%) to GS 8. There were no cases of upgrading to GS 9 or worse (Table 2). A total of 761 (96.1%) patients had cT2a disease compared to 31 (3.9%) with non-palpable disease at diagnosis. Of 28 613 patients with non-palpable disease, only 55 (0.2%) underwent RP and 20 (36.4%) of those patients were upgraded on final pathology specimen.

On univariable analysis, year of diagnosis (2014–2015 vs. 2010–2011 odds ratio [OR] 1.44, $p<0.001$), age at diagnosis (70–79 vs. 30–49 OR 1.97, $p=0.002$), T stage (overall variable significance $p=0.018$), PSA at diagnosis (5–10 vs. 0–2 ng/ml OR 2.07, $p<0.001$), percent positive cores (80–100% vs. 0–20% OR 2.50, $p=0.002$), and SES (highest vs. lowest OR 0.75, $p=0.007$) were significantly associated with risk of upgrading on final RP specimen.

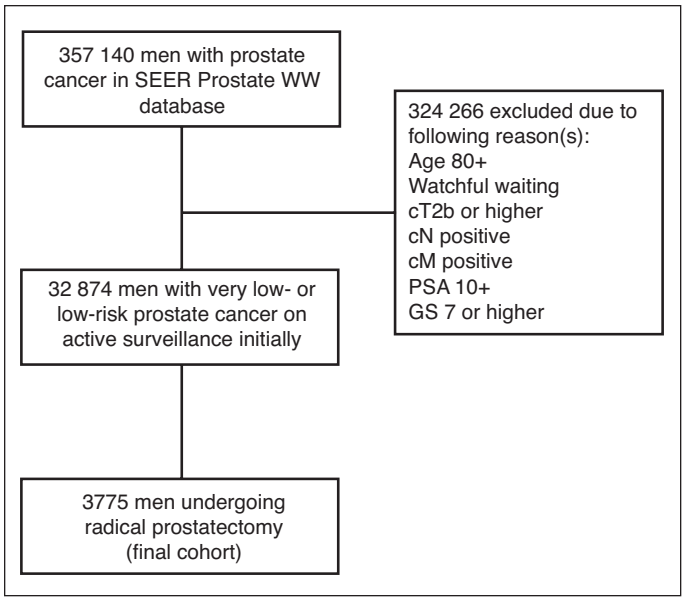

Fig. 1. Study flow chart. GS: Gleason score; PSA: prostate-specific antigen; SEER: Surveillance, Epidemiology, and End Results; WW: watchful waiting.

Table 1. Baseline patient demographics (n=3775)

Variable	Frequency (%) or median (IQR)
Year of diagnosis	
2010	1006 (26.6%)
2011	989 (26.2%)
2012	637 (16.9%)
2013	482 (12.8%)
2014	357 (9.5%)
2015	304 (8.1%)
Age at diagnosis, median (IQR)	60.0 (55.0–65.0)
Race	
Caucasian	2774 (73.5%)
African American	318 (8.4%)
Hispanic	441 (11.7%)
Asia/Pacific Islander	189 (5.0%)
American Indian/Alaska native	10 (0.3%)
Unknown	267 (7.1%)
Marital status	
Married	2981 (79.0%)
Not married	540 (21.0%)
SEER registry	
New Jersey	577 (15.3%)
San Fransisco-Oakland	156 (4.1%)
Los Angeles	371 (9.8%)
Louisiana	280 (7.4%)
Connecticut	151 (4.0%)
Detroit (metropolitan)	166 (4.4%)
Seattle (Puget Sound)	173 (4.6%)
Rural Georgia	5 (0.1%)
Atlanta (metropolitan)	114 (3.0%)
California (excluding SF/SJM/LA)	796 (21.1%)
Greater Georgia	248 (6.6%)
Kentucky	225 (6.0%)
San Jose-Monterey	99 (2.6%)
Utah	113 (3.0%)
Hawaii	44 (1.2%)
Iowa	172 (4.6%)
New Mexico	81 (2.1%)
Alaska natives	4 (0.1%)
Insurance status	
Insured	3548 (94.0%)
Uninsured	31 (0.8%)
Medicaid	110 (2.9%)
Unknown	310 (8.2%)
Socioeconomic status	
1 (lowest)	993 (26.3%)
2	719 (19.0%)
3	997 (26.4%)
4 (highest)	1066 (28.2%)

IQR: interquartile range; SEER: Surveillance, Epidemiology, and End Results.

Table 2. Study cohort oncological characteristics (n=3775)

Gleason score on biopsy/TURP	
<6	10 (0.3%)
6	3765 (99.7%)
Gleason score on final pathological specimen	
<6	44 (1.2%)
6	2714 (71.9%)
7 (3+4)	676 (17.9%)
7 (4+3)	84 (2.2%)
8	27 (0.7%)
9–10	0 (0%)
NA	230 (6.1%)
PSA at diagnosis, median (IQR)	4.9 (3.7–6.3)
Percent cores positive, median (IQR)	15.4% (8.3–25.0%)
cT stage	
cT1a	5 (0.1%)
cT1b	1 (0.0%)
cT1c	228 (6.0%)
cT2a	3541 (93.8%)
Prostate cancer as first diagnosed malignancy	
Yes	3590 (95.1%)
No (i.e., previous, separate cancer diagnosis)	3185 (4.9%)

IQR: interquartile range; PSA: prostate-specific antigen; TURP: transurethral resection of the prostate.

On multivariable analysis, higher PSA at diagnosis (5–10 vs. 0–2 ng/ml OR 2.38, p=0.003) and percent core involvement (80–100% vs. 0–20% OR 3.20, p<0.001) were significant predictors of upgrading on final RP specimen (Table 3). Higher SES was associated with a lower risk of upgrading (highest vs. lowest OR 0.66, p=0.013).

Discussion

In this nationally representative cohort of men with very low- and low-risk PCa initially managed with AS, we demonstrate that among men eventually opting for RP, 21.0% are upgraded to GS 7 (3+4) disease or worse. On multivariable logistic regression analysis, we demonstrate that increasing PSA and higher percent positive cores are significant predictors of increased odds of upgrading on final pathological specimen, which is consistent with results published in the literature.[2-5] Conversely, patients of higher SES are at lower risk of upgrading on final pathological specimen.

Notably, older age and African American race were not significant predictors of upgrading in our cohort after adjusting for demographic and oncological variables on multivariable analysis. This is in contrast to previous studies demonstrating their prognostic utility.[10,11]

This observed difference is likely due to two important reasons. The underlying nature of this cohort is distinct from that of other reported series. Whereas this is a cohort of patients who were initially managed with AS and subse-

quently opted for treatment after at least a year of surveillance, most previous studies report on the outcomes of PCa patients with AS-eligible disease, but who did not necessarily undergo AS.[3,4,5,11] This important difference leads to underlying selection biases that create two unique cohorts. Thus, results from previous studies are not necessarily translatable to this cohort.

Second, it is important to emphasize that multivariable analysis allows us to control for the effect of confounders. The SEER Prostate Watchful Waiting database contains a broad range of patient-level demographic and oncological variables, which is critical to minimize the impact of unknown confounders. Older age was predictive of increased risk of upgrading on our univariable analysis, however, on multivariable analysis, this was no longer significant after controlling for the effect of other demographic/oncological variables.

Notably, 93.8% of patients in our cohort of men undergoing RP were cT2a, which is significantly higher than that of our original cohort of 32 874 men with very low/low-risk PCa on AS (15.8%). This finding is consistent with results from large AS cohorts, which also demonstrated that ≥cT2a was a predictor for intervention (OR 1.96, p<0.001).[2]

Table 3. Predictors of upgrading to GS 7(3+4) or higher on radical prostatectomy pathological specimen on univariable and multivariable logistic regression analysis

Variable	OR	95% CI	p	OR	95% CI	p
Year of diagnosis (reference: 2010–11)			<0.001*			0.12
2012–13	1.06	0.88–1.27	0.55	1.08	0.84–1.39	0.55
2014–15	1.44	1.17–1.77	<0.001*	1.24	0.92–1.67	0.15
Age at diagnosis (reference: 30–49 years)			<0.001*			0.061
50–59	1.27	0.92–1.79	0.16	1.28	0.80–2.11	0.32
60–69	1.47	1.06–2.06	0.023*	1.62	0.99–2.67	0.051
70–79	1.97	1.30–3.02	0.002*	1.44	0.76–2.76	0.26
Race (reference: Caucasian)			0.38			0.18
African American	1.27	0.96–1.66	0.094	1.34	0.90–1.95	0.14
Hispanic	0.98	0.76–1.25	0.87	0.97	0.66–1.40	0.85
Asia/Pacific Islander/American Indian/Alaska Native	1.11	0.77–1.56	0.57	1.20	0.69–2.01	0.49
Insurance status (reference: insured)			0.90			0.51
Uninsured	1.22	0.48–2.77	0.65	1.92	0.28–8.69	0.43
Medicaid	0.98	0.59–1.56	0.95	1.15	0.60–2.10	0.66
Marital status (reference: married)						
Not married	1.06	0.84–1.32	0.62	0.98	0.72–1.33	0.91
PCa as first cancer diagnosis (reference: previously diagnosed with other cancer)	1.14	0.78–1.69	0.52	1.05	0.62–1.86	0.86
SEER registry region (reference: Northeast)			0.80			0.16
Southeast	0.92	0.72–1.17	0.49	0.73	0.49–1.07	0.10
Midwest	0.99	0.72–1.35	0.93	1.18	0.75–1.83	0.47
West	1.01	0.82–1.26	0.90	0.83	0.59–1.18	0.29
Socioeconomic status (reference: 1 [lowest])			0.049*			0.010
2	0.81	0.64–1.02	0.073	0.80	0.56–1.13	0.20
3	0.85	0.68–1.05	0.12	0.91	0.6–1.23	0.52
4 (highest)	0.75	0.60–0.92	0.007*	0.66	0.47–0.91	0.013*
cT stage (reference: T1a, b)			0.018*			0.93
cT1c	1.71	0.21–35.56	0.65	18.6	0.0–76.2	0.97
cT2a	0.84	0.11–17.07	0.88	75.0	0.21–102.7	0.97
PSA at diagnosis (reference: 0–2 ng/ml)			<0.001*			<0.001*
2–5 ng/ml	2.00	1.40–2.92	<0.001*	2.63	1.54–4.83	<0.001*
5–10 ng/ml	2.07	1.46–3.02	<0.001*	2.38	1.39–4.36	0.003*
Percentage of positive cores (reference: 0–20%)			<0.001*			<0.001*
20–40%	2.21	1.72–2.85	<0.001*	2.22	1.69–2.90	<0.001*
40–60%	2.86	1.97–4.12	<0.001*	2.74	1.83–4.08	<0.001*
60–80%	1.88	0.81–3.99	0.12	1.57	0.63–3.54	0.30
80–100%	2.50	1.36–4.46	0.002*	3.20	1.68–5.97	<0.001*

*Statistically significant. CI: confidence interval; OR: odds ratio; PCa: prostate cancer; PSA: prostate-specific antigen; SEER: Surveillance, Epidemiology, and End Results.

Although the exact reason for intervention was not available for our cohort, these findings suggest that palpable disease on rectal exam may trigger physician-level anxiety, subsequently prompting recommendation for intervention. This is consistent with previous literature suggesting that PCa patients' treatment decisions are largely based on urologists' recommendations and less on patients' personal views of the relative pros and cons of management alternatives.[12]

Our data also demonstrates that lower SES is associated with higher risk of upgrading, even after controlling for known confounders such as age and race. These findings are likely secondary to underlying biases, which have not been accounted for in our analysis. Patients of lower SES are less likely to follow up with their physicians,[13] and thus less likely to undergo serial PSA measurements, rectal exams, and confirmatory biopsies as dictated by most AS regimens.[2] This puts them at higher risk of being "under-staged," leading to a higher risk of adverse pathology on RP specimens.

Our study has several limitations. The SEER Prostate with Watchful Waiting database only provides demographic and pathological data at diagnosis. In other words, if a patient undergoes a confirmatory prostate biopsy with GS upgrading or has a significant rise in PSA on followup, this is not captured by the database. Consequently, we are unable to discern the triggers for intervention for these patients who were very low- or low-risk at initial diagnosis. Furthermore, results from preoperative imaging tools (e.g., transrectal ultrasound, multiparametric magnetic resonance imaging [MRI]) and pathological information (e.g., extent of core involvement, perineural invasion) were not available,[14] and thus not accounted for in our regression analysis. The significance of this is further magnified by the fact that 93.8% of our cohort was cT2a at diagnosis. It would be expected that such patients would undergo subsequent imaging with multiparametric MRI prior to being placed on AS. This may potentially result in targeted repeat biopsies, with results of that affecting subsequent decision to undergo definitive treatment with RP. This study is also limited by its retrospective nature and biases inherent to the use of health administrative databases.

Conclusions

Most (93.8%) patients with very low- and low-risk PCa initially managed with AS and opting for delayed RP are cT2a at diagnosis; 21.0% of such are subsequently upgraded to GS 7 (3+4) disease or worse on RP specimen. Increasing PSA and higher percent positive cores involved are associated with a significantly increased risk of pathological upgrading, whereas higher SES conversely predicts a lower risk of such an event. Notably, age at diagnosis and race are not associated with risk of upgrading after controlling for relevant demographic and oncological patient variables. These results may help identify patients at increased risk of adverse pathology on final specimen who may benefit from earlier definitive treatment.

Competing interests: The authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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