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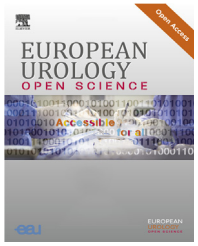

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Prostate Cancer

Prognostic Value of the Intermediate-risk Feature in Men with Favorable Intermediate-risk Prostate Cancer: Implications for Active Surveillance

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Abstract

Background: Guidelines suggest that active surveillance (AS) may be considered for select patients with favorable intermediate-risk (fIR) prostate cancer.
Objective: To compare the outcomes between fIR prostate cancer patients included by Gleason score (GS) or prostate-specific antigen (PSA). Most patients are classified with fIR disease due to either a 3 + 4 = 7 GS (fIR-GS) or a PSA level of 10–20 ng/ml (fIR-PSA). Previous research suggests that inclusion by GS 7 may be associated with worse outcomes.
Design, setting, and participants: We conducted a retrospective cohort study of US veterans diagnosed with fIR prostate cancer from 2001 to 2015.
Outcome measurements and statistical analysis: We compared the incidence of metastatic disease, prostate cancer–specific mortality (PCSM), all-cause mortality (ACM), and receipt of definitive treatment between fIR-PSA and fIR-GS patients managed with AS. Outcomes were compared with those of a previously published cohort of patients with unfavorable intermediate-risk disease using cumulative incidence function and Gray's test for statistical significance.
Results and limitations: The cohort included 663 men; 404 had fIR-GS (61%) and 249 fIR-PSA (39%). There was no evidence of difference in the incidence of metastatic disease (8.6% vs 5.8%, p = 0.77), receipt of definitive treatment (77.6% vs 81.5%, p = 0.43), PCSM (5.7% vs 2.5%, p = 0.274), and ACM (16.8% vs 19.1%, p = 0.14) between the fIR-PSA and fIR-GS groups at 10 yr. On multivariate regression, unfavorable intermediate-risk disease was associated with higher rates of metastatic disease, PCSM, and ACM. Limitations included varying surveillance protocols.
Conclusions: There is no evidence of difference in oncological and survival outcomes between men with fIR-PSA and fIR-GS prostate cancer undergoing AS. Thus,

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presence of GS 7 disease alone should not exclude patients from consideration of AS. Shared decision-making should be utilized to optimize management for each patient.

Patient summary: In this report, we compared the outcomes of men with favorable intermediate-risk prostate cancer in the Veterans Health Administration. We found no significant difference between survival and oncological outcomes.

1. Introduction

Active surveillance (AS) is a widely practiced management strategy for select men with prostate cancer to minimize overtreatment of indolent disease and delay definitive, potentially morbid measures until disease progression is apparent [1]. While AS has long been suggested for low-risk disease, recent National Comprehensive Cancer Network (NCCN) guidelines state that AS may also be considered for the management of men with favorable intermediate-risk (fIR) prostate cancer [2], and the usage of AS in this population has risen in recent years [3–6]. Favorable intermediate-risk prostate cancer includes patients with <50% positive biopsy cores and one intermediate-risk feature: a T2b-c tumor, a pathological Gleason score (GS) of 3 + 4 = 7 (grade group 2), or serum prostate-specific antigen (PSA) of 10–20 ng/ml.[7]. The relative importance of these intermediate-risk features within this heterogeneous group is unknown. Specifically, GS 3 + 4 is often thought to be a stronger risk factor than elevated PSA, and some guidelines caution against the use of AS for patients who are at an fIR due to a GS of 3 + 4 [8].

Previous studies investigating AS have compared outcomes between risk groups demonstrating the role of AS in fIR disease [9–11]. Outcomes have also been found to be similar for fIR patients regardless of race [12]. However, there exist no data comparing the outcomes of patients included in the fIR group by GS or serum PSA.

The Veterans Health Administration (VHA) is a relatively equal-access medical system that provides AS to a large and diverse population of men with prostate cancer. In this study, we identified men with fIR prostate cancer and assessed whether outcomes differed for men included by GS or serum PSA. We hypothesized that men included in the fIR group by GS would have a higher risk of metastatic disease and prostate cancer–specific mortality (PCSM) than men included by PSA.

2. Patients and methods

We performed a retrospective analysis using the VHA Corporate Data Warehouse (CDW) and the VHA Informatics and Computing Infrastructure. The study was reviewed and approved by the Institutional Review Board and the Research and Development Committee of the VHA San Diego Health Care System (protocol number 150169).

The study population consisted of African American or non-Hispanic White men diagnosed with fIR prostate cancer between January 1, 2001 and December 31, 2015, who pursued AS. Patients were classified as those undergoing AS if they received at least one additional prostate biopsy after their initial diagnostic biopsy. In addition, they must not have received a prostatectomy, definitive radiation therapy, or androgen deprivation therapy in the 1st year after diagnosis.

Patients were defined as having an fIR according to the NCCN criteria [2], with the exception that percentage biopsy cores positive was not considered as it cannot be ascertained reliably in the database. To examine the prognostic impact of GS and PSA as intermediate-risk features, these patients were classified as having either GS 3 + 4 = 7 with PSA <10 (fIR-GS) or GS 3 + 3 = 6 and PSA 10–20 (fIR-PSA). Patients who were at an fIR for other reasons (eg, clinical stage T2) were excluded from this analysis. Men were also excluded if they have a history of prior pelvic radiation or were missing demographic information used to estimate the median income and education level. The fIR outcomes were compared with the outcomes of a previously published cohort of unfavorable intermediate-risk (UnFav) to allow a comparison of both fIR subsets with a known higher-risk group [11].

Demographic and clinical information were collected from the VHA CDW, including race, age, Charlson Comorbidity Index (CCI), smoking status, and year of diagnosis. Education level (% with bachelor's degree) and median income were estimated based on patient ZIP code using the US census data. For multivariate analyses, patients were stratified as above versus below the median values for these measures. US geographic regions were classified as West, Midwest, South, and Northeast according to US census classifications [13].

The primary endpoint of the study was the incidence of metastatic prostate cancer, with the secondary endpoints including receipt of definitive prostate cancer treatment, PCSM, and all-cause mortality (ACM) [14]. Data collection for these endpoints has been described previously [11]. Briefly, receipt of definitive treatment is based on a combination of ICD9/10 and CPT codes. Metastatic disease was identified based on a targeted chart review of patients with ICD9/10 codes for metastases, PSA over 20, receipt of androgen deprivation therapy, or receipt of bone scans. Mortality (including whether the death was attributed to prostate cancer) was obtained from the National Death Index through 2015 and via a manual chart review subsequently.

2.1. Statistical analysis

Baseline characteristics were compared using Pearson chi-square and Wilcoxon rank sum tests for categorical variables, and analysis of variance for continuous variables. Receipt of definitive treatment, metastatic disease, PCSM, and ACM were analyzed with cumulative incidence functions, with Gray's test used to assess statistical significance. Death from any cause was censored as a competing event for the analysis of definitive treatment and metastatic disease. Death from non–prostate cancer causes was censored as a competing event for the analysis of PCSM. Multivariable Fine-Gray competing risk regressions were used to evaluate the predictors of definitive treatment, metastatic disease, and PCSM. Analyses were conducted in RStudio 3.5.1 with a significance level of $\alpha = 0.05$.

3. Results

The final cohort consisted of 663 men: 441 were non-Hispanic White patients and 222 were African American (Table 1). This included 404 (61%) fIR-GS and 259 (39%) fIR-PSA patients. These cohorts were compared with a group of veterans receiving AS for UnFav prostate cancer (n = 234) for whom outcomes have previously been published [11]. The median follow-up was 7.88 yr. The fIR-GS, fIR-PSA, and UnFav groups were balanced in terms of comorbidity burden, income level, and year of diagnosis. The only significant difference at baseline was that the fIR-GS patients were slightly younger than the other groups (mean age: 65.1 yr fIR-GS vs 66.3 yr fIR-PSA vs 66.3 yr UnFav, p = 0.034).

3.1. Incidence of metastatic disease

There was a total of 79 occurrences of metastatic disease (fIR-GS n = 28; fIR-PSA n = 17; UnFav n = 34) in the study population at 10 yr. Cumulative incidence function demonstrated a rate of development of metastatic disease at 10 yr of 5.8% for fIR-GS patients, 8.6% for fIR-PSA patients, and 15.2% for UnFav patients (Fig. 1). Pairwise testing showed that the lower rates of metastatic disease in fIR-GS (p = 0.002) and fIR-PSA (p = 0.016) patients were statistically significant compared with UnFav patients; however, there were no differences between fIR-GS and fIR-PSA patients (p = 0.77). A multivariable analysis (Table 2) confirmed that UnFav disease was the only significant predictor of the development of metastatic disease (subdistribution hazard ratio [sHR] 2.13, 95% confidence interval [CI] 1.29–3.53, p = 0.003)

3.2. Receipt of definitive treatment

There was a total of 697 definitive treatment events (fIR-GS n = 324; fIR-PSA n = 195; UnFav n = 178) in the study population at 10 yr. The estimated cumulative incidence rates from the model for definitive treatment at 10 yr were 81.5% for fIR-GS patients, 77.6% for fIR-PSA patients, and 76.4% for UnFav patients (p = 0.43). There was no significant difference in the receipt of definitive prostate cancer treatment between the intermediate-risk groups (Fig. 2A). On multivariate regression, the only significant predictors of receipt of definitive treatment were younger age at diagnosis and diagnosis later in the study period (2011–2015; Supplementary Table 1).

3.3. Prostate cancer–specific mortality

There was a total of 37 PCSM events (fIR-GS n = 10; fIR-PSA n = 11; UnFav n = 16) in the study population at 10 yr. The estimated cumulative incidence rates were 2.5% for fIR-GS patients, 5.7% for fIR-PSA patients, and 6.5% for UnFav

Table 1 – Baseline characteristics of the study population

	Favorable by GS	Favorable by PSA	Unfavorable [11]	p value
Total n	404 (61)	259 (39)	234	
Race				0.784
African American	143 (35.4)	79 (30.5)	78 (33.3)	
White	261 (64.6)	180 (69.5)	156 (66.7)	
Cigarette smoking				0.904
Yes	90 (22.3)	54 (20.8)	50 (21.4)	
No	314 (77.7)	205 (79.2)	184 (78.6)	
Comorbidities				0.784
CCI score = 0	304 (75.2)	203 (78.4)	180 (76.9)	
CCI score = 1	76 (18.8)	46 (17.8)	41 (17.5)	
CCI score = 2	24 (5.9)	10 (3.9)	13 (5.6)	
Region				0.334
West	98 (24.3)	65 (25.1)	45 (19.2)	
Midwest	104 (25.7)	70 (27.0)	54 (23.1)	
South	125 (30.9)	81 (31.3)	79 (33.8)	
Northeast	77 (19.1)	43 (16.6)	56 (23.9)	
Income ($) [a]				0.792
<30 000	34 (8.4)	19 (7.3)	18 (7.7)	
30 000–60 000	267 (66.1)	177 (68.3)	153 (65.4)	
60 000–100 000	93 (23.0)	56 (21.6)	52 (22.2)	
>100 000	10 (2.5)	7 (2.7)	11 (4.7)	
Education [b]				0.776
<10%	93 (23.0)	66 (25.5)	55 (23.5)	
10–20%	202 (50.0)	123 (47.5)	114 (48.7)	
20–30%	79 (19.6)	54 (20.8)	54 (23.1)	
>30%	30 (7.4)	16 (6.2)	11 (4.7)	
Year of diagnosis				0.870
2001–2005	31 (7.7)	19 (7.3)	18 (7.7)	
2006–2010	124 (30.7)	75 (29.0)	78 (33.3)	
2011–2015	249 (61.6)	165 (63.7)	138 (59.0)	
Age at diagnosis, mean (SD)	65.14 (6.20)	66.31 (5.96)	66.27 (7.67)	**0.034**
Follow-up (yr), mean (SD)	7.94 (2.77)	7.69 (2.83)	7.96 (2.58)	0.420

CCI = Charlson Comorbidity Index; GS = Gleason score; PSA = prostate-specific antigen; SD = standard deviation.
Data are shown as number (%). Significant p values are bolded.
[a] Median household income, by ZIP code.
[b] Percentage with at least a bachelor's degree, by ZIP code.

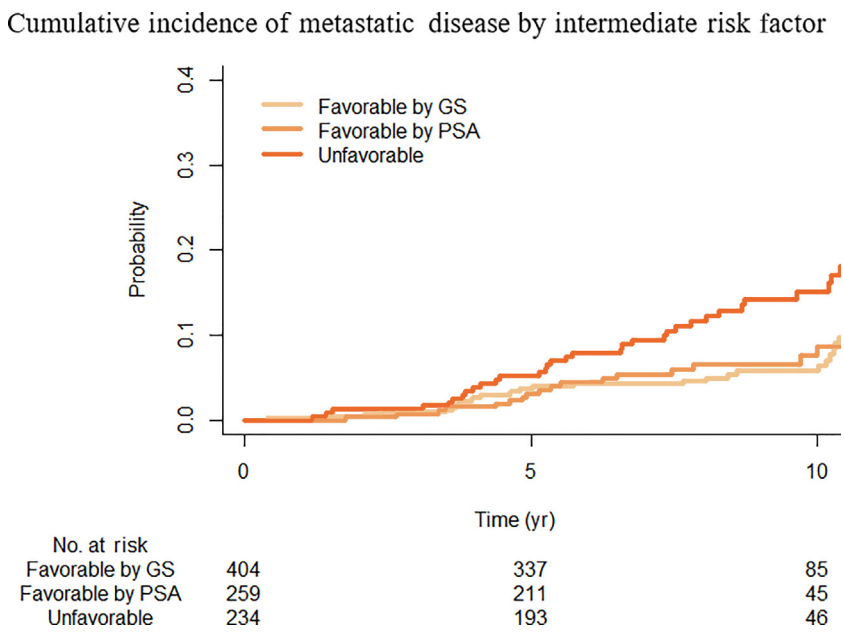

Fig. 1 – Cumulative incidence of metastatic disease by intermediate risk feature. GS = Gleason score; PSA = prostate-specific antigen.

Table 2 – Multivariable Fine-Grey regressions for incidence of metastatic disease and PCSM

	Metastatic disease		PCSM	
	Subdistribution hazard ratio	*p* value	Subdistribution hazard ratio	*p* value
Race (ref = White)				
African American	0.824	0.43	1.266	0.47
Cigarette Smoking (ref = no)				
Yes	1.307	0.34	0.910	0.83
Comorbidities (ref = 0)				
CCI score = 1	1.087	0.78	1.379	0.42
CCI score = 2	1.352	0.55	1.826	0.32
Region (ref = West)				
Midwest	0.952	0.87	0.567	0.23
South	0.747	0.35	0.804	0.59
Northeast	0.713	0.34	0.651	0.37
Income (ref ≤$47 990 [a])				
≥$47 990	1.295	0.31	1.363	0.32
Education (ref ≤14.3% [a])				
≥14.3%	0.710	0.18	0.795	0.47
Year of diagnosis (ref 2001–2005)				
2006–2010	0.765	0.44	**0.343**	**0.009**
2011–2015	0.618	0.18	**0.354**	**0.021**
Age at diagnosis	0.997	0.87	1.01	0.63
Intermediate risk factor (ref = favorable by GS)				
Favorable by PSA	1.050	0.87	1.629	0.26
Unfavorable	**2.130**	**0.003**	**2.839**	**0.005**

CCI = Charlson Comorbidity Index; GS = Gleason score; PCSM = prostate cancer–specific mortality; PSA = prostate-specific antigen; ref = reference.
Significant values are bolded.
[a] Total cohort study median.

patients (Fig. 2B). The rate of PCSM was significantly higher in the UnFav population than in the fIR-GS population (p = 0.006), but not in the fIR-PSA population compared with the fIR-GS population (p = 0.274). On multivariable regression, unfavorable disease (sHR 2.84, 95% CI 1.36–5.92, p = 0.005) predicted higher PCSM and more recent year of diagnosis (2006–2010: sHR 0.34, 95% CI 0.15–0.77, p = 0.009; 2011–2015: sHR 0.36, 95% CI 0.15–0.86, p = 0.021) predicted lower PCSM (Table 2).

3.4. *All-cause mortality*

There was a total of 162 ACM events (fIR-GS n = 71; fIR-PSA n = 33; UnFav n = 58) in the study population at 10 yr. The estimated cumulative incidence rates from the model were 19.1% for fIR-GS patients, 16.8% for fIR-PSA patients, and 27.9% for UnFav patients (Fig. 2C). There was no significant difference in ACM between fIR-GS and fIR-PSA patients (p = 0.14), while both groups had significantly lower ACM

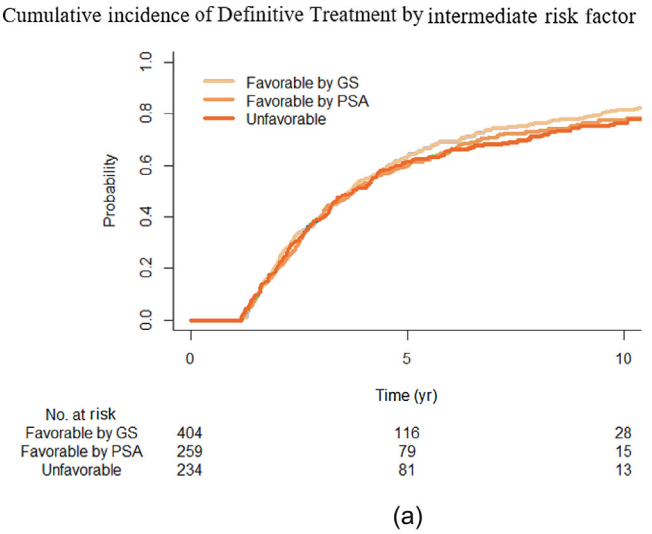

Fig. 2 – Cumulative incidence of (A) receipt of definitive prostate cancer treatment, (B) PCSM, and (C) ACM by intermediate-risk feature. ACM = all-cause mortality; GS = Gleason score; PCSM = prostate cancer–specific mortality; PSA = prostate-specific antigen.

than UnFav patients (p = 0.037 and p = 0.002, respectively). Significant predictors of higher ACM on multivariable regression included older age, higher CCI scores, cigarette smoking, and UnFav disease (Supplementary Table 2).

4. Discussion

In this large cohort of men managed with AS for fIR prostate cancer, we found that men included by GS, compared with men included by PSA, did not have a statistically significantly higher incidence of definitive prostate cancer treatment, metastatic prostate cancer, PCSM, or ACM. Both groups had a significantly lower risk of experiencing metastatic disease, PCSM, and ACM than a previously published cohort of UnFav patients. These findings are relevant for men with fIR prostate cancer as defined by GS or PSA, as these suggest that select men in either group may be considered for AS independent of their fIR risk factor.

The rate of AS compared with definitive treatment in men with fIR prostate cancer continues to rise [6]. Although the ProtecT trial, which demonstrated that AS does not compromise survival, included some fIR patients, no subgroup analysis was conducted to compare those included by GS or PSA [9]. Several studies have compared AS in men with fIR prostate cancer included by GS or PSA, suggesting that those included by GS have an increased risk of eventual adverse pathology [15] and decreased metastasis-free survival [16]. The latter study by Musunuru et al [16] included 213 intermediate-risk prostate cancer patients, and found that patients with GS 3 + 4 and PSA <20 had 10% lower metastasis-free survival at 15 yr than those with GS 3 + 3 and PSA 10–20; however, their results may have been driven by UnFav patients, as no differentiation between UnFav and fIR was performed. In contrast, our study suggests that at a median follow-up of 7.88 yr, there are no significant differences in outcome within the fIR group regardless of inclusion by GS or PSA.

For patients and clinicians, rising PSA during AS is a potential source of anxiety [17]. These rises may be due to benign prostate growth as patients continue to age or true cancer progression. Electing to undergo AS with fIR prostate cancer is a complex medical decision that should incorporate assessment of patient life expectancy, comorbidities, as well as patient and clinician preferences and concerns. We found that increasing age predicted a lower likelihood of receipt of definitive treatment. Age was also a significant predictor of increased ACM but not of increased PCSM when undergoing AS. Overall, these data suggest that AS may be an appropriate management option for select men with fIR prostate cancer independent of their inclusion criteria by GS or PSA and that older patients may be stronger candidates for AS to preserve quality of life in the setting of relatively increased ACM but similar PCSM [16].

With multiple appropriate management options, fIR prostate cancer represents a strong opportunity to integrate shared decision-making (SDM) into urological practice. SDM incorporates patient perspectives and understanding of disease with physician knowledge of treatment options to direct care [18]. SDM is particularly suitable for long-term disease management, where patients are more likely to report feeling informed or empowered in their decision, more likely to adhere to the treatment regimen, and less likely to regret their treatment choice [19–21]. Moreover, patients who elect to undergo AS demonstrate lower treatment-related regret than those undergoing radiation therapy or radical prostatectomy [22]. Patients with fIR prostate cancer may be able to undergo AS independent of their inclusion by GS or PSA, and clinicians should incorporate patient anxiety and understanding of disease into SDM to jointly elect a final treatment decision. Moreover, as data identifying prostate cancer biomarkers evolve, patients and clinicians will have additional individualized data points to guide management, further strengthening the importance of SDM for fIR disease.

This study has multiple limitations. We did not examine core involvement or percentage of GS pattern 4 in patients with grade group 2 disease, as it was not possible to reliably estimate these values in the database. As a retrospective study, protocols for AS may differ between providers and through time. We attempted to exclude watchful waiting patients by requiring all patients to have at least one follow-up prostate biopsy after the initial diagnosis of fIR prostate cancer. However, triggers for biopsy and definitive treatment were not standardized and may have varied throughout the study period. Despite this, our overall rates of definitive treatment, metastasis, PCSM, and ACM are similar to those reported in previous studies [16,23–25]. The substantial reduction in PCSM during the later periods of the study (2006 and beyond) likely reflects increasing usage of AS during this period and improvements in surveillance and treatment protocols. Second, screening for metastasis was not protocoled in these patients. It is possible that some patients with metastatic disease were not included in manual chart review because they underwent incomplete or insufficient clinical evaluation. Third, our outcome data were limited to 10 yr after the initial diagnosis with a median follow-up of <8 yr. It may be possible that differences in the rate of metastasis or survival will manifest at 15- or 20-yr time points. Finally, previous research has suggested that PSA density (PSAD) may be used to stratify the risk of prostate cancer patients and that fIR-PSA patients with PSAD values <0.15 ng/ml/cc may be classified inaccurately as having fIR instead of low-risk disease [26–30]. However, we do not have consistent data regarding prostate size and thus PSAD, which is an important factor that we could not account for. These patients may have had improved outcomes compared with fIR-PSA patients with abnormal PSAD and fIR-GS patients. Likewise, the use of 5a-reductase inhibitors may artificially decrease PSA values and could not be accounted for in our analysis. There also exists the likely selection bias that some AS-eligible men elected for early curative treatment. Despite these concerns, the geographic and ethnic representativeness of this cohort strengthen the generalizability of these findings.

5. Conclusions

In conclusion, this study found no evidence of different clinical outcomes after management with AS for men with fIR prostate cancer included by GS or PSA in the Veterans

Affairs Health Administration. This suggests that AS may be offered to select men with fIR prostate cancer independent of inclusion by GS or PSA, even with the presence of grade group 2 disease. However, prospective studies and continued, long-term follow-up are necessary to validate these findings.

***Author contributions*:** Austin J. Leonard had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.
Acquisition of data: All authors.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: All authors.
Obtaining funding: None.
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Appendix A. Supplementary data

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