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Modified Risk Stratification Grouping Using Standard Clinical and Biopsy Information for Patients Undergoing Radical Prostatectomy: Results from SEARCH

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Abstract

Introduction—Prostate cancer is a heterogeneous disease, and risk stratification systems have been proposed to guide treatment decisions. However, significant heterogeneity remains for those with unfavorable-risk disease.

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Methods—This study included 3335 patients undergoing radical prostatectomy without adjuvant radiotherapy in the SEARCH database. High-risk patients were dichotomized into standard and very high-risk (VHR) groups based on primary Gleason pattern, percentage of positive biopsy cores (PPBC), number of NCCN high-risk factors, and stage T3b-T4 disease. Similarly, intermediate-risk prostate cancer was separated into favorable and unfavorable groups based on primary Gleason pattern, PPBC, and number of NCCN intermediate-risk factors.

Results—Median follow-up was 78 months. Patients with VHR prostate cancer had significantly worse PSA relapse-free survival (PSA-RFS, P<0.001), distant metastasis (DM, P=0.004), and prostate cancer specific mortality (PCSM, P=0.015) in comparison to standard high-risk (SHR) patients in multivariable analyses. By contrast, there was no significant difference in PSA-RFS, DM, or PCSM between SHR and unfavorable intermediate-risk (UIR) patients. Therefore, we propose a novel risk stratification system: Group 1 (low-risk), Group 2 (favorable intermediate-risk), Group 3 (UIR and SHR), and Group 4 (VHR). The c-index of this new grouping was 0.683 for PSA-RFS and 0.800 for metastases, compared to NCCN risk groups which yield 0.666 for PSA-RFS and 0.764 for metastases.

Conclusions—Patients classified as VHR have markedly increased rates of PSA relapse, DM, and PCSM in comparison to SHR patients, whereas UIR and SHR patients have similar prognosis. Novel therapeutic strategies are needed for patients with VHR, likely involving multimodality therapy.

Keywords

Prostate Cancer; Very high risk prostate cancer; unfavorable intermediate risk; Risk Stratification

INTRODUCTION

The clinical behavior of prostate cancer is extraordinarily heterogeneous. For example, a significant proportion of prostate cancers have limited propensity for metastasis and can be safely managed without any local or systemic treatment.[1,2] On the other hand, prostate cancer remains a leading cause of death for men worldwide due to a minority of prostate cancers that exhibit a lethal phenotype, with eventual evolution to a disease state that is refractory to all known treatments despite aggressive therapy.[3,4] In order to identify where along this spectrum a given prostate cancer is likely to exist, risk stratification systems, based primarily on clinical and pathologic factors, have been developed.

The National Comprehensive Cancer Network (NCCN) risk stratification system is one of the most commonly employed prostate cancer risk stratification tools.[5] The NCCN system uses clinical tumor stage, biopsy ISUP grade group,[6] and pretreatment PSA to stratify patients into risk groups. Although the discriminatory ability of this classification has been validated in numerous studies, there remains substantial heterogeneity of outcomes within each risk group, especially for high risk patients.[3,7,8] Therefore, several modifications have been proposed.[3,7,8]

The NCCN is now incorporating a substratification of high risk prostate cancer into its guidelines by employing primary Gleason pattern, number of high grade cancer cores, gross

seminal vesicle or extra-prostate organ invasion, and number of NCCN high risk factors to identify a "very high risk" subgroup with poor outcomes.[3] However, these criteria have not been extensively validated in independent datasets. Moreover, the relationship of this high risk category modification to other proposed modifications to the NCCN system, such as the dichotomization of the intermediate risk group into favorable and unfavorable subgroups, is unclear.[9,10] Using the Shared Equal Access Regional Center Hospital (SEARCH) database, we sought to validate the NCCN very high risk prostate cancer classification, and attempt to combine both proposed dichotomizations of intermediate and high risk disease, respectively, into a single unified system.[3,9,10]

MATERIALS AND METHODS

Materials and Methods

Study Design—After obtaining Institutional Review Board approval, men who underwent radical prostatectomy at six Veterans Affairs Hospitals (Palo Alto, San Diego, West Los Angeles, CA; Augusta, GA; Durham, Asheville, NC) from 1988–2015 were combined in the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Men with neoadjuvant therapy were not included. Of 5,398 men in the database, we excluded men with missing biopsy grade group (n=484), PSA (n=87), clinical stage (n=334), percent of biopsy cores with cancer (n=870), race (n=29), pathological features (n=95), follow-up information (n=27), and men who received adjuvant treatment (n=137), resulting in a study population of 3,335 men.

Patients were grouped into five risk categories: low risk (biopsy ISUP grade group 1, T1a-T2a, and PSA <10ng/ml), favorable intermediate risk (FIR), unfavorable intermediate risk (UIR), standard high risk (SHR), very high risk (VHR). Patients defined as intermediate risk according to NCCN guidelines (T2b or T2c, biopsy ISUP grade group 2–3 (Gleason score 3+4 or 4+3), or PSA 10–20ng/ml) were considered UIR if they had biopsy ISUP grade group 3 (Gleason score 4+3), percentage of positive biopsy cores (PPBC) ≥50%, or multiple intermediate-risk factors (T2b or T2c, biopsy grade group 2–3, or PSA 10–20ng/ml).[5] All other intermediate risk patients were classified as FIR prostate cancer. Patients defined a high risk according to NCCN guidelines (biopsy ISUP grade group 4–5, T3-T4, or PSA ≥20ng/ml) were considered VHR if they had primary Gleason pattern 5, >50% positive biopsy cores, or multiple high-risk factors (biopsy ISUP grade group 4–5, T3-T4, or PSA ≥20ng/ml), and SHR otherwise. The criterion of >50% positive cores was used instead of the current VHR NCCN criterion, 5 or more cores of ISUP grade group 4–5 disease, for several reasons. First, PPBC has been repeatedly validated as an important predictor of outcome in multiple independent datasets,[9,11,12] and is current used as a factor to distinguish favorable from unfavorable intermediate risk.[9] Furthermore, the absolute number of cores with Gleason score ≥ 8 is highly dependent on the number of cores taken, whereas PPBC, being a relative measure, is independent of the number of cores taken, assuming oversampling of suspicious areas in not performed. Lastly, PPBC was available in our database, whereas absolute number of ISUP grade group 4–5 cores was not.

Patients were followed to determine clinical endpoints after surgery. PSA recurrence-free survival (PSA-RFS) was defined as a single PSA greater than 0.2 ng/ml, 2 values of 0.2

ng/ml, or secondary treatment for an elevated postoperative PSA. Development of distance metastases (DM) was determined by bone scans or other imaging. Prostate cancer-specific mortality (PCSM) was defined as having metastatic progressive CRPC at time of death with no obvious indication of another cause of death. All-cause mortality (ACM) was determined from the medical records.

Statistical Analysis—Characteristics of VHR patients vs. all others were compared using t-tests or rank sum tests for continuous variables and chi-squared tests for categorical variables. The association between risk group (low-risk, FIR, UIR, SHR, VHR) and the clinical endpoints (PSA-RFS, DM, ACM) was tested using Cox proportional hazards models. Competing risks models were used to test the association between risk group and PCSM, with non-prostate cancer death as the competing risk. Multivariable models were adjusted for age, race, year of surgery, and surgical center. Analyses were repeated changing the reference risk group to compare patients with SHR to those with UIR and VHR. Then, men with UIR and SHR were combined into one group and compared to those with low-risk or FIR, and men with VHR were also compared to those with low-risk or FIR. Cumulative incidence curves were plotted for the five risk groups and each of the clinical endpoints. A new stratification system was created by combining groups with similar risk. C-indices were compared between our new risk grouping and the standard 3-tiered NCCN risk groups. Statistical significance was defined as $P<0.05$. All analyses were performed using Stata v14.0.

RESULTS

Baseline characteristics are summarized in Table 1. Median follow-up for the entire cohort from date of prostatectomy was 78 months (IQR: 40–127). For patients with NCCN intermediate risk disease, 654 and 968 were classified as FIR and UIR disease, respectively. For patients with NCCN high risk disease, 291 were classified as SHR and 314 were classified as VHR. For VHR patients, 237 were classified as VHR due to PPBC ≥50%. During follow-up, there were 1105 recurrences, 125 metastases, 65 prostate cancer-related deaths, and 662 deaths due to causes other than prostate cancer.

We compared PSA-RFS, DM, PCSM, and ACM rates for patients with low risk, FIR, UIR, SHR, and VHR disease (Figure 1, Table 2). Compared to patients with low risk disease, those with VHR cancers had markedly higher rates of PSA-RFS (adjusted hazard ratio (AHR)=6.30, 95% confidence interval (CI): 5.15–7.69, $P<0.001$), DM (AHR=18.4, 95% CI: 9.27–36.3, $P<0.001$), PCSM (AHR = 14.0, 95% CI: 6.08–32.3, $P<0.001$) and ACM (AHR = 1.65, 95% CI: 1.27–2.15, $P<0.001$) in multivariable analyses. Notably, FIR had worse PSA-RFS (AHR=1.65, 95% CI: 1.35–2.01, $P<0.001$) and DM (AHR=2.42, 95% CI: 1.06, 5.50, $P=0.035$) in comparison to low risk patients, but there was no significant difference in PCSM (AHR = 2.03, 95% CI: 0.74–5.53, $P=0.17$), or OS (AHR = 1.16, 95% CI = 0.93–1.44, $P=0.19$) in multivariable analysis.

Compared to those with SHR disease (Figure 1a–d, Table 3), patients with VHR cancers had worse PSA-RFS (AHR=1.78, 95% CI: 1.41–2.24, $P<0.001$), DM (AHR=2.42, 95% CI: 1.32–4.46, $P=0.004$), and PCSM (AHR = 3.18, 95% CI: 1.25–8.11) in multivariable

analysis. By contrast, there was no difference in PSA-RFS (HR=0.86, 95% CI: 0.69–1.07, P=0.19), DM (HR= 0.68, 95% CI: 0.37–1.25, P=0.22), or PCSM (HR=0.66, 95% CI: 0.24–1.82, P=0.42) when comparing UIR to SHR patients. UIR and SHR patients had similar rates of both salvage ADT and salvage radiotherapy utilization (Supplementary Table 1). None of these groups had significantly different overall survival.

Given the similar outcomes for SHR and UIR patients, we create a 4-tiered risk stratification system: Group 1 (low risk), Group 2 (FIR), Group 3 (UIR and SHR), and Group 4 (VHR) (Figure 2). These groups had significantly different PSA-RFS, DM, and PCSM (Table 4). For example, Group 4 patients had significantly higher risk of PSA-RFS (HR=2.00; 95% CI: 1.69–2.37, P<0.001), DM (HR=2.47; 95% CI: 1.64–3.73; P<0.001), and PCSM (HR=3.04; 95% CI: 1.70–5.45; P<0.001) in comparison to Group 3 patients in multivariable analyses. Similarly, Group 3 patients had significantly higher risk of PSA-RFS (AHR=1.91; 95% CI: 1.61–2.27, P<0.001) and DM (HR=3.07; 95% CI: 1.66–5.68; P<0.001), and borderline significant difference in PCSM (HR=2.27; 95% CI: 1.00–5.20; P=0.052) in comparison to Group 2. These groups had 10 year PSA-RFS rates of 76.4%, 61.6%, 44.1%, and 31.5% (P<0.001), 10 year DM rates of 0.7%, 2.8%, 6.9%, and 16.3% (P<0.001), and 10 year PCSM of 0.3%, 1.9%, 3.3%, and 10.9% (P<0.001) following prostatectomy for Groups 1–4, respectively. The c-index of this new grouping was 0.683 for PSA-RFS and 0.800 for metastases, compared to NCCN risk groups which yield 0.666 for PSA-RFS and 0.764 for metastases.

DISCUSSION

In this study, we validated that high risk prostate cancer is a heterogeneous disease that can be dichotomized into SHR and VHR groups based on primary Gleason pattern, PPBC, and number of NCCN high risk features. These criteria, which are similar to the system now recommended by NCCN guidelines,[3] identify distinct clinical entities with disparate outcomes following prostatectomy. After adjustment for other factors in multivariable analysis, VHR patients were 2.4 times as likely to experience DM and 3.2 times as likely to die from prostate cancer as those with SHR disease. We note that these differences were observed despite the fact that patients with VHR disease in this study were selected to undergo surgery, and thus probably were more likely to have organ-confined disease, lower tumor bulk, lower comorbidity, and younger age than those VHR patients undergoing radiation and androgen deprivation. Overall, nearly 70% of VHR experienced PSA relapse within 10 years of prostatectomy, with 16% experiencing DM and 11% having PCSM during this time period. However, it is important to note that the median follow-up for the VHR cohort was 78 months, and increased prostate cancer related recurrences and deaths are likely with longer follow-up.

We also observed that SHR patients not meeting VHR criteria had no difference in PSA-RFS, DM, PCSM, or OS when compared to those with UIR disease. Given that SHR patients are much more similar to UIR patients than VHR patients, we propose modifying current NCCN criteria not only to separate high risk disease into SHR and VHR groups, as is currently allowed, but also combining UIR and SHR patients into a single risk group.

Our results are remarkably consistent with a recent study of prostate cancer patients undergoing dose-escalated radiation therapy (RT) with or without androgen deprivation therapy at a high-volume academic institution.[13] As in this study, VHR patients were found to have dramatically worse outcomes following RT in comparison to SHR patients. Additionally, SHR and UIR patients undergoing RT had identical clinical outcomes, similar to what was observed in our surgical cohort. The consistency of these findings across independent datasets from disparate practice settings and using different treatment paradigms provides strong support that these results may be broadly applicable to patients with localized prostate cancer, and provides independent validation of our results.

These results have important potential implications for therapeutic recommendations. Given the similar outcomes for UIR and SHR prostate cancer following prostatectomy, it is likely that these patients will benefit from similar therapeutic paradigms. This may mean that a proportion of high risk patients are able to undergo risk group de-escalation, and potentially receive deintensified treatment regimens. For example, SHR patients undergoing definitive radiation may be adequately treated according to intermediate-risk paradigms, using short-term rather than long-term androgen deprivation therapy. Similarly, radical prostatectomy and pelvic lymph node dissection without adjuvant treatment may cure a substantial proportion of SHR patients. On the other hand, VHR prostate cancer likely will require more aggressive management strategies and likely neoadjuvant systemic therapy based upon pre-surgical assessments of disease aggressiveness. Across cancer types, the majority of the most aggressive malignancies require a combination of surgery, radiation, and systemic therapy to maximize the likelihood of cure. Extrapolating from this paradigm to VHR prostate cancer, these patients may derive benefit from multi-modality approaches that combine radical prostatectomy with adjuvant radiotherapy and concomitant androgen deprivation. However, optimal management of SHR and VHR remains speculative, because few randomized studies incorporating surgery have been conducted in these patients. Prospective evaluation of therapeutic paradigms for SHR and VHR patients, especially those incorporating radical prostatectomy, is warranted.

We note that our VHR criteria differed slightly from those endorsed by the NCCN, first proposed by investigators from Johns Hopkins after a systematic evaluation of prognostic factors. First, no patients in our study had clinical invasion of the seminal vesicle, rectum, or bladder, which are considered very high risk criteria. Secondly, instead of using 5 or more cores of ISUP grade group 4–5 disease as a criterion for VHR classification, we chose to PPBC greater than 50% as a VHR feature, given that this number was readily available in our database and PPBC has been repeatedly validated as an important predictor of outcome in multiple independent datasets.[9,11,12] Furthermore, the absolute number of cores with Gleason score ≥ 8 is highly dependent on the number of cores taken, whereas PPBC, being a relative measure, is independent of the number of cores taken, assuming oversampling of suspicious areas in not performed. It is notable that approximately 75% of VHR patients in our study were classified as VHR due to PPBC ≥ 50%, likely as a result of patients with other aggressive features being preferentially treated with androgen deprivation and radiation at the institutions contributing to our database. Although this limits to a certain degree the comparison of our results to previous studies that used biopsies with greater than 4 cores of Gleason 8–10 prostate cancer to define VHR disease,[3] the hazard ratios we report

for DM (HR=2.4) and PCSM (HR=3.2) when comparing the VHR and SHR groups in this study are similar to those observed in the original study from Johns Hopkins that proposed this criterion (DM: HR=2.8, PCSM: HR=3.4). This suggests that either biopsy core metric is likely to be useful when identifying VHR patients, given that both identify high-risk patients with high-volume prostate cancer. However, at institutions that extensively use MRI-guided biopsy with oversampling suspicious areas on imaging, and the utility of PPBC or absolute number of high grade cores may be reduced given that it no longer provides as accurate a measure of overall tumor volume, and alternate metrics may be necessary.

Our study has several limitations that warrant further discussion. First, this is a retrospective study involving men treated at several VA hospitals across the country. Thus, these results are not necessarily applicable to all clinical practice environments or patient populations. However, our findings are consistent with what has been previously described for intermediate and high risk prostate cancer in other settings[3,7–9,13–16]. The follow-up for VHR patients was also significantly shorter than the follow-up time for other patients in the SEARCH database. This difference in follow-up is, in part, due to the fact that VHR patients were significantly more likely to be treated in recent years, likely related to national trends for increased use of prostatectomy in higher risk patients over the past decade.[17] Additionally, the use and timing of salvage therapy, which is known to impact DM and PCSM,[18] was not accounted for in our analysis. Nevertheless, we believe our study has several strengths, such as a relatively uniform treatment paradigm, excluding patients receiving androgen deprivation or adjuvant radiotherapy, a relatively large cohort, and a multi-institutional setting including numerous urologists, and we think that the results are robust despite their inherent limitations, especially in combination with similar reported results from patients undergoing radiotherapy.[13]

In summary, we have demonstrated that high risk prostate cancer is highly heterogeneous, and that primary Gleason pattern, number of positive biopsies cores, and number of NCCN high risk factors play an integral role in distinguishing those at highest risk for adverse outcomes following prostatectomy. Moreover, high risk patients not meeting VHR criteria have identical prognosis to those with UIR disease, and we therefore suggest combining these groups both for prognostic and therapeutic purposes. Further advancements in risk stratification using novel imaging, genomic, proteomic, and novel molecular biomarkers, will hopefully continue to improve our ability to risk stratify these patients in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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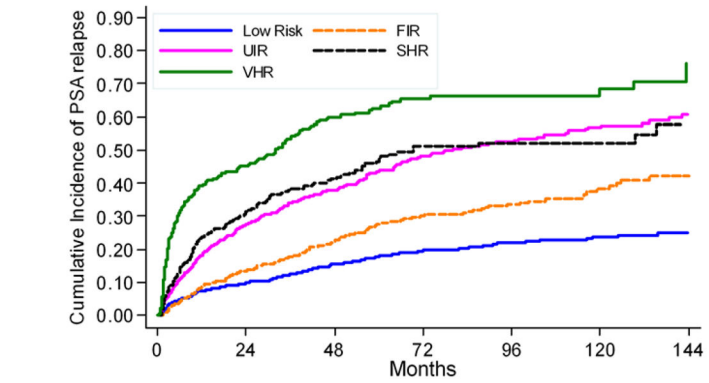
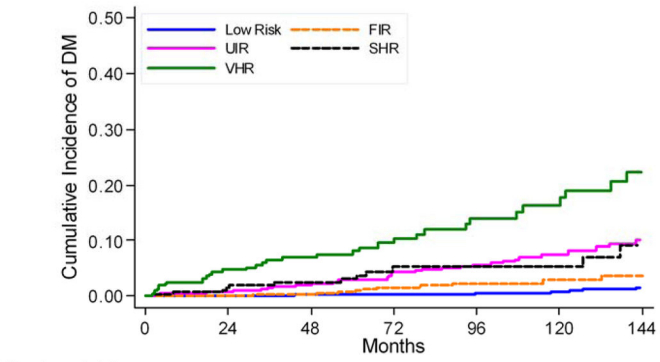


Number at risk

Low Risk	1108	723	407	163
FIR	654	307	134	44
UIR	968	340	122	40
SHR	291	99	36	12
VHR	314	70	25	9

Figure 1a



Number at risk

Low Risk	1108	905	599	288
FIR	654	429	237	98
UIR	968	618	308	127
SHR	291	168	94	39
VHR	314	173	83	43

Figure 1b

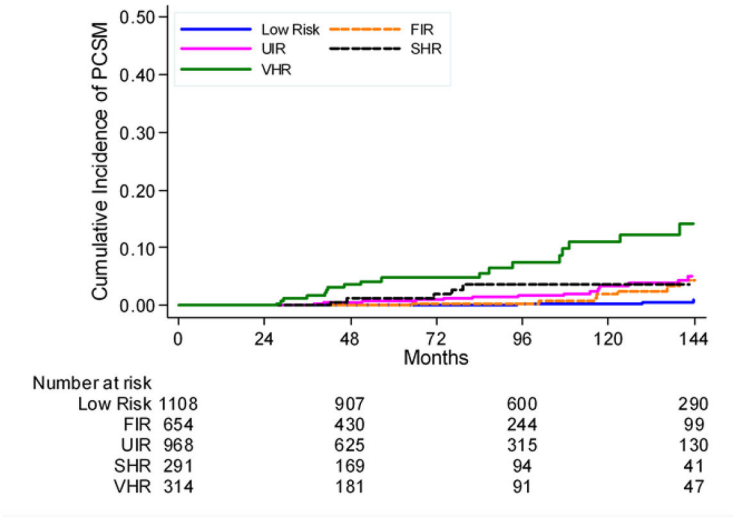


Figure 1c

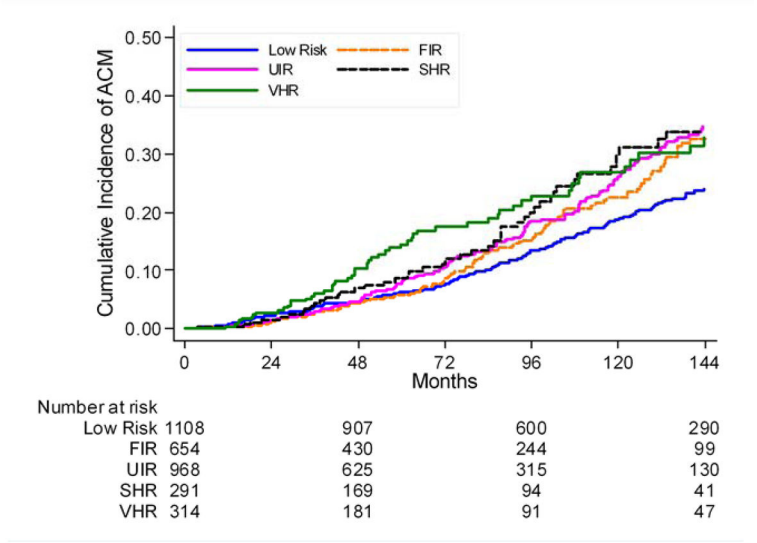


Figure 1d

Figure 1.

Cumulative incidence of A) PSA recurrence (PSA-RFS), B) distant metastasis (DM), C) prostate cancer-specific mortality (PCSM), and D) all cause-mortality (ACM) for low risk, favorable intermediate risk (FIR), unfavorable intermediate risk (UIR), standard high risk (SHR) and very high risk (VHR) cohorts.

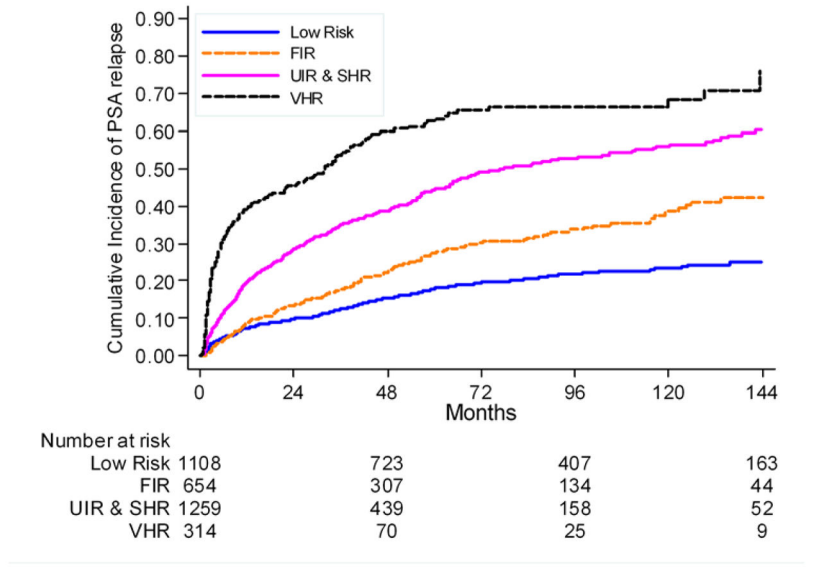
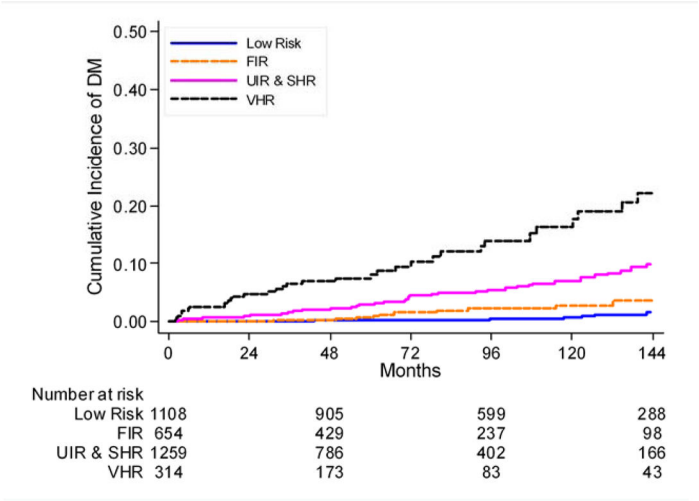


Figure 2a



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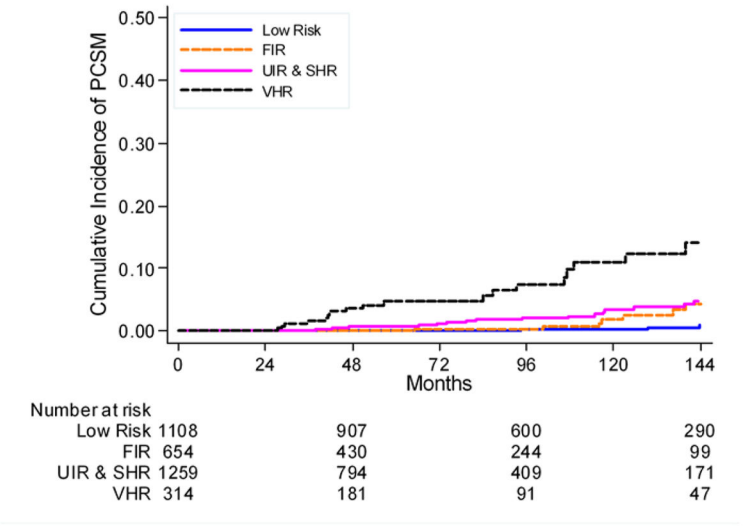

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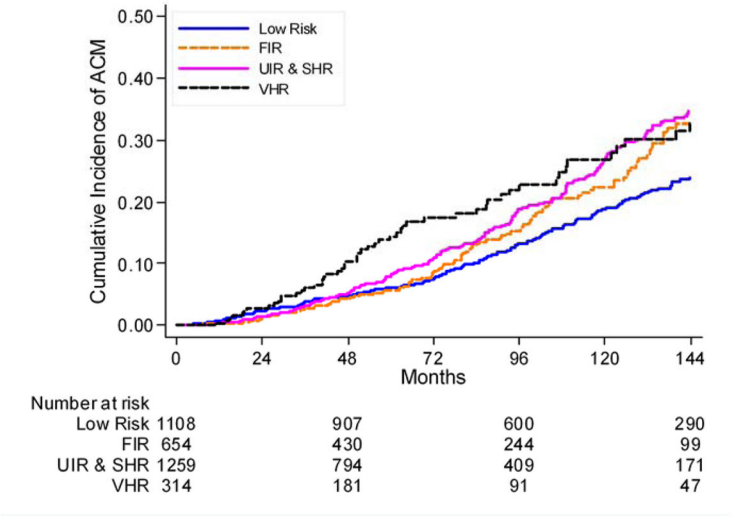

Figure 2d

Figure 2.

Cumulative incidence of A) PSA recurrence (PSA-RFS), B) distant metastasis (DM), C) prostate cancer-specific mortality (PCSM), and D) all cause-mortality (ACM) for proposed 4-tier risk stratification system.

Table 1

Baseline clinical and pathologic characteristics of the dataset.

	All Others	VHR	P-value
No. of Patient (%)	3021 (90.6)	314 (9.4)	-
PSA Follow-up mo, Median (IQR) *	61.3 (30.8, 106.7)	39.6 (18.1, 70.3)	<0.001[1]
Total Follow-up mo, Median (IQR) **	77.3 (39.4, 127.0)	52.4 (29.2, 98.7)	<0.001[1]
Age, yr, Mean (SD)	61.6 (6.2)	62.9 (5.8)	<0.001[2]
Race			0.725[3]
White	1703 (56.4)	184 (58.6)	
Black	1225 (40.5)	120 (38.2)	
Other	93 (3.1)	10 (3.2)	
Year of Surgery, Median (IQR)	2007 (2002, 2011)	2009 (2002, 2012)	<0.001[1]
Clinical T Stage, No. (%)			<0.001[3]
T1a-c	1915 (63.5)	158 (51.8)	
T2	83 (2.7)	8 (2.6)	
T2a	723 (24.0)	85 (27.9)	
T2b	162 (5.4)	34 (11.2)	
T2c	134 (4.4)	20 (6.5)	
Biopsy Gleason Score (%)			<0.001[3]
≤6	1493 (49.4)	28 (8.9)	
3+4	912 (30.2)	32 (10.2)	
4+3	408 (13.5)	22 (7.0)	
8–10	208 (6.9)	232 (73.9)	
PSA, Median (IQR)	6.2 (4.7, 9.1)	10.3 (6.1, 24.0)	<0.001[1]
Percentage Positive Biopsy Cores (%)			<0.001[3]
<50%	2207 (73.1)	32 (10.2)	
≥50%	814 (26.9)	282 (89.8)	
Pathological Gleason Score (%)			<0.001[3]
≤6	949 (31.4)	24 (7.6)	
3+4	1267 (42.0)	70 (22.3)	
4+3	508 (16.8)	87 (27.7)	
8–10	297 (9.8)	133 (42.4)	
Pathological Stage (%)			<0.001[3]
T0–T2	2389 (79.1)	144 (45.9)	
T3	540 (17.9)	151 (48.1)	
T4	92 (3.0)	19 (6.0)	
Positive Surgical Margins (%)	1150 (38.1)	176 (56.1)	<0.001[3]
Extracapsular Extension (%)	480 (15.9)	139 (44.3)	<0.001[3]
Seminar Vesicle Invasion (%)	201 (6.7)	102 (32.5)	<0.001[3]

	All Others	VHR	P-value
Lymph Nodes (%)			<0.001[3]
No	1921 (63.6)	276 (87.9)	
Yes	34 (1.1)	26 (8.3)	
Not Done	1066 (35.3)	12 (3.8)	
Number of Lymph Nodes Removed Median (IQR)	4 (2, 9)	6 (4, 11)	<0.001[1]
Received Salvage ADT (%)	368 (12.2)	116 (36.9)	<0.001[3]
Received Salvage XRT (%)	573 (19.0)	108 (34.4)	<0.001[3]

Abbreviations: SD, standard deviation; ADT, androgen-deprivation therapy; PSA, prostate-specific antigen; XRT, radiation therapy

P-value calculated using [1]rank sum test [2]student t test [3]chi-squared test

*Reported among those who did not recur

**Reported among those who did not die

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Table 2

Association between low risk patients vs. other categories (5 risk groups) and prostate cancer outcomes

Comparison of outcomes among low risk, favorable intermediate risk (FIR), unfavorable intermediate risk (UIR), standard high risk (SHR) and very high risk (VHR) cohorts using Cox univariable and multivariable regression assessing PSA recurrence free survival (PSA-RFS), distant metastasis (DM), prostate cancer-specific mortality (PCSM), and all cause-mortality (ACM). CI, confidence interval. HR, hazard ratio.

		Univariable		Multivariable*	
	Events/N	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
PSA-RFS					
Low Risk	225/1108	Ref.		Ref.	
FIR	172/654	1.58 (1.30, 1.93)	<0.001	1.65 (1.35, 2.01)	<0.001
UIR	400/968	2.97 (2.52, 3.51)	<0.001	3.09 (2.62, 3.65)	<0.001
SHR	123/291	3.17 (2.54, 3.95)	<0.001	3.33 (2.67, 4.17)	<0.001
VHR	185/314	5.57 (4.58, 6.78)	<0.001	6.30 (5.15, 7.69)	<0.001
DM					
Low Risk	11/1108	Ref.		Ref.	
FIR	12/654	2.50 (1.10, 5.66)	0.029	2.42 (1.06, 5.50)	0.035
UIR	51/968	7.59 (3.95, 14.58)	<0.001	7.42 (3.86, 14.3)	<0.001
SHR	15/291	7.57 (3.47, 16.49)	<0.001	7.42 (3.39, 16.2)	<0.001
VHR	36/314	17.78 (9.04, 34.96)	<0.001	18.4 (9.27, 36.3)	<0.001
PCSM					
Low Risk	8/1108	Ref.		Ref.	
FIR	7/654	2.02 (0.73, 5.57)	0.175	2.03 (0.74, 5.53)	0.168
UIR	23/968	4.75 (2.14, 10.51)	<0.001	4.75 (2.14, 10.6)	<0.001
SHR	6/291	4.25 (1.47, 12.30)	0.008	4.14 (1.41, 12.2)	0.010
VHR	21/314	14.02 (6.19, 31.76)	<0.001	14.0 (6.08, 32.3)	<0.001
ACM					
Low Risk	233/1108	Ref.		Ref.	
FIR	123/654	1.24 (0.99, 1.54)	0.057	1.16 (0.93, 1.44)	0.193
UIR	183/968	1.33 (1.09, 1.61)	0.004	1.26 (1.04, 1.53)	0.020
SHR	54/291	1.34 (0.99, 1.80)	0.055	1.26 (0.93, 1.70)	0.130

		Univariable		Multivariable*	
	Events/N	HR (95% CI)	p-value	HR (95% CI)	p-value
VHR	74/314	1.74 (1.34, 2.26)	<0.001	1.65 (1.27, 2.15)	<0.001

*Adjusted for: age, race, year of surgery and center.

Abbreviation: PSA-RFS: Prostate-specific antigen recurrence-free survival; DM: distant metastasis; PCSM: prostate cancer specific mortality; ACM: all-cause mortality

**Note: Out of 3335 patients, there were 1105 recurrences, 125 distant metastases, 65 death of prostate cancer and 667 all-cause deaths

Table 3

Comparison of unfavorable intermediate risk (UIR) and very high risk (VHR) to standard high risk (SHR) patients using Cox regression. CI, confidence interval. HR, hazard ratio.

	Univariable		Multivariable*	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
PSA-RFS				
UIR vs. SHR	0.94 (0.77, 1.15)	0.547	0.92 (0.75, 1.12)	0.407
VHR vs. SHR	1.75 (1.39, 2.19)	<0.001	1.86 (1.48, 2.35)	<0.001
DM				
UIR vs. SHR	1.00 (0.56, 1.78)	0.991	0.98 (0.55, 1.74)	0.936
VHR vs. SHR	2.36 (1.29, 4.31)	0.005	2.44 (1.33, 4.46)	0.004
PCSM				
UIR vs. SHR	1.11 (0.45, 2.73)	0.823	1.12 (0.45, 2.77)	0.806
VHR vs. SHR	3.29 (1.32, 8.22)	0.011	3.33 (1.32, 8.39)	0.011
ACM				
UIR vs. SHR	0.98 (0.72, 1.33)	0.907	0.99 (0.73, 1.34)	0.942
VHR vs. SHR	1.30 (0.92, 1.85)	0.142	1.33 (0.93, 1.86)	0.118

*Adjusted for: age, race, year of surgery and center.

Abbreviation: PSA-RFS: Prostate-specific antigen recurrence-free survival; DM: distant metastasis; PCSM: prostate cancer specific mortality; ACM: all-cause mortality

**Note: Out of 1573 patients, there were 708 recurrences, 102 distant metastases, 50 death of prostate cancer and 311 all-cause deaths

Table 4

Multivariable pairwise comparison of proposed 4 tiered risk group system for PSA recurrence free survival (PSA-RFS), distant metastasis (DM), prostate cancer-specific mortality (PCSM), and all cause-mortality (ACM). CI, confidence interval. HR, hazard ratio.

	Univariable		Multivariable*	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
PSA-RFS				
Group 2 vs. Group 1	1.58 (1.30, 1.93)	<0.001	1.65 (1.35, 2.01)	<0.001
Group 3 vs. Group 1	3.02 (2.58, 3.53)	<0.001	3.15 (2.68, 3.69)	<0.001
Group 4 vs. Group 1	5.57 (4.58, 6.78)	<0.001	6.29 (5.15, 7.69)	<0.001
Group 1 vs. Group 2	0.63 (0.52, 0.77)	<0.001	0.61 (0.50, 0.74)	<0.001
Group 3 vs. Group 2	1.91 (1.61, 2.27)	<0.001	1.91 (1.61, 2.27)	<0.001
Group 4 vs. Group 2	3.52 (2.86, 4.34)	<0.001	3.82 (3.10, 4.71)	<0.001
DM				
Group 2 vs. Group 1	2.50 (1.10, 5.66)	0.029	2.42 (1.06, 5.50)	0.035
Group 3 vs. Group 1	7.59 (4.00, 14.4)	<0.001	7.42 (3.91, 14.1)	<0.001
Group 4 vs. Group 1	17.8 (9.04, 35.0)	<0.001	18.4 (9.27, 36.3)	<0.001
Group 1 vs. Group 2	0.40 (0.18, 0.91)	0.029	0.41 (0.18, 0.94)	0.035
Group 3 vs. Group 2	3.04 (1.64, 5.62)	<0.001	3.07 (1.66, 5.68)	<0.001
Group 4 vs. Group 2	7.12 (3.70, 13.7)	<0.001	7.58 (3.93, 14.6)	<0.001
PCSM				
Group 2 vs. Group 1	2.02 (0.73, 5.57)	0.18	2.03 (0.74, 5.54)	0.17
Group 3 vs. Group 1	4.63 (2.13, 10.1)	<0.001	4.61 (2.11, 10.1)	<0.001
Group 4 vs. Group 1	14.0 (6.19, 31.8)	<0.001	14.0 (6.08, 32.3)	<0.001
Group 1 vs. Group 2	0.50 (0.18, 1.37)	0.18	0.49 (0.18, 1.35)	0.17
Group 3 vs. Group 2	2.30 (1.01, 5.23)	0.048	2.27 (1.00, 5.20)	0.052
Group 4 vs. Group 2	6.95 (2.95, 16.4)	<0.001	6.91 (2.89, 16.5)	<0.001
ACM				
Group 2 vs. Group 1	1.24 (0.99, 1.54)	0.057	1.16 (0.93, 1.44)	0.19
Group 3 vs. Group 1	1.33 (1.11, 1.59)	0.002	1.26 (1.05, 1.51)	0.013
Group 4 vs. Group 1	1.74 (1.34, 2.26)	<0.001	1.65 (1.27, 2.15)	<0.001
Group 1 vs. Group 2	0.81 (0.65, 1.01)	0.057	0.86 (0.69, 1.08)	0.19
Group 3 vs. Group 2	1.07 (0.86, 1.34)	0.52	1.09 (0.87, 1.35)	0.45
Group 4 vs. Group 2	1.41 (1.05, 1.88)	0.021	1.42 (1.07, 1.90)	0.017

*Adjusted for: age, race, year of surgery and center.

Abbreviation: PSA-RFS: Prostate-specific antigen recurrence-free survival; DM: distant metastasis; PCSM: prostate cancer specific mortality; ACM: all-cause mortality