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Unification of favourable intermediate-, unfavourable intermediate-, and very high-risk stratification criteria for prostate cancer

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Objective

To improve on the existing risk-stratification systems for prostate cancer.

Patients and Methods

This was a retrospective investigation including 2 248 patients undergoing dose-escalated external beam radiotherapy (EBRT) at a single institution. We separated National Comprehensive Cancer Network (NCCN) intermediate-risk prostate cancer into 'favourable' and 'unfavourable' groups based on primary Gleason pattern, percentage of positive biopsy cores (PPBC), and number of NCCN intermediate-risk factors. Similarly, NCCN high-risk prostate cancer was stratified into 'standard' and 'very high-risk' groups based on primary Gleason pattern, PPBC, number of NCCN high-risk factors, and stage T3b–T4 disease. Patients with unfavourable-intermediate-risk (UIR) prostate cancer had significantly inferior prostate-specific antigen relapse-free survival (PSA-RFS, $P < 0.001$), distant metastasis-free survival (DMFS, $P < 0.001$), prostate cancer-specific mortality (PCSM, $P < 0.001$), and overall survival (OS, $P < 0.001$) compared with patients with favourable-intermediate-risk (FIR) prostate cancer. Similarly, patients with very high-risk (VHR) prostate cancer had significantly worse PSA-RFS ($P < 0.001$), DMFS ($P < 0.001$), and PCSM ($P = 0.001$) compared with patients with standard high-risk (SHR) prostate cancer. Moreover, patients with FIR and low-risk prostate cancer had similar outcomes, as did patients with UIR and SHR prostate cancer.

Results

Consequently, we propose the following risk-stratification system: Group 1, low risk and FIR; Group 2, UIR and SHR; and Group 3, VHR. These groups have markedly different outcomes, with 8-year distant metastasis rates of 3%, 9%, and 29% ($P < 0.001$) for Groups 1, 2, and 3, respectively, and 8-year PCSM of 1%, 4%, and 13% ($P < 0.001$) after EBRT. This modified stratification system was significantly more accurate than the three-tiered NCCN system currently in clinical use for all outcomes.

Conclusion

Modifying the NCCN risk-stratification system to group FIR with low-risk patients and UIR with SHR patients, results in modestly improved prediction of outcomes, potentially allowing better personalisation of therapeutic recommendations.

Keywords

high risk, intermediate risk, prognostic factors, prostate cancer, risk stratification, very high risk

Introduction

Prostate cancer represents one of the most heterogeneous diseases in oncology, exhibiting a wide diversity in clinical behaviour. Many prostate cancers have essentially no metastatic potential and are unlikely to impact overall mortality even if untreated [1,2], whereas others are highly lethal and eventually become refractory to all known therapies [3,4]. To cope with this heterogeneity, risk-stratification systems aid in distinguishing indolent from aggressive tumours. These systems play critical roles in both prognostication and therapeutic recommendations.

The National Comprehensive Cancer Network (NCCN) risk-stratification system has been widely utilised for many years [5]. Although its prognostic accuracy has been reproducibly validated in numerous settings, clinical heterogeneity, particularly within the intermediate-risk (IR)

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and high-risk (HR) groups, is well established [4,6–8]. This is partly because the traditional NCCN system does not incorporate primary Gleason pattern or percentage of positive biopsy cores (PPBC), which have been repeatedly validated as critical prognostic factors in independent datasets [7,9–11].

Therefore, several modifications of the NCCN system have recently been proposed. For example, Zumsteg and Zelefsky [7,8,12] have proposed stratifying NCCN IR disease into 'favourable' and 'unfavourable' subgroups based on primary Gleason pattern, PPBC, and number of NCCN IR factors. In addition, the NCCN has recently recognised a 'very-high-risk' (VHR) group [4,5]. Although the proposed dichotomisation of the IR group has been validated in several independent datasets [13,14], the validity of the NCCN VHR definition has been less rigorously examined, especially in patients undergoing radiotherapy.

These refinements have the potential to improve personalisation of therapeutic recommendations by more accurately determining the inherent aggressiveness of a patient's prostate cancer. However, there is also increased complexity, and the implications of these new divisions within risk groups for therapeutic recommendations are unclear. Further, given that different institutions have proposed disparate modifications, it is unclear how these proposed modifications relate to one another or to the original NCCN risk groups. To overcome these challenges, we sought to simplify updated risk-stratification modifications to the dichotomised IR and HR groups, and create a single unified risk-stratification system.

Patients and Methods

Patient Selection

The study cohort included 2 248 patients with localised prostate cancer and complete biopsy core information undergoing external beam radiotherapy (EBRT) with doses of ≥75.6 Gy at Memorial Sloan Kettering Cancer Center (MSKCC) from 1991 to 2010. Institutional Review Board approval was obtained before initiation of the project.

Risk Stratification

Low-risk (LR), IR, and HR groups were defined as per the NCCN system [5]. Unfavourable-IR (UIR) disease was defined as NCCN IR disease and any of the following unfavourable risk factors: primary Gleason pattern of 4, ≥50% PPBC, or ≥2 NCCN IR factors (clinical stage T2b or T2c, total Gleason score = 7 or PSA level = 10–20 ng/mL) [7,8]. All other IR patients were defined as having favourable-IR (FIR) disease. VHR prostate cancer was defined as a patient with NCCN HR disease and any of the following: clinical stage T3b–T4, primary Gleason pattern of 5, ≥50% PPBC, or ≥2 NCCN HR factors (clinical stage T3–T4, total Gleason score ≥8 or a PSA level >20 ng/mL). HR patients not meeting VHR criteria were considered to have standard-HR (SHR) disease.

Staging and Treatment

At our institution, the departmental policy during the period of this study was that all patients receive imaging of the pelvis with MRI or CT before consultation. The radiation techniques used at our institution have been described in detail previously [7,11]. In brief, patients were immobilised in the supine position using an Aquaplast mould and underwent CT-based treatment planning. Treatment was delivered with intensity modulation, typically using 15 MV photons, to the prostate and seminal vesicles and in general the pelvic lymph nodes were not electively treated in this patient cohort. Patients with node-positive disease based on pretreatment studies including CT or pelvic MRI were excluded from this study. Androgen-deprivation therapy (ADT) was administered at the discretion of the treating physician. When used, ADT generally was administered both neoadjuvantly and concurrently, with a median duration of 6 months.

Endpoints

The Phoenix definition of PSA recurrence was used for this study [15]. Distant metastasis (DM) was defined as any clinically detectable site of prostate cancer occurring outside of the prostate, seminal vesicles, or pelvic lymph nodes. Confirmation of DM required biopsy of at least one site, response to ADT initiation, or clinical plus rising PSA in castration-resistant disease. Prostate cancer-specific mortality (PCSM) was defined as death either from causes directly related to prostate cancer progression or from unknown causes in castration-resistant disease. Time to all events was measured from the end of EBRT.

Statistical Methods

The primary purpose of this study was to define risk groups that more accurately predict DM and PCSM after EBRT than the current NCCN system. Kaplan–Meier analysis was used to estimate PSA relapse-free survival (PSA-RFS), DM-free survival (DMFS), and overall survival (OS), and a Cox proportional hazards model was used for univariate and multivariate analyses. The log-rank test was used to compare risk subgroups. PCSM was evaluated using competing-risks analyses. The risk of PCSM was estimated using a cumulative-incidence function that accounted for death due to other causes and compared using Gray's test. The Fine and Gray method was used for univariate and multivariate analyses. The discriminatory abilities of the NCCN risk group and the proposed MSKCC risk group for

Table 1 Baseline clinical and pathological characteristics.

Variable	*N* (%)
Total patients	2 248
Age, years	
<60	235 (10)
60–70	982 (44)
>70	1 031 (46)
NCCN risk group	
Low	480 (21)
Intermediate	1 166 (52)
Favourable	481 (21)
Unfavourable	685 (30)
High	602 (27)
Standard	166 (7)
Very high	436 (19)
Tumour stage	
≤T2a	1 662 (74)
T2b–T3a	466 (21)
T3b–T4	120 (5)
Total Gleason score	
≤6	795 (35)
7	1 088 (48)
8	220 (10)
9–10	145 (6)
Primary Gleason pattern	
≤3	1 506 (67)
4	693 (31)
5	49 (2)
PSA level, ng/mL	
<10	1 450 (65)
10–20	531 (24)
≥20	267 (12)
Radiation dose, Gy	
<81	196 (9)
81–86	2 052 (91)
ADT	
No	1 008 (45)
Yes	1 240 (55)
PPBC	
<50	1 452 (65)
≥50	796 (35)

PSA-RFS, DMFS, and OS were evaluated using Gönen and Heller's [16] concordance probability estimate (CPE) and compared using bootstrap methods. The discriminatory abilities of the two risk-group systems for PCSM were evaluated using the Wolbers et al. [17] *c*-index for regression in the presence of competing risks and compared using bootstrap methods. Separate multivariate models were built using the patient factors of interest or risk group plus treatment variables. Statistical analyses were performed using R (version 3.2.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

The baseline characteristics are summarised in Table 1. The median follow-up for survivors from the end of EBRT was 7.4 years. In all, 480 patients were LR, 1 166 IR, and 602 HR per the NCCN criteria. Of those with IR disease, 481 and 685 were classified as FIR and UIR, respectively. In all, 436 patients with HR prostate cancer were classified as VHR.

Given that our proposed stratification for both IR and HR prostate cancer uses primary Gleason pattern and PPBC, two variables not included in the NCCN system, we sought to study the importance of these variables amongst other standard prognostic variables. In multivariate analysis, only clinical stage T3b–T4, primary Gleason pattern, and PPBC of ≥50% predicted for both DMFS and PCSM (Table 2), validating these variables as excellent candidates for risk-stratification determinates.

We next analysed outcomes for patients stratified by LR, FIR, UIR, SHR, and VHR disease (Fig. 1, Table 3). We found that VHR patients had significantly worse PSA-RFS ($P < 0.001$), DMFS ($P < 0.001$), and PCSM ($P = 0.001$) than SHR patients, validating these groups as distinct in terms of prostate cancer prognosis after EBRT. Similarly, patients with UIR had significantly worse PSA-RFS ($P < 0.001$), DMFS ($P < 0.001$), and PCSM ($P < 0.001$) than those with FIR. Although there was no difference in OS when comparing SHR and VHR patients ($P = 0.29$), UIR patients had significantly worse OS than FIR patients ($P < 0.001$). These results were similar when adjusting for differences in ADT use between these subgroups. In contrast, in our cohort we found no difference in outcome when comparing the LR and FIR groups for PSA-RFS (89.1% vs 88.3% at 8 years, $P = 0.84$), DMFS (2.3% vs 2.8%, $P = 0.46$), PCSM (0.8% vs 1.5%, $P = 0.80$), or OS (89.6% vs 88.2%, $P = 0.91$). Similarly, we found no significant difference when comparing the UIR and SHR groups for PSA-RFS (74.2% vs 80.3% at 8 years, $P = 0.16$), DMFS (7.8% vs 12.0%, $P = 0.44$), PCSM (4.0% vs 3.0%, $P = 0.54$), or OS (79.6% vs 76.6%, $P = 0.87$). These results persisted even after correcting for ADT use amongst the cohorts.

Given these results, we defined a risk-stratification system that groups LR patients with FIR patients (Group 1) and UIR patients with SHR patients (Group 2), and separating VHR patients into their own group (Group 3). These groups had highly statistically significant differences ($P < 0.001$) in all pairwise comparisons for PSA-RFS, DMFS, PCSM, and OS (Table 4, Fig. 2), except when comparing OS for Group 2 and Group 3 ($P = 0.091$).

For all endpoints, our modified system was significantly, but modestly, more accurate in predicting PSA-RFS (CPE = 0.651 vs 0.623, bootstrap $P < 0.001$), DMFS (CPE = 0.693 vs 0.662, bootstrap $P = 0.005$), PCSM (CPE = 0.736 vs 0.701, bootstrap $P = 0.002$), and OS (CPE 0.587 vs 0.566, bootstrap $P = 0.003$) than the classic NCCN system (Table S1).

Discussion

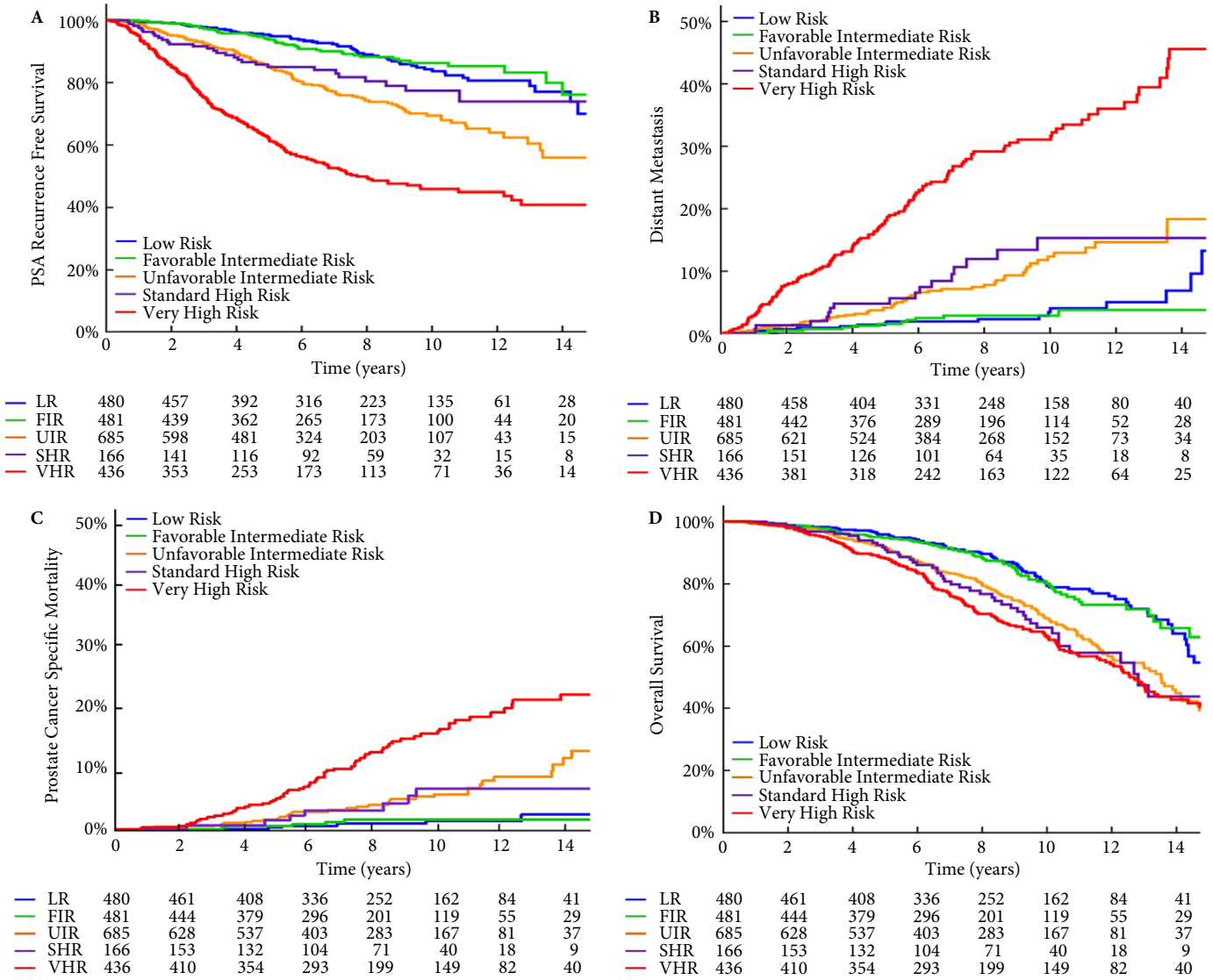
In the present study, comprising a large cohort of patients undergoing dose-escalated EBRT, we validated IR and HR prostate cancer as heterogeneous groups subclassifiable based on the primary Gleason pattern, PPBC, number of NCCN

Table 2 Univariate and multivariate analyses assessing individual clinical, pathological, and treatment variables in the study cohort.

Variable	PSA-RFS			DM			PCSM			OS		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Univariate analysis												
Tumour stage												
≤T2a	1.0	–	Reference	1.0	–	Reference	1.0	–	Reference	1.0	–	Reference
T2b–3a	2.06	1.68, 2.51	<0.001	2.28	1.69, 3.08	<0.001	2.07	1.37, 3.15	<0.001	1.32	1.10, 1.60	0.004
T3b–T4	4.57	3.50, 5.97	<0.001	6.51	4.60, 9.21	<0.001	6.69	4.21, 10.63	<0.001	1.87	1.42, 2.47	<0.001
Primary Gleason pattern												
≤3	1.0	–	Reference	1.0	–	Reference	1.0	–	Reference	1.0	–	Reference
4	2.41	2.01, 2.89	<0.001	4.40	3.31, 5.85	<0.001	5.05	3.40, 7.52	<0.001	1.70	1.43, 2.02	<0.001
5	4.36	2.86, 6.64	<0.001	8.14	4.74, 13.98	<0.001	5.20	2.15, 12.59	<0.001	2.06	1.30, 3.27	0.002
Radiation dose, Gy												
≥81 vs <81	0.62	0.48, 0.79	<0.001	0.54	0.39, 0.76	<0.001	0.50	0.32, 0.77	0.002	0.90	0.72, 1.13	0.36
ADT												
Yes vs no	1.11	0.93, 1.33	0.25	1.51	1.15, 1.98	0.003	1.60	1.10, 2.33	0.014	1.31	1.11, 1.55	0.002
PPBC												
≥50 vs <50	2.63	2.20, 3.15	<0.001	3.06	2.33, 4.01	<0.001	3.06	2.11, 4.44	<0.001	1.42	1.20, 1.67	<0.001
PSA (continuous)	1.013	1.01, 1.016	<0.001	1.014	1.01, 1.018	<0.001	1.01	1.01, 1.02	<0.001	1.004	0.999, 1.01	0.13
Multivariate analysis												
Tumour stage												
≤T2a	1.0	–	Reference	1.0	–	Reference	1.0	–	Reference	1.0	–	Reference
T2b–3a	1.53	1.22, 1.90	<0.001	1.42	1.02, 1.98	0.039	1.24	0.77, 2.02	0.38	1.12	0.91, 1.38	0.29
T3b–T4	2.73	2.03, 3.67	<0.001	2.97	2.01, 4.39	<0.001	3.07	1.76, 5.36	<0.001	1.43	1.05, 1.93	0.021
Primary Gleason pattern												
≤3	1.0	–	Reference	1.0	–	Reference	1.0	–	Reference	1.0	–	Reference
4	1.89	1.53, 2.32	<0.001	3.26	2.37, 4.49	<0.001	3.72	2.36, 5.84	<0.001	1.51	1.25, 1.83	<0.001
5	2.80	1.79, 4.38	<0.001	4.99	2.79, 8.92	<0.001	3.35	1.30, 8.62	0.012	1.68	1.04, 2.71	0.035
Radiation dose, Gy												
≥81 vs <81	0.95	0.73, 1.23	0.70	0.89	0.63, 1.28	0.54	0.79	0.48, 1.29	0.34	1.02	0.81, 1.29	0.86
ADT												
Yes vs no	0.63	0.51, 0.78	<0.001	0.70	0.51, 0.96	0.025	0.80	0.53, 1.20	0.29	1.08	0.89, 1.30	0.43
PPBC												
≥50% vs <50	1.86	1.53, 2.26	<0.001	1.78	1.32, 2.39	<0.001	1.80	1.20, 2.70	0.005	1.19	0.995, 1.43	0.056
PSA (continuous)	1.008	1.005, 1.01	<0.001	1.008	1.003, 1.01	0.004	1.00	0.994, 1.01	0.55	1.00	0.99, 1.004	0.63

HR, hazard ratio.

Fig. 1 LR, FIR, UIR, SHR, and VHR patient outcomes after definitive dose-escalated EBRT. (**A**) PSA-RFS. (**B**) DM. (**C**) PCSM. (**D**) OS.



risk factors, and presence of gross invasion into adjacent structures, such as seminal vesicles, bladder, or rectum. These substratification groups identify patients within the IR and HR groups that have markedly different rates of PSA-RFS, DMFS, and PCSM. Additionally, we found that patients with FIR disease had identical prognoses to those with LR disease, and UIR patients have outcomes similar to SHR patients after EBRT. Thus, we propose a modified risk-stratification system that integrates NCCN LR and FIR patients (Group 1) and UIR and SHR patients (Group 2), and separates VHR patients into a distinct group (Group 3). These groups stratify patients into categorisations with markedly different prognoses. For example, about 3%, 9%, and 29% of patients in Groups 1, 2, and 3, respectively, will experience DM and 1%, 4%, and 13% will experience PCSM within 8 years of EBRT. For all outcomes, this modified risk-stratification system had better predictive capability than the standard three-tiered NCCN system.

Our present modified risk-stratification system has important practical implications for therapeutic recommendations. First, we think that the notion that all NCCN IR prostate cancer represents clinically significant disease requiring aggressive local treatment may warrant reconsideration. In our present cohort, patients with FIR prostate cancer had identical outcomes to those with LR disease, with an 8-year risk of DM and PCSM of 2.8% and 1.5%, respectively, after EBRT. Similarly, another recent study reported that patients with FIR disease undergoing brachytherapy had outcomes identical to LR patients, with PCSM occurring in 0.5% of FIR at 8 years. This suggests that single-modality therapy EBRT is sufficient to eradicate

Table 3 Survival outcomes according to risk group.

	8-year estimate, %	HR	95% CI	*P*
PSA-RFS				
LR	89.1	1.00	Reference	–
FIR	88.3	0.92	0.63, 1.35	0.67
UIR	74.2	2.26	1.67, 3.06	<0.001
SHR	80.3	1.70	1.09, 2.66	0.019
VHR	49.4	5.36	4.39, 7.05	<0.001
DM				
LR	2.3	1.00	Reference	–
FIR	2.8	0.74	0.35, 1.59	0.44
UIR	7.8	2.70	1.56, 4.64	<0.001
SHR	12.0	3.38	1.73, 6.63	<0.001
VHR	29.2	9.31	5.61, 15.47	<0.001
PCSM				
LR	0.8	1.00	Reference	–
FIR	1.5	1.18	0.34, 4.07	0.79
UIR	4.0	5.67	2.23, 14.41	<0.001
SHR	3.0	4.36	1.38, 13.74	0.012
VHR	12.5	14.38	5.80, 35.66	<0.001
OS				
LR	89.6	1.00	Reference	–
FIR	88.2	0.95	0.70, 1.31	0.77
UIR	79.6	1.83	1.42, 2.36	<0.001
SHR	76.6	1.87	1.31, 2.66	<0.001
VHR	70.3	2.18	1.68, 2.82	<0.001

PCSM was analysed using a competing-risks methodology. HR, hazard ratio.

FIR disease in the vast majority of patients. Moreover, although equivalent outcomes after definitive radiation for LR and FIR prostate cancer do not necessarily mean that they will have equivalent outcomes without up-front treatment, we think active surveillance for FIR warrants further investigation. In fact, several prospective studies of active surveillance have included selected patients with IR disease, and low rates of disease-specific mortality have been reported [1,18–20]. In addition, the Prostate Testing for Cancer and Treatment (ProtecT) study, which enrolled a substantial number of IR patients, showed similar PCSM rates of ~1% of patients at 10 years with either active surveillance or definitive treatment [21]. Given that FIR patients have an extremely low incidence of DM and PCSM after treatment, combined with the lack of benefit reported from the addition of ADT in this population [7,12,14], we think single-modality therapy with EBRT, brachytherapy, or surgery is appropriate for FIR patients who choose to undergo definitive treatment.

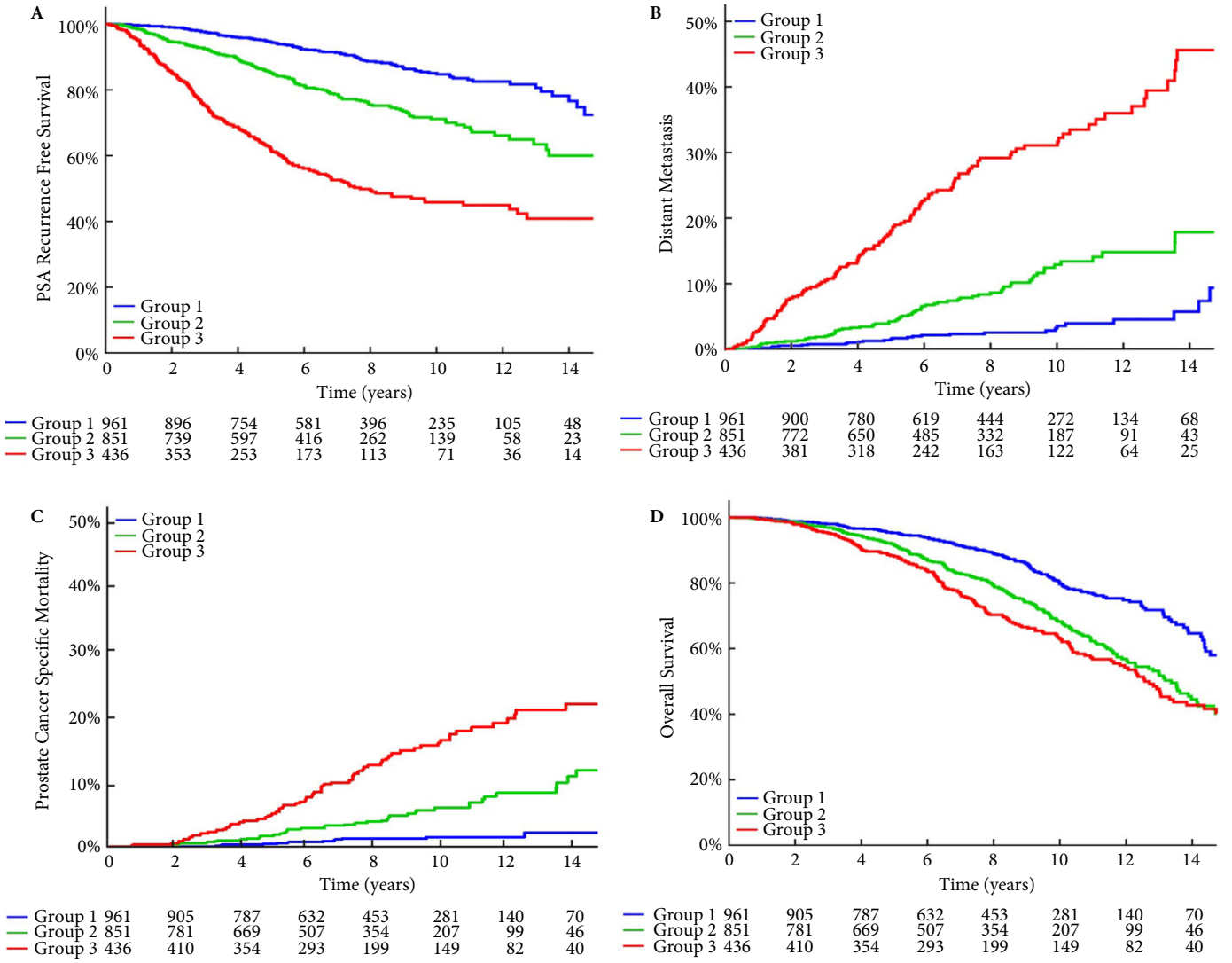
By contrast, Group 3 patients with VHR prostate cancer, representing nearly 20% of the patients treated at our institution with EBRT over the past two decades, have poor outcomes even with dose-escalated EBRT and ADT. At 8 years after EBRT, about half of these patients had PSA relapse, nearly one in three had DM, and one in eight had PCSM. Clearly, novel therapeutic paradigms are needed. Given their high risk of DM, the VHR population represents an ideal cohort to study second-generation anti-androgens, chemotherapy, and other novel systemic therapies in the definitive setting. However, another possible, and complementary approach, would be to further escalate local therapy to maximise eradication of the primary tumour. Despite the conventional notion that local control is less important in patients with a high risk of subclinical micrometastases at presentation, the most common initial recurrence site for patients with NCCN HR disease is the prostate itself [22]. Multiple randomised Phase III clinical trials have shown that adding radiotherapy to ADT significantly improves survival in patients with HR prostate cancer compared with ADT alone [23,24]. Therefore, we think that trimodality approaches, such as combined EBRT, brachytherapy, and ADT, or prostatectomy followed by adjuvant EBRT and ADT, could improve clinical outcomes in VHR patients.

Table 4 Survival outcomes according to the proposed modified risk groupings.

	8-year estimate, %	Unadjusted			Adjusted for ADT, RT dose		
		HR	95% CI	*P*	HR	95% CI	*P*
PSA-RFS							
Group 1 (LR + FIR)	88.7	1.00	Reference	–	1.00	Reference	–
Group 2 (UIR + SHR)	75.5	2.23	1.75, 2.84	<0.001	2.57	2.00, 3.29	<0.001
Group 3 (VHR)	49.4	5.56	4.39, 7.05	<0.001	7.46	5.70, 9.77	<0.001
DM							
Group 1 (LR + FIR)	2.5	1.00	Reference	–	1.00	Reference	–
Group 2 (UIR + SHR)	8.6	3.21	2.08, 4.97	<0.001	3.53	2.26, 5.50	<0.001
Group 3 (VHR)	29.2	10.58	7.01, 15.94	<0.001	12.81	8.14, 20.16	<0.001
PCSM							
Group 1 (LR + FIR)	1.1	1.00	Reference	–	1.00	Reference	–
Group 2 (UIR + SHR)	3.8	4.99	2.51, 9.93	<0.001	5.22	2.63, 10.36	<0.001
Group 3 (VHR)	12.5	13.28	6.83, 25.83	<0.001	14.25	7.21, 28.19	<0.001
OS							
Group 1 (LR + FIR)	89.0	1.00	Reference	–	1.00	Reference	–
Group 2 (UIR + SHR)	79.0	1.88	1.53, 2.30	<0.001	1.86	1.51, 2.29	<0.001
Group 3 (VHR)	70.3	2.22	1.79, 2.76	<0.001	2.19	1.73, 2.79	<0.001

HR, hazard ratio.

Fig. 2 Outcomes for Group 1 (LR and FIR), Group 2 (UIR and SHR), and Group 3 (VHR) after definitive dose-escalated EBRT. (**A**) PSA-RFS. (**B**) DM. (**C**) PCSM. (**D**) OS.



The absolute improvement in prediction using the MSKCC classification system was relatively modest compared with the NCCN system. Nevertheless, we think that our proposed classification has several advantages over the NCCN system beyond mildly improved concordance indices. First, we think that the MSKCC system more accurately groups together patients that would benefit from similar therapies than the NCCN system. Second, the MSKCC classification system results in risk-group downstaging for many patients. For example, in our present dataset, the proportion of patients in the lowest risk tier, Group 1, was twice as high as the proportion classified as LR by the NCCN system (42% vs 21%). We hope that this system will allow less-aggressive therapeutic approaches to be recommended by practitioners in more patients. Additionally, our present system unifies and simplifies several proposed modifications to the IR and HR NCCN groups. Lastly, other classification systems, such as the Candiolo classifier, have reported higher concordance indices than ours [25]. However, they tend to be much more complicated than our present system, potentially overfitting their proposed models to their own datasets and precluding simple applicability in the clinic. For example, the Candiolo classification table has 360 different possible combinations based on clinicopathological features, each mapped to one of five risk groups. Thus, although our proposed classification is an incremental modification of the NCCN system, we feel that it is useful for guiding clinical recommendations.

Our present study has several limitations. First, this is a retrospective, single-institution study. Additionally, our new system was not validated by an independent data set. It will be particularly important to validate these results in a

prostatectomy cohort, given that a risk-classification system should be applicable all men with localised prostate cancer. However, we note that many of our present findings have been separately validated in part by outside groups using independent patients cohorts, including the divergent prognoses of FIR and UIR prostate cancer [13,14], and the similar outcomes of LR and FIR disease [26]. Another major limitation of our present study is that ADT was not uniformly administered, in terms of either presence or duration, to IR and HR patients. Additionally, long-term ADT (>6 months) was relatively uncommonly used at our institution during the period of the study. Although we could not control for ADT duration, given that this was not uniformly available for all patients, we did adjust for ADT use in our multivariate models, and found that our risk-stratification system remained robust. We also note that the criteria we used to define VHR disease were slightly different than that of the NCCN and Johns Hopkins [4]. We chose to use ≥50% of PPBC instead of >4 cores with a total Gleason score ≥8 because PPBC does not depend on the absolute number of cores sampled, unlike the number of high-grade cores, which can be increased simply by taking more biopsies. Moreover, PPBC is a better-established adverse risk factor that has been validated across numerous independent datasets [7,9,27], and PPBC is already used in the definition of UIR, allowing for harmonisation of the UIR and VHR stratifications.

In summary, we have proposed a modification to the NCCN risk-stratification system that is modestly more accurate in predicting outcome than the classic NCCN system. Further, we think that it may more accurately group patients who would benefit from similar treatment paradigms. These results require validation in independent datasets. Further refinement of risk stratification for prostate cancer using imaging, genomics, proteomics, and novel molecular biomarkers will hopefully continue to improve our ability to personalise therapy for patients.

Conflicts of Interest

The authors have no conflicts of interest to disclose related to the submitted work. Dr Zumsteg is on the Scripps Proton Therapy Center external advisory board and has been a paid consultant for EMD Serono outside of the submitted work.

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Abbreviations: (F)(U)IR, (favourable) (unfavourable) intermediate-risk prostate cancer; (V)HR, (very) high-risk prostate cancer; ADT, androgen-deprivation therapy; CPE, concordance probability estimate; DM(FS), distant metastasis (-free survival); EBRT, external beam radiotherapy; LR, low-risk prostate cancer; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; PCSM, prostate cancer-specific mortality; PPBC, percentage of positive biopsy cores; PSA-RFS, PSA relapse-free survival; SHR, standard high-risk prostate cancer.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Concordance probability estimates for the NCCN and proposed modified risk-group stratification systems.

