Unification of favorable intermediate, unfavorable intermediate, and very high risk-stratification criteria for prostate cancer

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Abstract: Objective

To improve on the existing risk-stratification systems.

Patients and Methods

This was a retrospective investigation including 2248 patients undergoing dose-escalated external beam radiotherapy (EBRT) at a single institution. We separated National Comprehensive Cancer Network (NCCN) intermediate-risk prostate cancer into favorable and unfavorable 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 unfavorable intermediate risk (UIR) had significantly inferior prostate-specific antigen relapse-free survival (PSA-RFS, P<0.001), distant metastasis-free survival (P<0.001), prostate cancer–specific mortality (PCSM, P<0.001), and overall survival (OS, P<0.001) compared with favorable intermediate-risk (FIR) patients. Similarly, very-high-risk (VHR) patients had significantly worse PSA-RFS (P<0.001), distant metastasis (P<0.001), and PCSM (P=0.001) compared with standard high-risk (SHR) patients. Moreover, FIR and low-risk patients had similar outcomes, as did UIR and SHR patients.

Results

Therefore, 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) following radiotherapy. 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 personalization of therapeutic recommendations.

Introduction

Prostate cancer represents one of the most heterogeneous diseases in oncology, exhibiting a wide diversity in clinical behavior. 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 tumors. These systems play critical roles in both prognostication and therapeutic recommendations.

The National Comprehensive Cancer Network (NCCN) risk-stratification system has for many years been widely utilized [5]. Although its prognostic accuracy has been reproducibly validated in numerous settings, clinical heterogeneity, particularly within the intermediate-risk (IR) 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 have proposed stratifying NCCN IR disease into favorable and unfavorable subgroups based on primary Gleason pattern, PPBC, and number of NCCN IR factors [7, 8, 12]. In addition, the NCCN has recently recognized a “very-high-risk” (VHR) group [4, 5]. Although the proposed dichotomization 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 personalization 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 dichotomized IR and HR groups and create a single, unified risk-stratification system.

Materials and Methods

Patient Selection

This study cohort included 2248 patients with localized 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 prior to initiation of the project.

Risk Stratification

Low-risk (LR), IR, and HR groups were defined as per the NCCN system [5]. Unfavorable IR (UIR) was defined as NCCN IR disease and any of the following unfavorable risk factors: primary Gleason pattern of 4, ≥50% of biopsy cores containing prostate cancer, or ≥2 NCCN IR factors (clinical stage T2b or T2c, total Gleason score = 7, or PSA = 10-20 ng/mL) [7, 8]. All other IR patients were defined as having favorable 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% of biopsy cores containing prostate cancer, or ≥2 NCCN HR factors (clinical stage T3-T4, total Gleason score ≥8, or a PSA >20 ng/mL). HR patients not meeting VHR criteria were considered standard HR (SHR).

Staging and Treatment

At our institution, the departmental policy during the time period of this study was that all patients receive imaging of the pelvis with MRI or CT scan prior to consultation. The radiation techniques utilized at our institution have been described in detail previously [7, 11]. In brief, patients were immobilized in the supine position using an Aquaplast mold and underwent computed tomography–based treatment planning. Treatment was delivered with intensity modulation typically utilizing 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 employed, 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 distant metastases 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 radiotherapy.

Statistical Methods

The primary purpose of this study was to define risk groups that more accurately predict DM and PCSM following EBRT than the current NCCN system. Kaplan-Meier analysis was used to estimate PSA relapse-free survival (PSA-RFS), distant metastasis-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 PSA-RFS, DMFS, and OS were evaluated using Gönen and Heller's concordance probability estimate (CPE) and compared using bootstrap methods [16]. The discriminatory abilities of the two risk-group systems for PCSM was evaluated using Wolbers et al's c-index for regression in the presence of competing risks and compared using bootstrap methods [17]. 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

Baseline characteristics are summarized in Table 1. Median follow-up for survivors from the end of radiotherapy was 7.4 years. In total, 480 patients were LR, 1166 IR, and 602 HR per NCCN criteria. Of those with IR disease, 481 and 685 were classified as FIR and UIR, respectively. 436 patients with HR prostate cancer were classified as VHR.

Given that our proposed stratification for both IR and HR prostate cancer utilizes 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 ≥50% predicted for both DM and PCSM, validating these variables as excellent candidates for risk-stratification determinates.

We next analyzed outcomes for patients stratified by LR, FIR, UIR, SHR, and VHR disease (Figure 1, Table 3). We found that VHR patients had significantly worse PSA-RFS (P<0.001), DM (P<0.001), and PCSM (P=0.001) than SHR patients, validating these groups as distinct in terms of prostate cancer prognosis following radiotherapy. Similarly, patients with UIR had significantly worse PSA-RFS (P<0.001), DM (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 in terms of PSA-RFS (89.1% vs. 88.3% at 8 years, *P*=0.84), DM (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), DM (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, Figure 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), DM (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 (Supplementary Table 1).

Discussion

In this 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 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, DM, 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 following radiotherapy. 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 categorizations with markedly different prognoses. For example, approximately 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 radiotherapy. For all outcomes, this modified risk-stratification system had better predictive capability than the standard three-tiered NCCN system.

Our modified risk-stratification system has important practical implications for therapeutic recommendations. First, we believe that the notion that all NCCN IR prostate cancer represents clinically significant disease requiring aggressive local treatment may warrant reconsideration. In our 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, following radiotherapy. 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 FIR disease in the vast majority of patients. Moreover, although equivalent outcomes following definitive radiation for LR and FIR prostate cancer do not necessarily mean that they will have equivalent outcomes without up-front treatment, we believe 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 ProtecT study, which enrolled a substantial number of intermediate risk patients, showed similar PCSM rates of approximately 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 following treatment, combined with the lack of benefit reported from the addition of ADT in this population [7, 12, 14], we believe 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 radiotherapy, approximately half of these patients experienced PSA relapse, nearly 1 in 3 experienced DM, and 1 in 8 experienced PCSM. Clearly, novel therapeutic paradigms are needed. Given their HR 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 maximize eradication of the primary tumor. Despite the conventional notion that local control is less important in patients with a HR of subclinical micrometastases at presentation, the most common initial recurrence site for patients with NCCN HR disease is the prostate itself [22]. Multiple randomized Phase III clinical trials have demonstrated that adding radiotherapy to ADT significantly improves survival in HR prostate cancer patients compared with ADT alone [23, 24]. Therefore, we believe 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.

The absolute improvement in prediction using the MSKCC classification system was relatively modest compared with the NCCN system. Nevertheless, we believe that our proposed classification has several advantages over the NCCN system beyond mildly improved concordance indices. First, we believe 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 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 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 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 clinicopathologic 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 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 localized prostate cancer. However, we note that many of our 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 study is that ADT was not uniformly administered, in terms of either presence or duration, to intermediate and high risk patients. Additionally, long-term ADT (>6 months) was relatively uncommonly employed at our institution during the time period of this 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 utilize ≥50% of biopsy cores containing prostate cancer 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 utilized in the definition of UIR, allowing for harmonization 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 believe 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 personalize therapy for patients.

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Table 1 Baseline clinical and pathologic characteristics.

Variable	N (%)
Total patients	2248
Age (years)	
<60	235 (10)
60-70	982 (44)
>70	1031 (46)
NCCN risk group	
Low	480 (21)
Intermediate	1166 (52)
Favorable	481 (21)
Unfavorable	685 (30)
High	602 (27)
Standard	166 (7)
Very high	436 (19)
Tumor stage	
T2a or less	1662 (74)
T2b-T3a	466 (21)
T3b-T4	120 (5)
Total Gleason score	
≤6	795 (35)
7	1088 (48)
8	220 (10)
9-10	145 (6)
Primary Gleason pattern	
≤3	1506 (67)
4	693 (31)
5	49 (2)

PSA	
<10	1450 (65)
10 to 20	531 (24)
≥20	267 (12)
Radiation dose	
<81 Gy	196 (9)
81-86 Gy	2052 (91)
ADT	
No	1008 (45)
Yes	1240 (55)
% positive biopsy cores	
<50%	1452 (65)
≥50%	796 (35)

ADT, androgen-deprivation therapy; PSA, prostate-specific antigen.

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

Univariate analyses		**PSA-RFS**			**DM**			**PCSM**			**OS**	
Factor	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Tumor stage												
T2a or less	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												
≥81 Gy vs. <81 Gy	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
% positive biopsy core												
≥ 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												
Tumor stage												
T2a or less	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												
≥81 Gy vs. <81 Gy	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
% positive biopsy core												
≥ 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

CI, confidence interval; DM, distant metastasis; HR, hazard ratio; OS, overall survival; PCSM, prostate cancer–specific mortality; PSA-RFS, prostate-antigen specific relapse-free survival.

Table 3 Survival outcomes according to risk group.

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

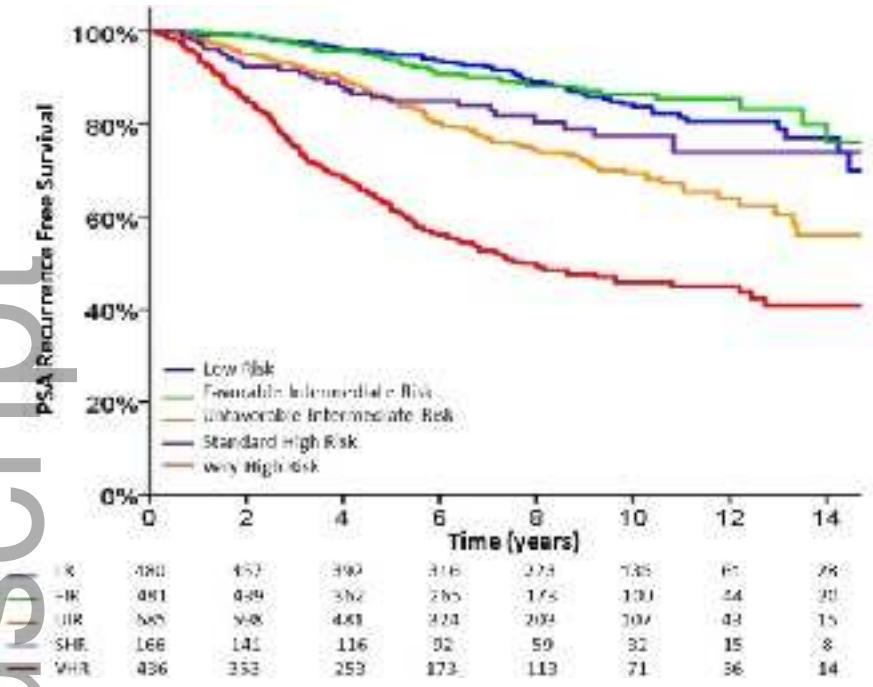
PCSM was analyzed using a competing-risks methodology.

CI, confidence interval; DM, distant metastasis; HR, hazard ratio; OS, overall survival; PCSM, prostate cancer–specific mortality; PSA-RFS, prostate-specific antigen relapse-free survival.

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

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

ADT, androgen-deprivation therapy; CI, confidence interval; DM, distant metastasis; HR, hazard ratio; OS, overall survival; PCSM, prostate cancer–specific mortality; PSA-RFS, PSA relapse–free survival; RT, radiotherapy.



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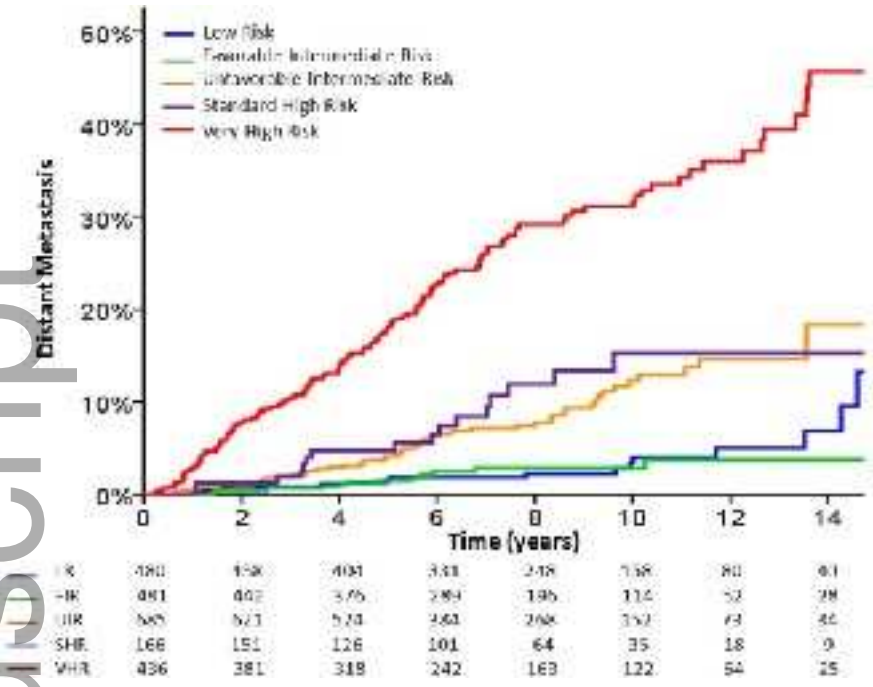

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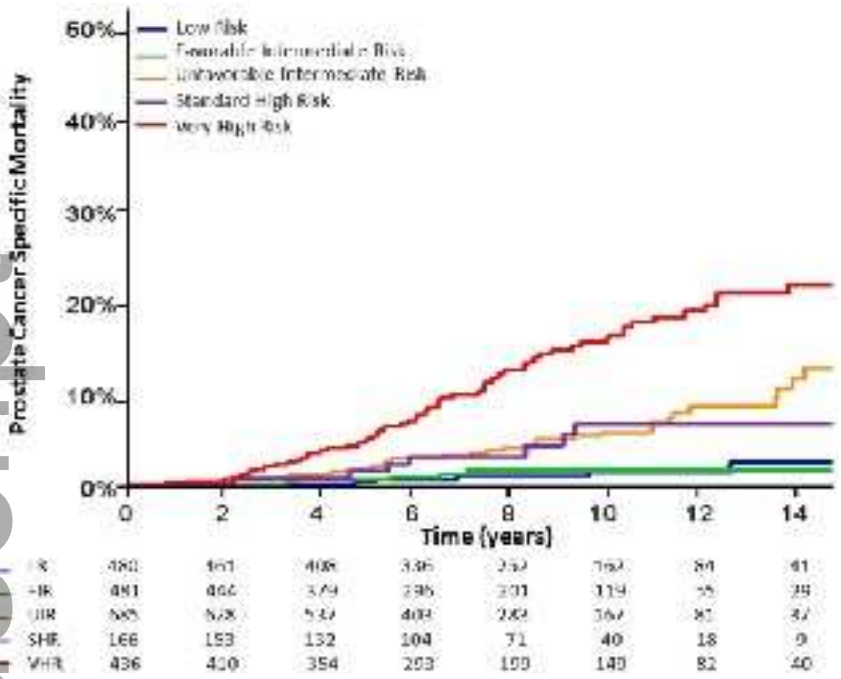

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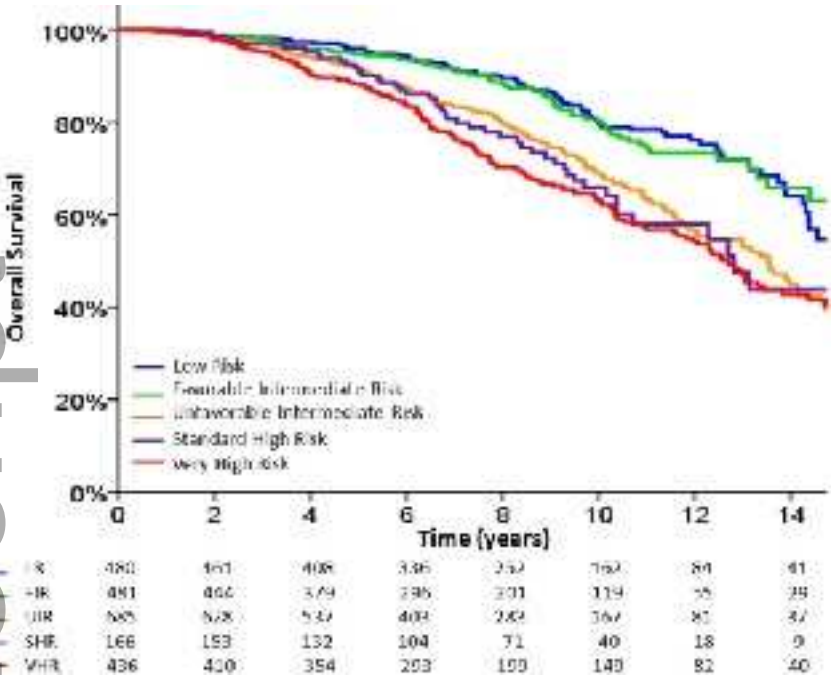

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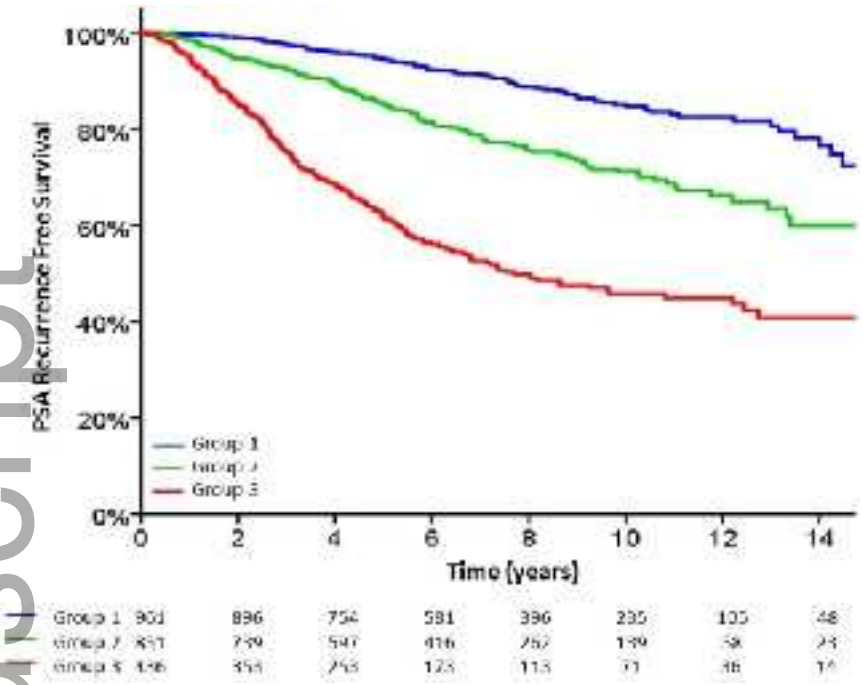

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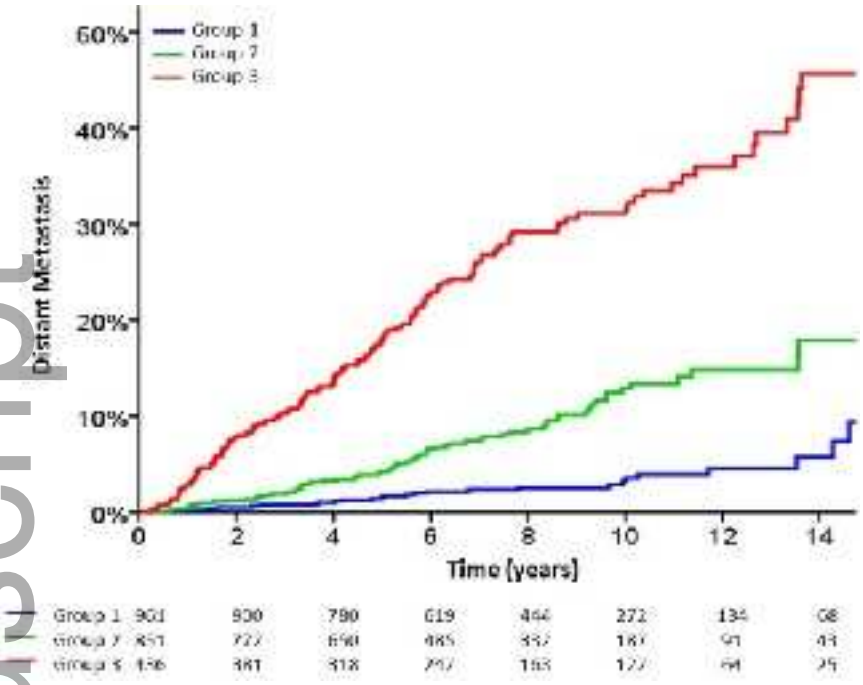

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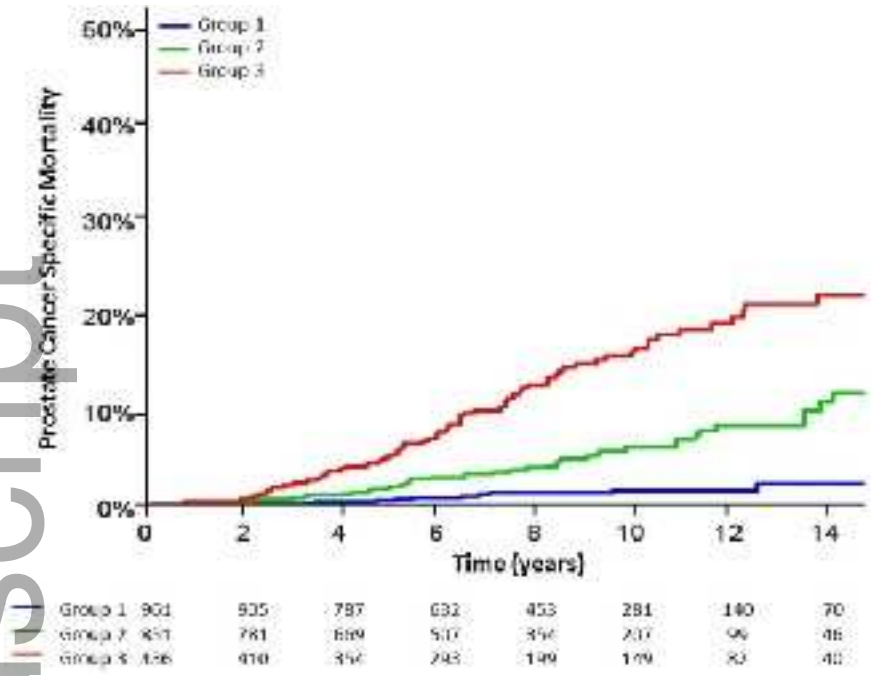

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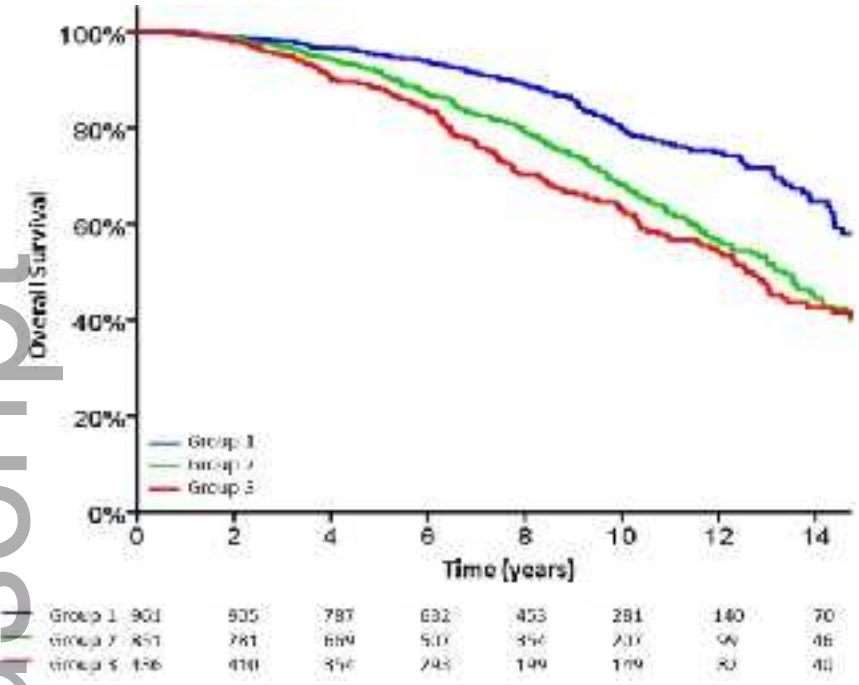

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