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A New Risk Classification System for Therapeutic Decision Making with Intermediate-risk Prostate Cancer Patients Undergoing Dose-escalated External-beam Radiation Therapy

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Abstract

Background: The management of intermediate-risk prostate cancer (PCa) is controversial, in part due to the heterogeneous nature of patients falling within this classification.
Objective: We propose a new risk stratification system for intermediate-risk PCa to aid in prognosis and therapeutic decision making.
Design, setting, and participants: Between 1992 and 2007, 1024 patients with National Comprehensive Cancer Network intermediate-risk PCa and complete biopsy information were treated with definitive external-beam radiation therapy (EBRT) utilizing doses ≥81 Gy. Unfavorable intermediate-risk (UIR) PCa was defined as any intermediate-risk patient with a primary Gleason pattern of 4, percentage of positive biopsy cores (PPBC) ≥50%, or multiple intermediate-risk factors (IRFs; cT2b–c, prostate-specific antigen [PSA] 10–20, or Gleason score 7).
Intervention: All patients received EBRT with ≥81 Gy with or without neoadjuvant and concurrent androgen-deprivation therapy (ADT).
Outcome measurements and statistical analysis: Univariate and multivariate analyses were performed using a Cox proportional hazards model for PSA recurrence-free survival (PSA-RFS) and distant metastasis (DM). PCa-specific mortality (PCSM) was analyzed using a competing-risk method.
Results and limitations: Median follow-up was 71 mo. Primary Gleason pattern 4 (hazard ratio [HR]: 3.26; $p < 0.0001$), PPBC ≥50% (HR: 2.72; $p = 0.0007$), and multiple IRFs (HR: 2.20; $p = 0.008$) all were significant predictors of increased DM in multivariate analyses. Primary Gleason pattern 4 (HR: 5.23; $p < 0.0001$) and PPBC ≥50% (HR: 4.08; $p = 0.002$) but not multiple IRFs (HR: 1.74; $p = 0.21$) independently predicted for increased PCSM. Patients with UIR disease had inferior PSA-RFS (HR: 2.37; $p < 0.0001$), DM (HR: 4.34; $p = 0.0003$), and PCSM (HR: 7.39; $p = 0.007$) compared with those with favorable intermediate-risk disease, despite being more likely to receive neoadjuvant ADT. Short follow-up and retrospective study design are the primary limitations.
Conclusions: Intermediate-risk PCa is a heterogeneous collection of diseases that can be separated into favorable and unfavorable subsets. These groups likely will benefit from divergent therapeutic paradigms.

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1. Introduction

Defining the optimal treatment algorithm for localized prostate cancer (PCa) represents a unique challenge in oncology. The vast majority of men with this disease will die of causes unrelated to their malignancy [1–3]. However, given its high prevalence and heterogeneous clinical behavior, PCa remains the second leading oncologic cause of mortality in men in the United States [4]. Differentiating indolent tumors from those that behave aggressively remains challenging, leading to overtreatment of men with relatively indolent disease and undertreatment of those with aggressive tumors [5–7].

Risk classification subgroups, such as those defined by the National Comprehensive Cancer Network (NCCN), have been proposed to stratify men into low-, intermediate-, and high-risk groups [8]. However, even within a given risk group, significant clinical heterogeneity remains, particularly for those with intermediate-risk disease, and more precise stratification is desirable [9]. Primary Gleason pattern, percentage of positive biopsy cores (PPBCs), and number of intermediate-risk factors (IRFs) have been shown to be independent predictors of outcome for localized PCa but are not included in the current NCCN system [10–14]. We have previously suggested stratifying intermediate-risk PCa into favorable and unfavorable categories based on these criteria to aid radiation and medical oncologists in treatment recommendations [15].

To provide clinical evidence for this approach, we assembled a large cohort of men with intermediate-risk PCa undergoing definitive dose-escalated external-beam radiation therapy (EBRT). We compared prostate-specific antigen recurrence-free survival (PSA-RFS), incidence of distant metastasis (DM), and PCa-specific mortality (PCSM) in patients classified as favorable intermediate risk (FIR) or unfavorable intermediate risk (UIR). Given that androgen-deprivation therapy (ADT) has been shown to improve survival in high- but not low-risk PCa, we also investigated the effect of ADT on outcome for FIR and UIR groups.

2. Materials and methods

2.1. Patient selection and pretreatment evaluation

Between 1992 and 2007, 1208 patients with intermediate-risk PCa were treated with dose-escalated EBRT, defined as $\geq$81 Gy, at Memorial Sloan-Kettering Cancer Center and its affiliated satellite sites. Intermediate risk was defined according to NCCN criteria as patients with clinical stage T2b or T2c, Gleason score of 7, or prostate-specific antigen (PSA) of 10–20 ng/ml but without high-risk features (clinical stage T3a or higher, Gleason score 8–10, or PSA >20 ng/ml) [8]. A total of 184 patients had incomplete biopsy core information and were excluded because it was not possible to determine the PPBC, leaving 1024 patients to form our study cohort. Additionally, 511 and 582 patients with NCCN low-risk and high-risk PCa, respectively, representing all patients treated with EBRT to a total dose of at least 81 Gy from 1992 to 2007, were compared with subgroups of intermediate-risk patients. Institutional review board approval was granted prior to data collection.

2.2. Treatment

Detailed description of the radiation techniques used was provided previously [16]. Briefly, patients were simulated in the supine position with planning based on computed tomography. Patients received EBRT with 81 or 86.4 Gy in 1.8-Gy daily fractions, prescribed to the isodose line encompassing the planning target volume, with 15-MV photons. Radiation was not administered to the pelvic lymph nodes. The decision to use ADT was based on the clinical discretion of the treating radiation oncologist. ADT generally consisted of neoadjuvant and concurrent administration, and it was discontinued at the end of radiation therapy. The median duration of ADT was 6 mo for both FIR and UIR patients.

2.3. End points

PSA recurrence was defined according to the Phoenix definition as a serum PSA at least 2 ng/ml greater than the posttreatment nadir PSA. Local failure (LF) was defined as a positive postradiotherapy biopsy, clinical examination revealing a new or growing tumor, and/or magnetic resonance imaging showing a tumor in the prostate or seminal vesicles described as "suspicious" or "consistent" with locally recurrent disease. Distant metastatic disease was defined as PCa occurring in any anatomic location other than the prostate, seminal vesicles, or pelvic lymph nodes. All DMs were confirmed by either biopsy of at least one site, response to ADT initiation, or progression in combination with rising PSA in the setting of castration-resistant disease. PCSM was defined as death directly attributable to PCa or death in the setting of castration-resistant metastatic disease from unknown causes. Time to all events was calculated from the end of radiation therapy.

2.4. Definition of favorable versus unfavorable intermediate-risk prostate cancer

We defined FIR PCa as a patient with NCCN intermediate-risk disease and all of the following: a single NCCN IRF, Gleason $\leq$3 + 4 = 7, and <50% of biopsy cores containing cancer. All others were classified as UIR [15].

2.5. Statistical methods

Baseline clinical characteristics were compared using chi-square tests for categorical variables and an analysis of variance test for continuous variables. The Kaplan-Meier method was used to generate survival curves and to estimate actuarial event-time probabilities for PSA-RFS and DM. A Cox proportional hazards model was used to general hazard ratios and 95% confidence intervals for both univariate analysis (UVA) and multivariate analysis (MVA) for PSA-RFS and DM. The cumulative incidence method was used to estimate PCSM at a given time point, with death from causes other than PCa defined as a competing risk. Comparisons of PCSM for different subgroups were performed using a κ sample test. Multivariate competing-risk analysis for PCSM was performed using the Fine and Gray method [17]. All statistical analysis was performed using R v.2.14.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Table 1 shows the baseline clinical characteristics for our cohort. The median follow-up was 71 mo.

To investigate their utility as risk-stratification factors for intermediate-risk PCa, primary Gleason pattern, PPBC, and number of IRFs were included in a Cox proportional hazards analysis. As shown in Table 2, both primary Gleason pattern of 4 and PPBC $\geq$50% were highly significant predictors of PSA-RFS, DM, and PCSM in UVA and MVA. Multiple IRFs

Table 1 – Baseline clinical characteristics

	Favorable	Unfavorable	Total	*p* value
No. of patients	424	600	1024	–
Median follow-up, mo	70	71	71	–
Age, yr				0.370
Median	70	70	70	
Mean	68.9	69.6	69.3	
≤70	229	307	536	
>70	195	293	488	
Clinical T stage				<0.001
T1b–c	281	283	564	
T2a	105	154	259	
T2b	29	118	147	
T2c	9	45	54	
Biopsy Gleason score				<0.001
≤6	153	40	193	
3 + 4	271	284	555	
4 + 3	0	276	276	
PSA				<0.001
Median	7	8.14	7.6	
Mean	7.91	8.97	8.53	
<10	309	372	681	
≥10	115	228	343	
Percentage positive biopsy cores				<0.001
Median, %	22.2	50.0	33.3	
Mean, %	23.6	46.7	37.2	
<50%	424	286	710	
≥50%	0 (0%)	314	314	
ADT				<0.001
No	254	249	503	
Yes	170	351	521	
Median duration, mo	6	6	6	0.096
Salvage treatment				–
Salvage ADT	12	65	77	
Salvage prostatectomy	10	6	16	
Salvage brachytherapy	4	11	15	

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

Table 2 – Univariate and multivariate analysis for prostate-specific antigen recurrence-free survival, distant metastasis, and prostate cancer–specific mortality based on the unfavorable risk factors of interest and androgen deprivation

	UVA		MVA	
PSA-RFS	HR (95% CI)	*p* value	HR (95% CI)	*p* value
ADT	0.58 (0.43–0.79)	0.0006	0.45 (0.32–0.61)	<0.0001
Gleason 4 + 3	1.94 (1.41–2.66)	<0.0001	1.89 (1.37–2.61)	0.0001
PPBC ≥50%	2.20 (1.62–2.98)	<0.0001	1.99 (1.46–2.71)	<0.0001
≥2 IRFs	1.78 (1.31–2.41)	0.0002	1.82 (1.33–2.50)	0.002
Local failure	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
ADT	0.46 (0.30–0.72)	0.001	0.40 (0.25–0.63)	<0.001
Gleason 4 + 3	1.52 (0.97–2.37)	0.068	1.57 (0.99–2.47)	0.054
PPBC ≥50%	2.03 (1.33–3.10)	0.001	1.98 (1.29–3.04)	0.002
≥2 IRFs	1.20 (0.77–1.86)	0.423	1.28 (0.81–2.01)	0.293
DM	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
ADT	0.61 (0.32–1.08)	0.09	0.40 (0.22–0.73)	0.003
Gleason 4 + 3	3.49 (1.97–6.18)	<0.0001	3.26 (1.81–5.87)	<0.0001
PPBC ≥50%	3.33 (1.88–5.88)	<0.001	2.72 (1.53–4.86)	0.0007
≥2 IRFs	2.40 (1.37–4.21)	0.0002	2.20 (1.23–3.92)	0.008
PCSM	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
ADT	0.38 (0.16–0.91)	0.03	0.23 (0.10–0.56)	0.001
Gleason 4 + 3	5.15 (2.26–11.74)	<0.0001	5.23 (2.28–12.01)	<0.0001
PPBC ≥50%	5.02 (2.11–11.93)	0.0003	4.08 (1.68–9.89)	0.002
≥2 IRFs	2.03 (0.91–4.55)	0.09	1.74 (0.73–4.18)	0.21

ADT = androgen-deprivation therapy; CI = confidence interval; DM = distant metastasis; HR = hazard ratio; IRFs = intermediate risk factors; MVA = multivariate analysis; PCSM = prostate cancer–specific mortality; PPBC = percentage of positive biopsy cores; PSA-RFS = prostate-specific antigen recurrence-free survival; UVA = univariate analysis.

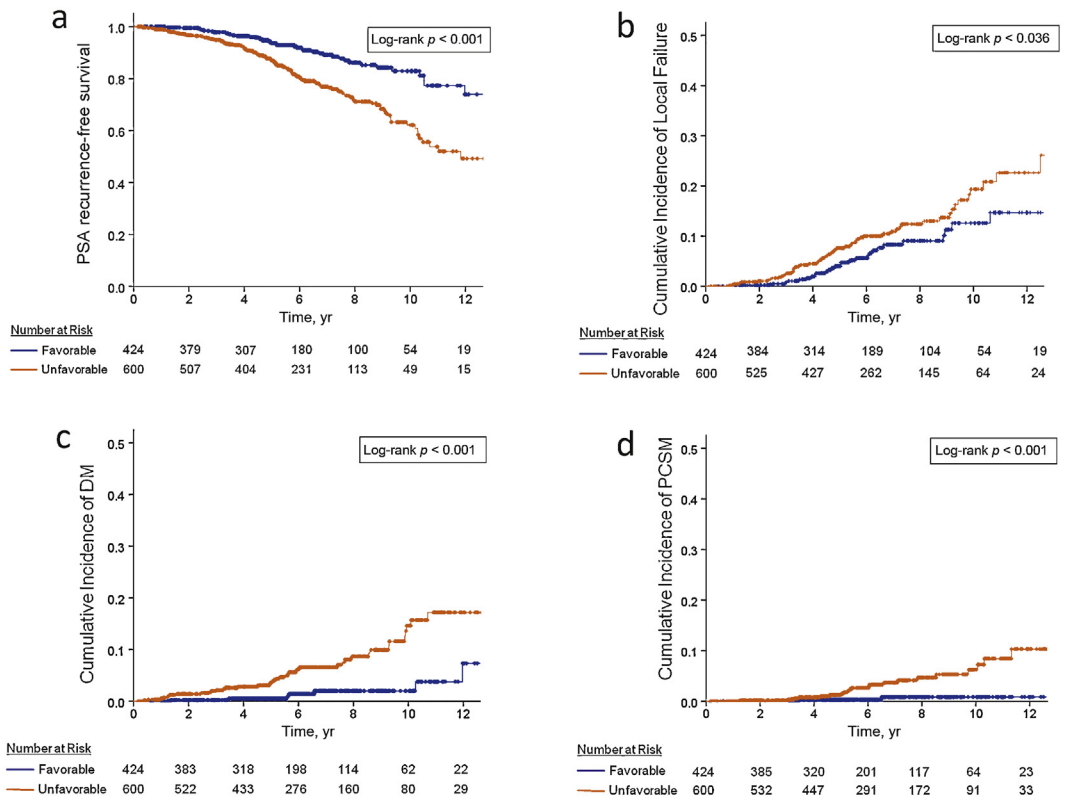

Fig. 1 – A comparison of favorable versus unfavorable intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy showing significant differences in (a) prostate-specific antigen (PSA) recurrence-free survival, (b) local failure, (c) distant metastasis (DM), and (d) prostate cancer–specific mortality (PCSM).

predicted for worse PSA-RFS and DM, but not PCSM, in UVA and MVA. Of note, ADT also was an independent predictor for improved PSA-RFS ($p < 0.0001$), LF ($p < 0.001$), DM ($p = 0.003$), and PCSM (0.001) in our multivariate models.

Given that primary Gleason grade, PPBC, and number of IRFs independently predicted for inferior outcomes, we classified patients with any one of these factors as having UIR disease. All others were classified as FIR. Figure 1 and Table 3 show a comparison of outcome for FIR patients versus patients with UIR PCa. Despite being significantly more likely to receive ADT (58.5% vs 30.1%; $p < 0.001$), patients classified as UIR PCa had worse PSA-RFS ($p < 0.0001$), LF ($p = 0.038$), DM ($p = 0.0003$), and PCSM ($p = 0.007$) than patients with FIR PCa. The estimated 8-yr rates for PSA-RFS, LF, DM, and PCSM were 86.1%, 9.1%, 2.0%, and 0.8% for patients with FIR PCa, respectively, compared with 71.1%, 12.4%, 8.6%, and 4.2% in the UIR subgroup. Notably, as shown in Supplementary Figure 1, there was no difference in outcome between FIR patients and 511 low-risk patients treated with radiation doses of at least

Table 3 – Comparison of favorable versus unfavorable intermediate-risk prostate cancer

	UVA		Adjusted for ADT	
PSA-RFS	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Unfavorable vs favorable	2.37 (1.68–3.36)	<0.0001	2.69 (1.89–3.82)	<0.001
Local failure	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Unfavorable vs favorable	1.62 (1.03–2.55)	0.038	1.87 (1.18–2.96)	0.008
DM	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Unfavorable vs favorable	4.34 (1.95–9.67)	0.0003	4.86 (2.17–10.87)	<0.001
PCSM	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Unfavorable vs favorable	7.39 (1.75–31.31)	0.007	9.03 (2.16–37.82)	0.0003

ADT = androgen-deprivation therapy; CI = confidence interval; DM = distant metastasis; HR = hazard ratio; PCSM = prostate cancer–specific mortality; PSA-RFS = prostate-specific antigen recurrence-free survival; UVA = univariate analysis.

Table 4 – Analysis of the effect of multiple unfavorable risk factors on outcome in intermediate-risk prostate cancer

	UVA		Adjusted for ADT	
PSA-RFS	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Favorable	1.0 (reference)	–	1.0 (reference)	–
1 unfavorable risk factor	2.07 (1.44–2.98)	<0.001	2.36 (1.62–3.37)	<0.001
2–3 unfavorable risk factors	3.97 (2.52–6.26)	<0.001	5.011 (3.15–7.97)	<0.001
Local failure	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Favorable	1.0 (reference)	–	1.0 (reference)	–
1 unfavorable risk factor	1.40 (0.87–2.27)	0.168	1.59 (0.98–2.88)	0.059
2–3 unfavorable risk factors	2.65 (1.44–4.86)	0.002	3.53 (1.90–6.57)	<0.001
DM	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Favorable	1.0 (reference)	–	1.0 (reference)	–
1 unfavorable risk factor	2.96 (1.28–6.88)	0.012	3.310 (1.42–7.71)	0.006
2–3 unfavorable risk factors	11.45 (4.76–27.53)	<0.001	14.6 (6.00–35.62)	<0.001
PCSM	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Favorable	1.0 (reference)	–	1.0 (reference)	–
1 unfavorable risk factor	4.30 (0.94–19.65)	0.069	4.96 (1.10–22.60)	0.038
2–3 unfavorable risk factors	25.67 (5.67–116.18)	<0.001	33.71 (7.76–147.93)	<0.001

ADT = androgen-deprivation therapy; CI = confidence interval; DM = distant metastasis; HR = hazard ratio; PCSM = prostate cancer–specific mortality; PSA-RFS = prostate-specific antigen recurrence-free survival; UVA = univariate analysis.

81 Gy in terms of PSA-RFS ($p = 0.142$), DM ($p = 0.693$), or PCSM ($p = 0.697$).

We next examined the effect of ADT in patients with both FIR and UIR PCa (Supplementary Fig. 2). For patients with FIR PCa, there was a significant prolongation of 8-yr PSA-RFS with ADT (93.6% vs 80.9%; $p = 0.001$) but no significant difference in 8-yr DM (0% vs 3.3%; $p = 0.125$) or 8-yr PCSM (0% vs 1.3%; $p = 0.450$). For patients with UIR PCa, ADT significantly improved 8-yr PSA-RFS (75.1% vs 65.3%; $p = 0.002$), DM (6.4% vs 10.6%; $p = 0.045$), and PCSM (2.2%

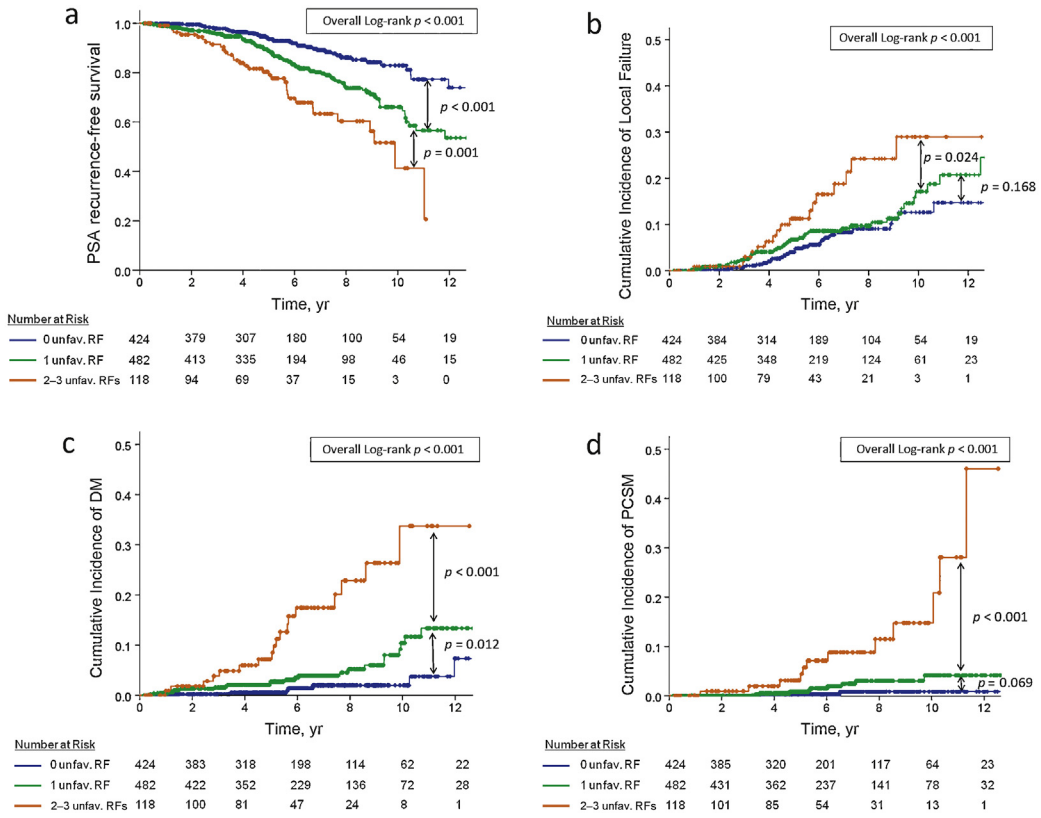

Fig. 2 – Outcomes with no unfavorable risk factors (RFs), one unfavorable RF, or two or three unfavorable RFs (ie, Gleason 4 + 3 = 7, ≥50% of biopsy cores with cancer, or more than one intermediate risk factor): (a) prostate-specific antigen (PSA) recurrence-free survival, (b) local failure, (c) distant metastasis (DM), and (d) prostate cancer–specific mortality (PCSM).

vs 7.2%; $p = 0.013$) for UIR disease. However, a test of interaction between ADT and risk group was nonsignificant for PSA-RFS ($p = 0.102$) or DM ($p = 0.450$). A test of interaction could not be performed for PCSM given that no patient with FIR disease treated with ADT experienced a PCa-related death.

Patients with multiple unfavorable risk factors had significantly decreased 8-yr PSA-RFS (60.3% vs 73.7%; $p = 0.001$), increased LF (24.2% vs 9.7%; $p = 0.024$), increased DM (22.9% vs 5.2%; $p < 0.001$), and increased PCSM (10.5% vs 2.7%; $p < 0.001$) compared with those with only one unfavorable risk factor (Table 4; Fig. 2). This disparity was observed despite the fact that 68.0% of patients with multiple unfavorable risk factors received ADT, compared with 56.2% of patients with one unfavorable risk factor (chi-square p value = 0.022). As shown in Supplementary Figure 3, no significant difference in outcome was detected between intermediate-risk patients with multiple unfavorable risk factors and 582 high-risk patients treated with EBRT doses of at least 81 Gy in terms of PSA-RFS ($p = 0.198$), DM ($p = 0.523$), or PCSM ($p = 0.738$).

4. Discussion

To our knowledge, this is the largest series in the literature comprising men exclusively with intermediate-risk PCa undergoing modern dose-escalated EBRT. Our results show that in the dose-escalation era, patients with intermediate-risk PCa are a heterogeneous group that can be stratified into favorable and unfavorable groups based on the primary Gleason pattern, PPBC, and number of IRFs, and that these risk groups have markedly different prognoses. Specifically, in our population, patients with UIR PCa had a 2.4-fold increase in PSA recurrence, a 4.3-fold increase in DM, and a 7.4-fold increase in PCSM despite being nearly twice as likely to receive ADT.

Given this clinical heterogeneity, a uniform treatment paradigm is unlikely to be the optimal approach for intermediate-risk PCa. This is perhaps most relevant in determining the role of short-term ADT in intermediate-risk PCa, a controversial issue in both the radiation oncology and the medical oncology communities [15]. Two randomized trials enrolling mostly intermediate-risk patients showed prolonged overall survival with the addition of short-term ADT to definitive EBRT [18,19], but these trials used anachronistic radiation techniques and doses far below the current standard of care. Recent retrospective series have come to conflicting conclusions regarding the influence of short-term ADT on outcomes in the dose-escalation era [11,20–22]. Given this controversy and the fact that ADT is associated with significant morbidity and decreased quality-of-life outcomes [23–25], it is appealing to use a refined risk-stratification system for intermediate-risk patients to optimize the cost–benefit ratio of short-term ADT [15,22].

In our series, ADT resulted in significantly lower DM and PCSM rates for patients with UIR, but not FIR, PCa. However, a test of interaction for DM failed to show a significant interaction for ADT and unfavorable risk and could not be performed for PCSM given a lack of events. Thus we are not able to state with statistical certainty that unfavorable patients derive a greater relative benefit from ADT than FIR patients. Nevertheless, we are still able to draw several practical clinical conclusions regarding the absolute benefit of ADT in these groups. Intuitively, those at greatest absolute risk of an adverse outcome are those that will derive the greatest absolute benefit from additional therapy. Given that patients with FIR PCa had indistinguishable outcomes from low-risk patients and only a 3.3% risk of experiencing DM and a 1.3% risk of PCSM at 8 yr with EBRT alone, there appears to be little margin for clinically meaningful improvement from the addition of ADT to dose-escalated EBRT in this group, at least in the first decade following treatment. Taking into consideration the well-described phenomenon of Gleason score inflation over the last 20 yr and the resulting *Will Rogers effect* [26,27], formalized into standard practice by the 2005 International Society of Urologic Pathology consensus conference [28,29], our study including patients treated as early as 1992 almost certainly overestimates the risk of DM and PCSM for men with FIR PCa treated with dose-escalated EBRT in the modern era. Thus omitting short-term ADT may be a reasonable option for patients with FIR disease undergoing dose-escalated EBRT, especially in older men or those with cardiac comorbidities [19,24], although this should be investigated in a prospective trial.

We did observe a significant prolongation in PSA-RFS by ADT for the FIR group. This is consistent with data from Radiation Therapy Oncology Group trial 94-08, where patients with low-risk PCa had an absolute biochemical progression-free survival benefit of 10% when treated with short-term ADT (78% vs 68%; $p < 0.001$) that did not translate into a DM or PCSM benefit [18]. This discordance between biochemical failure and other outcomes like metastasis and mortality may be related to inadequate follow-up in a disease with a long natural history or, alternatively, a reflection of a pattern of failure favoring persistent local disease over occult DM for this population.

Given that the unfavorable risk factors investigated in this study each independently predicted for adverse outcome, it is unsurprising that those with multiple unfavorable risk factors had particularly poor outcomes in comparison with other intermediate-risk patients. In patients with two or more unfavorable risk factors, 40% experienced biochemical failure, 23% experienced DM, and 11% experienced PCSM within 8 yr. These results were similar to those observed with high-risk PCa patients treated at our institution with dose-escalated EBRT. Therefore, it may be reasonable to consider treating these patients with a paradigm similar to that used with patients with high-risk disease including long-term ADT. However, patients with a single unfavorable risk factor have an intermediate prognosis in comparison with low- and high-risk patients, and they may represent a cohort effectively treated with short-term ADT and EBRT.

Our results add to a growing body of literature suggesting that clinical and pathologic factors other than tumor stage, total Gleason score, and pretreatment PSA play

an important role in determining a patient's risk of experiencing DM and PCSM. Primary Gleason pattern, PPBC, and number of IRFs have all been repeatedly shown to independently predict for adverse outcomes in PCa [10–14]. Therefore, previous risk-stratification systems or nomograms that neglect these outcomes, including those previously developed at our institution [30,31], are unlikely to provide optimally accurate risk prediction, especially for patients with intermediate-risk disease.

Several weaknesses of this study warrant further discussion. Most importantly, this is a retrospective study, and the standard caveats associated with any retrospective study apply. The median follow-up of our cohort was only 71 mo, a relatively short follow-up for a disease with a long natural history like intermediate-risk PCa. However, these caveats are unlikely to change significantly our conclusions regarding the different prognoses of favorable and unfavorable groups. Additionally, ADT was not a randomized variable, and the duration of ADT was not standardized. Nevertheless, the median duration of ADT was 6 mo in both the favorable and unfavorable groups. Finally, because dose escalation was likely a critical ingredient in the excellent outcomes observed for FIR PCa in this series, our conclusions regarding the role of short-term ADT in this group should not be extrapolated to patients in this population receiving substantially lower radiation doses.

We further acknowledge there are inherent weaknesses in any stratification system that separates patients into categorical risk groups. Some have argued that risk represents a continuous variable, and thus a nomogram-based approach may be superior to categorical risk grouping [32]. We are currently investigating both nomogram and recursive partitioning analysis-based approaches including patients of all risk groups. Nevertheless, categorical risk-stratification systems such as the NCCN system are widely used in clinical practice for making therapeutic decisions, and refining this system while maintaining its backbone is of great practical utility for clinicians. We are also hopeful that improved understanding of the biochemical pathogenesis of PCa will enable novel molecular-based approaches that can supplement risk stratification based on clinical variables.

5. Conclusions

We have shown that intermediate-risk PCa is a heterogeneous disease that can be stratified into favorable and unfavorable risk groups that have markedly different prognoses based on clinical and pathologic factors that are not currently included in most risk-stratification systems. Thus, a risk-adaptive therapeutic approach is more likely to optimize balance between oncologic outcome and adverse effects than a uniform approach for intermediate-risk disease. Whether FIR and UIR PCa patients derive different magnitudes of benefit from short-term ADT warrants prospective evaluation.

Author contributions: Michael J. Zelefsky 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: Zumsteg, Zelefsky.
Acquisition of data: Zumsteg, Spratt, Pei.
Analysis and interpretation of data: Zumsteg, Zhang, Zelefsky.
Drafting of the manuscript: Zumsteg, Zelefsky.
Critical revision of the manuscript for important intellectual content: Spratt, Pei, Kollmeier, Yamada, Zelefsky.
Statistical analysis: Zumsteg, Zhang.
Obtaining funding: Zelefsky.
Administrative, technical, or material support: Zelefsky.
Supervision: Zelefsky.
Other (specify): None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2013.03.033.

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