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Detectable end of radiation prostate specific antigen assists in identifying men with unfavorable intermediate-risk prostate cancer at high risk of distant recurrence and cancer-specific mortality

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Background: Undetectable End of Radiation PSA (EOR-PSA) has been shown to predict improved survival in prostate cancer (PCa). While validating the unfavorable intermediate-risk (UIR) and favorable intermediate-risk (FIR) stratifications among Johns Hopkins PCa patients treated with radiotherapy, we examined whether EOR-PSA could further risk stratify UIR men for survival.

Methods: A total of 302 IR patients were identified in the Johns Hopkins PCa database (178 UIR, 124 FIR). Kaplan-Meier curves and multivariable analysis was performed via Cox regression for biochemical recurrence free survival (bRFS), distant metastasis free survival (DMFS), and overall survival (OS), while a competing risks model was used for PCa specific survival (PCSS). Among the 235 patients with known EOR-PSA values, we then stratified by EOR-PSA and performed the aforementioned analysis.

Results: The median follow-up time was 11.5 years (138 months). UIR was predictive of worse DMFS and PCSS ($P = 0.008$ and $P = 0.023$) on multivariable analysis (MVA). Increased radiation dose was significant for improved DMFS ($P = 0.016$) on MVA. EOR-PSA was excluded from the models because it did not trend towards significance as a continuous or binary variable due to interaction with UIR, and we were unable to converge a multivariable model with a variable to control for this interaction. However, when stratifying by detectable versus undetectable EOR-PSA, UIR had worse DMFS and PCSS among detectable EOR-PSA patients, but not undetectable patients. UIR was significant on MVA among detectable EOR-PSA patients for DMFS ($P = 0.021$) and PCSS ($P = 0.033$), while RT dose also predicted PCSS ($P = 0.013$).

Conclusions: EOR-PSA can assist in predicting DMFS and PCSS among UIR patients, suggesting a clinically meaningful time point for considering intensification of treatment in clinical trials of intermediate-risk men.

Jonathan Hayman and Ryan Phillips contributed equally to the manuscript.

KEYWORDS
cancer, prostate, risk stratification, unfavorable intermediate risk

1 | INTRODUCTION

Accurate risk stratification of men with localized PCa is paramount to selecting optimal treatment intensity. As such, risk stratification into low-, intermediate-, and high-risk prostate cancer (PCa) has been developed using various cut-offs of initial prostate-specific antigen (PSA) level, biopsy Gleason score, and clinical stage.[1] Intermediate-risk localized disease may be further broken down into favorable and unfavorable intermediate-risk (UIR) disease based upon additional factors, such as primary Gleason 4 disease and percent of positive biopsy cores.[2] FIR disease has significantly improved survival relative to UIR, but UIR men as a group still only have a distant metastasis rate of 8.6% at 8 years with modern dose-escalated radiation therapy.[2] Since over 90% of UIR patients will either have no recurrence or locoregional recurrence at year eight post-treatment, there is a need to determine specifically which men in this group will recur in order to provide additional treatment only to those that require it. Recently published data has shown the prognostic utility of EOR-PSA in PCa patients treated definitively with or without ADT, allowing for the incorporation of dynamic treatment information into risk stratification at a clinically actionable time.[3,4] In this study, we attempted to determine whether utilizing EOR-PSA was able to increase the prognostic utility of another risk stratification model by comparing UIR classification with and without further stratification by EOR-PSA status.

2 | MATERIALS AND METHODS

2.1 | Study population

The study was approved by the institutional review board of Johns Hopkins Hospital (Baltimore, MD). We reviewed a prospectively acquired database of 302 IR patients with clinically localized PCa who were consecutively treated with definitive radiation between January 1, 1993 and December 31, 2006 by a single provider (TL DeWeese). Biopsies that were performed at an outside hospital were reviewed by the genitourinary pathologists at our institution before treatment. Patients were defined as having intermediate-risk disease if their disease was characterized by only one of the following factors: PSA >10 ng/mL but <20 ng/mL, Gleason score 7, and Stage cT2b. UIR was defined as based upon prior definitions: Gleason 4 + 3 disease, more than 50% biopsy cores positive, or at least 2 IR factors.[2]

2.2 | Treatment

Patients were treated with definitive radiation using either three-dimensional conformal radiation therapy (79%) or intensity-modulated radiation therapy (21%), with the latter technique increasingly utilized at the end of the study period. Treatment fields generally included the prostate and seminal vesicles with a boost. The prescription dose for the initial field was 45-46 Gy, delivered in 1.8-2 Gy fractions. The prescription dose for the boost field varied over the study period, with higher doses administered in more recent years. Median total dose for the cohort was 70.2 Gy (range: 59.4-75.6 Gy). When administered, neoadjuvant ADT was initiated 2 months before the radiation start date and consisted of a luteinizing hormone-releasing hormone agonist and an oral antiandrogen. Of those receiving ADT, all but 18 patients received only 6 months of ADT.

During the last week of radiation treatment, EOR-PSA was measured. Following treatment, patients underwent routine follow-up with serial PSA measurements and digital rectal exam (DRE), generally at 6-month intervals. Frequency of PSA measurements and DRE was altered based on the PSA trend and clinical symptoms. Similarly, clinical imaging was obtained in the setting of concerning PSA trends or clinical symptoms. Salvage ADT was administered at provider discretion, but was generally influenced by PSA doubling time, co-morbidity, and life expectancy. No patients received salvage local therapy.

2.3 | Statistical analysis

The primary endpoint of our study was PCSS. PCSS was recorded if patient had a documented history of hormone-refractory metastatic PCa or evidence of a rising PSA at last follow-up visit with no other obvious cause of death. Additionally, the National Death Index (NDI) was cross-referenced to confirm cause of death. Secondary endpoints included bRFS, DMFS, and OS. Biochemical failure, defined as nadir PSA plus 2.0 ng/mL, was based on the RTOG-ASTRO Phoenix Consensus Conference definition.[5] For the purpose of calculating bRFS, patients without biochemical failure were censored at time of last PSA measurement. Metastasis was defined by a radiographic abnormality on bone scan and/or computed tomography, with biopsy performed as needed for confirmation. Failure points were measured from the last Day of radiation.

Differences in patient and treatment characteristics were compared between UIR and FIR patients using the t and χ^2 test where appropriate. An undetectable EOR-PSA was considered < = 0.1 ng/mL, the minimum detectable level by our assay, and was measured during the last week of treatment. Univariate and MV analyses were performed using a univariate/multivariable Cox proportional hazards model to determine associations between UIR and bRFS, DMFS, and OS. PCSS was calculated using a competing risks regression. Kaplan-Meier survival curves were also constructed for all endpoints, with stratification by EOR-PSA and comparison using the

log-rank test. EOR-PSA was not included in MVA as a variable since its effect is not estimable at the same time as the effect of UIR. Instead, we stratified by EOR-PSA status and performed MVA on each subset to see the effect of EOR-PSA on UIR prognostication. Given that there were very few undetectable EOR PSA patients that did not receive ADT, we also attempted to include a variable to control for this interaction, but were unable to estimate a multivariable model with this variable included due to non-convergence. All analyses were performed with Stata and SPSS software. Two-sided significance testing was used, and a *P*-value less than 0.05 was considered statistically significant.

3 | RESULTS

Demographic, tumor, and treatment characteristics of this cohort are detailed in Table 1. There were 178 (59%) unfavorable and 124 (41%) FIR patients with similar proportions receiving ADT in each group, similar age distributions, and comparable radiation doses and techniques.

Overall for the entire intermediate-risk cohort, 10-year bRFS, DMFS, PCSS, and OS were 42%, 86%, 95%, and, 68%, respectively. When stratified by FIR versus UIR, bRFS was 45% versus 41% (Figure 1A, $P = 0.358$), DMFS was 96% versus 80% (Figure 1B, $P = 0.004$), PCSS was 96% versus 93% (Figure 1C, $P = 0.0159$), and OS was 72% versus 65% (Figure 1D, $P = 0.71$). There were no significant differences in the endpoints analyzed at 10 years for FIR patients when stratified by multiple different disease and treatment-related variables including by EOR-PSA. Among men with undetectable EOR-PSA, FIR, and UIR had insignificant differences in outcomes for bRFS (40% vs 34%), DMFS (96% vs 100%), PCSS (100% vs 100%), and OS (67% vs 75%) for FIR versus UIR, respectively. UIR patient outcomes were able to be significantly stratified by detectable EOR-PSA status for bRFS (34% vs 23%, $P = 0.003$), DMFS (100% vs 74%, $P = 0.012$), and PCSS (100% vs 92%, $P = 0.034$) at 10 years, as can be seen in Figure 2. Thus, undetectable EOR-PSA was able to prognosticate improved bRFS, DMFS, and PCSS among UIR patients. UIR patients did experience some benefit from ADT use, but this was not statistically significant. For example, at 10 years, UIR patients had DMFS of 90% with ADT use, compared to 78% with no ADT use ($P = 0.1152$). There was no difference in DMFS among FIR patients with or without ADT use ($P = 0.9288$). Please see Supplementary Figure S1 for Kaplan-Meier curves of DMFS comparing ADT versus No ADT in UIR and FIR. Thus, ADT may be of benefit in UIR disease, but showed no benefit in FIR patients.

UIR was significant on univariate analysis for DMFS ($P = 0.008$) and PCSS ($P = 0.026$), but not bRFS or OS. MVA of factors independently associated with outcome (including UIR grouping as a variable) demonstrated that year of treatment ($P = 0.021$) was significant for bRFS, UIR grouping ($P = 0.008$) and radiation dose ($P = 0.016$) for DMFS, UIR grouping ($P = 0.023$) for PCSS, and age ($P = 0.013$) for OS (Table 2). Notably, ADT did not have a significant impact on outcomes when accounting for other variables. Therefore, the main determinate of DMFS and PCSS among this IR cohort was UIR grouping with increasing radiation dose potentially decreasing distant metastasis.

Of the patients that had distant failure with known EOR-PSA, 84% had both detectable EOR-PSA and UIR grouping, reducing each other's significance in MVA since they predict almost the exact same patients to have events. Because of this close coincidence between UIR and EOR PSA and the low number of events for DMFS/PCSS, it was not possible to converge a multivariable model that included an interaction variable. Controlling for this interaction by stratifying undetectable versus detectable EOR-PSA, MVA analysis was performed to see if sufficient power existed within the data to form significant conclusions. Even with almost 60% fewer patients and significantly less power, UIR ($P = 0.021$) remained predictive among detectable EOR-PSA patients for DMFS, while UIR ($P = 0.033$) and RT dose ($P = 0.013$) were predictive for PCSS (Table 3). Importantly, these findings were independent of ADT use as over 40% of distant recurrences in the UIR group with detectable EOR-PSA received ADT.

Combining UIR grouping with EOR-PSA improved risk stratification by filtering out the 39% of UIR patients with undetectable EOR-PSA who would not recur, allowing improved prediction of recurrences. For example, by utilizing a combined UIR with detectable EOR-PSA stratification for predicting DMFS, specificity increased from 44% to 66% and positive predictive value from 12% to 18% without significantly changing sensitivity or negative predictive value (Supplementary Table S1). Thus, stratification by EOR-PSA status was able to increase the prognostic capacity of UIR grouping for DMFS by further isolating those UIR patients that had high likelihood of recurrence after treatment.

4 | DISCUSSION

This study has a number of clinically relevant conclusions. First, we have validated that UIR designation is prognostic for worse DMFS and PCSS in our cohort with 11-year plus follow-up. Second, we demonstrated the utility of EOR-PSA as a separate prognostic tool that can further risk stratify UIR and that may allow for treatment intensification during a clinically actionable time point. Third, we demonstrated that ADT had no effect on outcomes of FIR patients.

Our analysis showed that UIR was a significant predictor for worse DMFS and PCSS, thus validating this risk stratification system using our cohort of men treated homogenously by a single provider with long follow-up. UIR disease classification has worse outcomes as it likely proxies for treatment resistant disease as independently proposed by other groups.[2] Given that at least 58% of intermediate-risk disease local recurrences were isolated as shown by a retrospective study of 2694 patients, local dose escalation may improve outcomes in this population significantly.[6] With the limitations of increasing dose using external beam radiation therapy (EBRT), brachytherapy has high level evidence to support its use. In ASCENDE-RT, a randomized trial of 400 intermediate- and high-risk

TABLE 1 Demographics

	Favorable *N* (%)	Unfavorable *N* (%)	Total *N* (%)	*P* value
Number of patients	124	178	302	-
Age, yr				
Mean	68.82 (7.03)	68.83 (7.18)	68.83 (7.11)	0.991*
< = 70	65 (52.42)	96 (53.93)	161 (53.31)	0.795**
>70	59 (47.58)	82 (46.07)	141 (46.69)	
Clinical T stage				
T1c	72 (58.06)	75 (42.13)	147 (48.68)	0.001**
T2a	30 (24.19)	31 (17.42)	61 (20.2)	
T2b	14 (11.29)	46 (25.84)	60 (19.87)	
T2c	8 (6.45)	26 (14.61)	34 (11.26)	
Biopsy gleason score				
< = 6	70 (56.45)	44 (24.72)	114 (37.75)	< 0.001**
3 + 4	50 (40.32)	80 (44.94)	130 (43.05)	0.425**
4 + 3	0 (0)	50 (28.09)	50 (16.56)	< 0.001**
PSA				
Mean	9.44 (4.48)	10.29 (4.56)	9.94 (4.54)	0.109*
<10	71 (57.26)	87 (48.88)	158 (52.32)	0.151**
> = 10	53 (42.74)	91 (51.12)	144 (47.68)	
Percentage positive biopsy cores				
<50%	100 (100)	59 (35.76)	159 (60)	< 0.001**
> = 50%	0 (0)	106 (64.24)	106 (40)	
ADT				
Yes	78 (62.9)	114 (64.77)	192 (64)	0.74**
No	46 (37.1)	62 (35.23)	108 (36)	
RT dose				
59.4 Gy	0 (0.00)	1 (0.56)	1 (0.33)	0.217**
64.8 Gy	1 (0.81)	1 (0.56)	2 (0.66)	
66.6 Gy	7 (5.65)	21 (11.80)	28 (9.27)	
68.4 Gy	10 (8.06)	18 (10.11)	28 (9.27)	
70.2 Gy	45 (36.29)	57 (32.02)	102 (33.77)	
72 Gy	12 (9.68)	20 (11.24)	32 (10.60)	
73.8 Gy	39 (31.45)	37 (20.79)	76 (25.17)	
75.6 Gy	10 (8.06)	23 (12.92)	33 (10.93)	
EORT-PSA				
Detectable	54 (55.67)	90 (65.22)	144 (61.28)	0.139**
Undetectable	43 (44.33)	48 (34.78)	91 (38.72)	

Demographics and treatment characteristics table, stratified by unfavorable and favorable intermediate risk disease. T-stage and Gleason score were significantly higher among unfavorable intermediate risk patients. There was no difference in initial PSA, radiation dose or androgen deprivation therapy use. *t* test (*) and χ^2 test (**) were used to assess for significance of differences.

localized PCa patients who received 46 Gy whole pelvis radiation with either a 32 Gy external beam prostate boost or I-125 brachytherapy boost of 115 Gy minimal peripheral dose, the brachytherapy dose escalated boost had significantly higher bRFS of 86% versus 71% for EBRT at 7 years.[7] There was no significant difference in OS in ASCENDE-RT and further follow-up is warranted to re-examine this endpoint. As such, it may be possible to reduce the rate of recurrence in intermediate-risk disease through dose escalation with brachytherapy using UIR classification as a treatment guide.

The results of this study suggest that there may not be a requirement of ADT in FIR patients, supporting the conclusions of

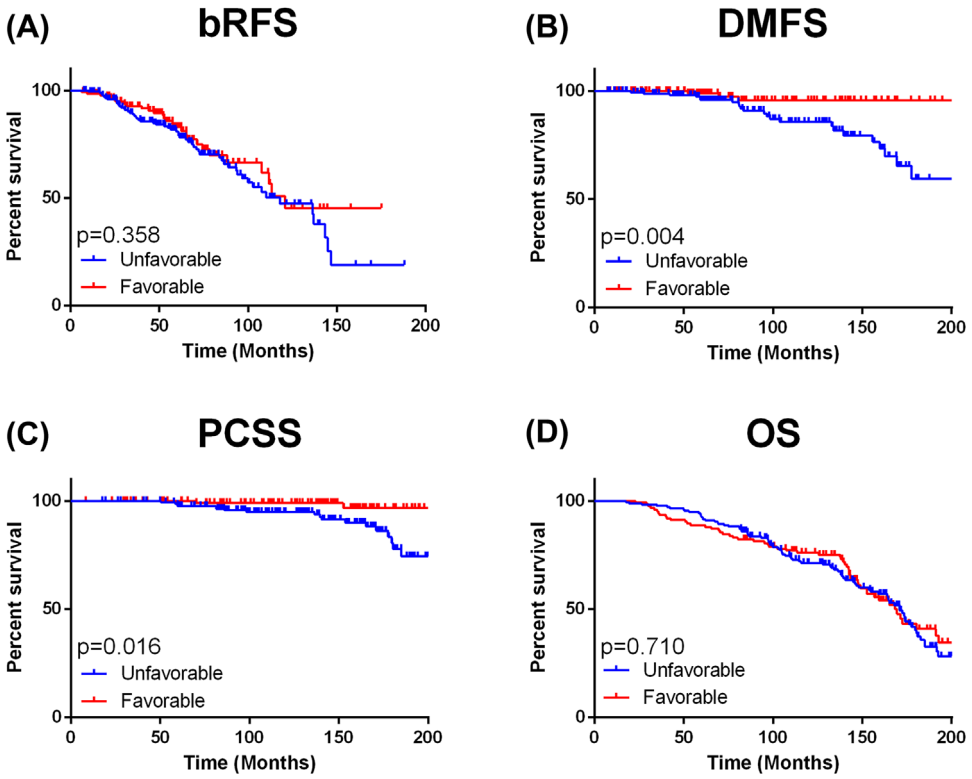

FIGURE 1 Kaplan-Meier curves comparing various measures of survival, stratified by favorable versus UIR disease. Unfavorable disease has significantly worse distant metastasis free survival and PCa specific survival

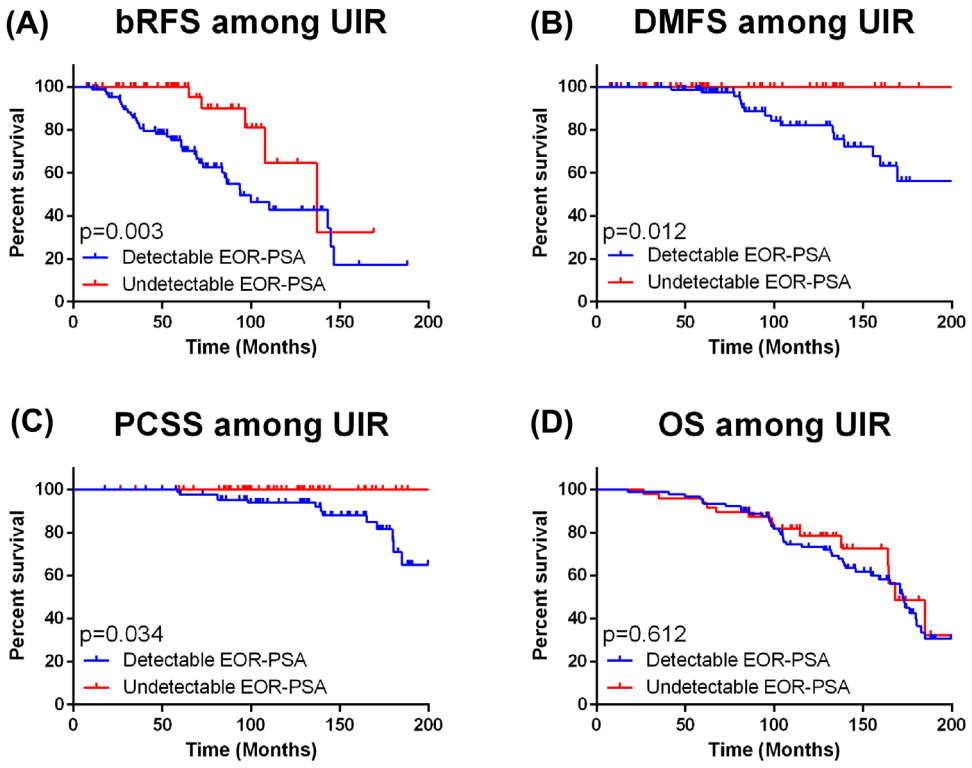

FIGURE 2 Kaplan-Meier curves comparing various measures of survival among UIR patients, stratified by undetectable versus detectable end of radiation prostate specific antigen (EOR-PSA). Detectable EOR-PSA is associated with significantly worse biochemical recurrence free survival, distant metastasis free survival and PCa specific survival among patients with UIR disease

TABLE 2 Multivariable analysis

	HR	P	95% confidence interval	
bRFS				
UIR	1.31	0.26	0.82	2.11
Age	1.02	0.35	0.98	1.05
White race	0.67	0.09	0.42	1.06
ADT	0.79	0.46	0.42	1.48
Radiation dose > = 72 Gy	1.13	0.77	0.50	2.53
PNI	1.04	0.89	0.60	1.81
Year	0.85	0.02	0.75	0.98
DMFS				
UIR	4.33	0.01	1.47	12.74
Age	1.00	0.93	0.95	1.06
White race	0.74	0.47	0.32	1.70
ADT	1.08	0.88	0.40	2.93
Radiation dose > = 72 Gy	0.12	0.02	0.02	0.67
PNI	1.26	0.64	0.48	3.32
Year	1.07	0.62	0.83	1.37
PCSS				
UIR	4.03	0.02	1.21	13.36
Age	0.98	0.47	0.93	1.04
White race	0.62	0.32	0.24	1.61
ADT	1.06	0.93	0.35	3.21
Radiation dose > = 72 Gy	0.29	0.21	0.04	1.97
PNI	1.14	0.82	0.38	3.45
Year	0.93	0.60	0.70	1.23
OS				
UIR	1.04	0.83	0.74	1.46
Age	1.03	0.01	1.01	1.06
White race	0.73	0.09	0.51	1.05
ADT	0.85	0.48	0.55	1.32
Radiation dose > = 72 Gy	0.69	0.26	0.37	1.31
PNI	1.21	0.36	0.81	1.82
Year	1.04	0.46	0.94	1.15

Multivariable analysis for biochemical recurrence free survival (bRFS), distant metastasis free survival (DMFS), prostate cancer specific survival (PCSS), and overall survival (OS) found that treatment year was significant for bRFS, UIR grouping, and radiation dose > = 72 Gy were significant for DMFS, UIR grouping was significant for PCSS, and age was significant for overall survival.

TABLE 3 Multivariable analysis among patients with detectable end of radiation PSA

	HR	P	95% confidence interval	
bRFS				
UIR	1.26	0.46	0.68	2.34
Age	1.00	0.93	0.96	1.04
White race	0.81	0.50	0.44	1.49
ADT	0.80	0.58	0.36	1.77
Radiation dose > = 72 Gy	1.37	0.53	0.52	3.63
PNI	0.88	0.80	0.34	2.32
Year	0.83	0.04	0.70	0.99
DMFS				
UIR	12.58	0.02	1.46	108.37
Age	1.01	0.80	0.94	1.09
White race	0.69	0.51	0.23	2.06
ADT	1.96	0.35	0.48	8.08
Radiation dose > = 72 Gy	0.16	0.08	0.02	1.27
PNI	1.59	0.60	0.28	9.02
Year	0.95	0.77	0.69	1.32
PCSS				
UIR	8.07	0.03	1.18	55.23
Age	0.99	0.74	0.93	1.05
White race	0.57	0.33	0.19	1.75
ADT	1.66	0.49	0.40	6.98
Radiation dose > = 72 Gy	0.09	0.01	0.01	0.60
PNI	2.52	0.28	0.48	13.26
Year	1.00	0.99	0.65	1.52
OS				
UIR	1.01	0.97	0.61	1.66
Age	1.02	0.23	0.99	1.06
White race	0.80	0.42	0.46	1.38
ADT	0.66	0.23	0.33	1.30
Radiation dose > = 72 Gy	0.79	0.60	0.32	1.96
PNI	0.74	0.52	0.29	1.87
Year	1.06	0.39	0.92	1.23

Multivariable analysis among patients with detectable end of radiation prostate specific antigen (EOR-PSA) for biochemical recurrence free survival (bRFS), distant metastasis free survival (DMFS), prostate cancer specific survival (PCSS), and overall survival (OS) found treatment year was significant for bRFS, UIR grouping was significant for DMFS, and UIR and radiation dose > = 72 Gy were significant for PCSS.

other retrospective studies.[8,9] In a recursive partitioning analysis performed among 188 FIR and 274 Low risk PCa patients, there was no benefit of ADT in FIR patients, who had survival similar to low-risk patients.[10] Another large retrospective study including 1902 FIR patients treated with brachytherapy with and without ADT also reported no significant benefit to ADT in addition to brachytherapy among FIR patients.[11] The largest retrospective study involving 18 598 men with FIR PCa who received at least 75.6 Gy of EBRT or EBRT with a brachytherapy boost reported ADT was not associated with improved overall survival, even when stratifying by age.[12] Given the aforementioned retrospective evidence which our series is in agreement with, the hypothesis that ADT may not be beneficial for

FIR patients treated with radiation therapy is reasonable and has been tested in RTOG 0815, a phase III randomized trial whose data is maturing. Radiotherapy alone for FIR men is a particularly attractive option for men with comorbidities for whom the toxicities of ADT, such as cardiac mortality, should be avoided.[13]

We also demonstrated that detectable EOR-PSA can be used to determine which UIR patients are more likely to recur distantly and suffer worse PCSS. Thus, EOR-PSA and UIR if further validated may be used together as a dual risk stratification system to accurately determine which UIR patients require additional radiation dose and potentially identify those necessitating combined modality therapy. While EOR-PSA has been previously described as being a significant predictor for bRFS, DMFS, PCSS, and OS,[3,4] the combination of EOR-PSA with other risk stratification systems is novel. Notably, pre-radiation PSA following neoadjuvant ADT as a measure of response to ADT has also been suggested as a prognostic factor in PCa treated with dose-escalated radiation, with elevated values predicting for worse bRFS, DMFS, PCSS, and OS in one retrospective study of 196 patients[14] and bRFS, DMFS, and PCSS in another retrospective study of 1045 patients.[15] However, EOR-PSA may offer more optimal timing beyond the pre-radiation post-ADT PSA level, with potential implications on the dose of radiation administered and selection of adjuvant therapy. Data suggest that radiation can upregulate the androgen receptor (AR) pathway and thus the EOR-PSA biomarker allows for integration of this radiation-AR axis, not allowed by the pre-radiation post-ADT PSA.[16] Accordingly, EOR-PSA may be better able to predict survival in conjunction with existing risk stratification tools, specifically for UIR men, but this must first be validated through other studies.

While we believe this study has discovered novel relevant findings that may help guide clinicians through treatment, there are also multiple limitations. First, the relatively smaller number of patients limits the power of the study and prevented some MVA models from converging since there were very few events overall. Second, the patients were not treated with modern levels of radiation dose, with a max dose of around 75 Gy in the study. Third, this is a non-randomized, retrospective study, so these results could be the effect of unmeasured confounding variables. Fourth, ADT was administered heterogeneously, potentially limiting the findings of this study. Fifth, ADT may not have been administered to UIR patients for a long enough time to see benefit. Sixth, Gleason score and clinical stage migration could have affected results, although this was compensated for by including treatment year in our models. Finally, EOR-PSA has only been validated in the Johns Hopkins PCa dataset, thus limiting its ability to be applied more widely until a separate group validates our findings.

5 | CONCLUSIONS

By using EOR-PSA with UIR stratification, clinicians can determine which UIR patients are at greater risk for recurrence. Dose escalation or multimodality treatment might then be considered for appropriate poor-risk UIR patients, potentially preventing recurrence.

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CONFLICTS OF INTEREST

The authors of this study have no conflicts of interest with regards to the information published. No authors have any conflicts of interest to disclose related to authorship of this paper.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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