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Clinical Investigation

Genomic Classifier for Guiding Treatment of Intermediate-Risk Prostate Cancers to Dose-Escalated Image Guided Radiation Therapy Without Hormone Therapy

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Summary

We demonstrate the utility of genomic classifiers over the existing National Comprehensive Cancer Network subclassification for predicting disease outcomes (biochemical recurrence and metastasis) in intermediate-risk prostate cancer. We therefore recommend the use of clinicogenomic risk stratification to identify patients with intermediate-risk prostate cancer who can be treated with dose-escalated image guided radiation therapy and safely omit combinatorial androgen deprivation therapy.

Purpose: The National Comprehensive Cancer Network (NCCN) has recently endorsed the stratification of intermediate-risk prostate cancer (IR-PCa) into favorable and unfavorable subgroups and recommend the addition of androgen deprivation therapy (ADT) to radiation therapy (RT) for unfavorable IR-PCa. Recently, more accurate prognostication was demonstrated by integrating a 22-feature genomic classifier (GC) to the NCCN stratification system. Here, we test the utility of the GC to better identify patients with IR-PCa who are sufficiently treated by RT alone.

Methods and Materials: We identified a novel cohort comprising 121 patients with IR-PCa treated with dose-escalated image guided RT (78 Gy in 39 fractions) without ADT. GC scores were derived from tumors sampled in diagnostic biopsies. Multivariable analyses, including both NCCN subclassification and GC scores, were performed for biochemical failure (prostate-specific antigen nadir + 2 ng/mL) and metastasis occurrence.

Results: By NCCN subclassification, 33 (27.3%) and 87 (71.9%) of men were classified as having favorable and unfavorable IR-PCa, respectively (1 case unclassifiable). GC scores were high in 3 favorable IR-PCa and low in 60 unfavorable IR-PCa. Higher GC scores, but not NCCN risk subgroups, were associated with biochemical relapse (hazard ratio, 1.36; 95% confidence interval [CI], 1.09-1.71] per 10% increase; $P = .007$) and metastasis (hazard ratio, 2.05; 95% CI, 1.24-4.24; $P = .004$). GC predicted biochemical failure at 5 years (area under the curve, 0.78; 95% CI, 0.59-0.91), and the combinatorial NCCN + GC model significantly outperformed the NCCN alone model for predicting early-onset metastasis (area under the curve for 5-year metastasis of 0.89 vs 0.86 [GC alone] vs 0.54 [NCCN alone]).

Conclusions: We demonstrated the accuracy of the GC for predicting disease recurrence in IR-PCa treated with dose-escalated image guided RT alone. Our findings highlight the need to evaluate this GC in a prospective clinical trial investigating the role of ADT-RT in clinicogenomic-defined IR-PCa subgroups.

Introduction

Image guided radiation therapy (IGRT) represents a primary treatment modality for localized prostate cancer.[1] Prospective evidence supports combination androgen deprivation therapy (ADT) and IGRT to both improve local control (ie, radiosensitization) and target occult metastases,[2] reducing the disease-specific mortality in high-risk prostate cancer.[3,4] However, the benefit of systemic intensification is debatable for intermediate-risk prostate cancer (IR-PCa), especially when treated with dose-escalated IGRT (DE-IGRT). The National Comprehensive Cancer Network (NCCN) now endorses including additional factors to subclassify an unfavorable IR-PCa subgroup that is at higher risk of metastatic relapse and prostate cancer-specific mortality[5] and therefore more likely to benefit from combined modality treatments such as ADT with radiation therapy (RT).[4,6,7]

Comprehensive molecular profiling of IR-PCa has revealed multiple genomic features of aggression within tumor foci harboring the same histomorphologic grade,[8,9] highlighting the role of genomics for enhanced prognostication beyond conventional indices. On this note, a clinically approved RNA-based 22-gene genomic classifier (GC; Decipher, GenomeDx BioSciences) has been validated as a stratification tool for risk of metastatic relapse and PCa-specific mortality and for predicting response to postoperative RT.[10-13] Additionally, the 22-gene GC has been included in a novel clinicogenomic classification that was proposed to represent a more precise method for risk-stratifying localized PCa.[14]

Here, we evaluate the validity of the 22-gene GC test performed on diagnostic biopsies, accounting for clinicopathologic NCCN risk grouping, for predicting biochemical and metastatic relapse in a cohort of IR-PCa treated with single-modality DE-IGRT at a tertiary cancer center. Of note, there has been only 1 prior study reporting on the utility of a biopsy-derived GC score; it focused on a mixed cohort of intermediate- and high-risk PCa treated with combined ADT and RT.[15] We show that the GC score outperforms the NCCN criteria in distinguishing patients with IR-PCa with favorable outcomes after DE-IGRT without ADT from those who are at risk of metastatic relapse. The GC test may thus be useful for personalizing treatment strategies in IR-PCa, providing actionable information to identify men who should receive combination ADT and DE-IGRT.

Materials and Methods

Study cohort

After obtaining institutional approval (REB #06-0822-CE), we queried our prospective registry between 2005 and 2011

to identify men diagnosed with NCCN-defined IR-PCa treated with curative-intent DE-IGRT without neoadjuvant, concomitant, or adjuvant ADT. All patients underwent dedicated computed tomography simulation. The planning target volume was created by adding 1 cm isotropic expansion in all directions except 7 mm posteriorly to the prostate and the caudal 1-2 cm of seminal vesicles. All patients received 78 Gy (2.0 Gy per fraction) delivered by intensity modulated RT, with daily image guidance based on fiducial- and/or soft tissue–based matching on cone beam computed tomography.

During the study period, diagnostic systematic biopsies consisted of 11 to 12 samples obtained under transrectal ultrasound guidance. The pathology database was cross-referenced to identify those who had paraffin-embedded prostate core biopsy blocks available in-house for genomic characterization. Clinical and genomic data were collected and added to the GenomeDx prostate cancer genomic resource information database (GRID, NCT02609269). This is, therefore, an unpublished cohort with complete clinical and genomic annotation.

Specimen collection and processing

Hematoxylin and eosin–stained slides of diagnostic prostate biopsies were centrally reviewed by an expert genitourinary pathologist (TvdK) for demarcating representative cores containing the highest Gleason score (GS), and ≥6 mm tumor length with ≥70% cellularity. Two distinct tumor regions were demarcated and punched (2 mm diameter) from the corresponding paraffin blocks. Total RNA was extracted in a Clinical Laboratory Improvement Amendments–certified laboratory using the Maxwell 16 LEV RNA FFPE Kit (Promega, Madison, WI) as per specifications. RNA was labeled and hybridized to Human Exon 1.0 ST microarrays (Affymetrix, Santa Clara, CA) by GenomeDx Biosciences Laboratory (San Diego, CA) using the Decipher Clinical Laboratory Improvement Amendments–certified commercial platform, as previously described.[10] Microarray quality control was performed using the Affymetrix Power Tools packages.[16] Probeset summarization and normalization was subsequently performed using the single channel array normalization algorithm.[17]

Calculation of GC score and NCCN subclassification

The 22-gene GC score was determined from the Decipher prostate cancer classifier assay (GenomeDx Biosciences Laboratory) as previously described.[10,15,18] Briefly, GC was calculated based on a locked random forest model to produce a score between 0 and 1. Formerly established cut-points of 0.45 and 0.6 for GC were used for categorical analyses. As per NCCN-endorsed subclassification, unfavorable IR-PCa was defined as any patient with a primary Gleason grade 4, percentage of positive biopsy cores ≥50%, and/or ≥2 NCCN intermediate risk factors.[5]

Statistical considerations

The primary and secondary endpoints of the study were biochemical failure and metastasis occurrence, respectively. Biochemical failure was defined as per Phoenix criteria (prostate-specific antigen nadir + 2ng/mL). The performance of the GC to predict response to DE-IGRT was evaluated by its ability to (1) independently predict biochemical failure and metastasis after DE-IGRT using multivariable Cox regression with Firth's penalized bias reduction method; (2) stratify biochemical failure and metastasis rate among patients using Kaplan-Meier survival curves with an adaptation of Fine-Gray analysis; and (3) distinguish biochemical failure and metastasis rate among patients using survival receiver operating characteristic curves at 5 years.[19] The survival *C*-index of the combined models was estimated by subjecting the model to bootstrapping with 500 resamples for optimism correction. Ninety-five percent confidence intervals (95% confidence intervals) for the *C*-index were computed using bootstrapping methods. Decision curve analysis was performed to evaluate the net benefit of GC and NCCN across clinically relevant threshold probabilities. Statistical significance was defined by $P < .05$. All analyses were performed in R v3.3 (R Foundation for Statistical Computing, Austria).

Results

A total of 121 patients met our study eligibility criteria, comprising 33 (27.3%) NCCN-favorable and 87 (71.9%) NCCN-unfavorable IR-PCa (Table 1). Median follow-up of the cohort was 7.5 years (interquartile range, 6.5-8.7 years). Overall, GC classified 87 (71.9%) patients as low risk, whereas 18 (14.9%) and 15 (12.4%) patients were classified as intermediate and high risk, respectively. In the NCCN-unfavorable subgroup, GC classified 60 (69.0%), 15 (17.2%), and 12 (13.8%) cases into low, intermediate, and high risk, respectively; GC stratified 3 of 33 (9.1%) NCCN-favorable patients with IR-PCa as high risk (Fig. E1; available online at https://dx.doi.org/10.1016/j.ijrobp.2018.08.030). Interestingly, the combinatorial NCCN subclassification and GC as per the new clinicogenomic risk grouping system[14] yielded a stratification of high-risk cases comparable to that using the GC alone (N = 12 [9.9%]; Table 1).

We recorded 24 biochemical failures and 5 metastasis occurrences in our cohort. The NCCN IR-PCa subclassification was not associated with risk of biochemical or metastatic relapse ($P = .235$ and $P = .885$, respectively; Fig. 1A; Tables 2 and 3). Conversely, GC scores were a strong predictor of biochemical and metastatic relapses (hazard ratio of biochemical failure, 1.33 [1.08-1.66], $P = .009$; hazard ratio of metastasis, 2.05 [1.24-4.23], $P = .003$; Fig. 1B; Tables 2 and 3; Tables E1 and E2,

Table 1 Clinical characteristics of patients with intermediate-risk prostate cancer treated with dose-escalated image guided radiation therapy alone

Clinical parameters	N = 121 (%*)
Median follow-up (range), y	7.7 (0.7-11.2)
Age (median [IQR]), y	72.4 (68.4-75.0)
Prediagnostic PSA (median [IQR]), ng/mL	7.8 (5.7-11.2)
Clinical T-category	
cT1c/T2a	95 (78.5)
cT2b/T2c	26 (21.5)
ISUP grade (GS)	
1 (3 + 3)	12 (9.9)
2 (3 + 4)	75 (62.0)
3 (4 + 3)	34 (28.1)
Percentage of positive biopsy cores	
<50%	69 (57.0)
≥50%	48 (39.7)
Unknown	4 (3.3)
NCCN subclassification	
Favorable	33 (27.3)
Unfavorable†	87 (71.9)
Unknown	1 (0.8)
Genomic classifier score	
Low (<0.45)	88 (72.7)
Intermediate (0.45-0.6)	18 (14.9)
High (>0.6)	15 (12.4)
Clinical genomic risk group	
Low (0-1)	27 (22.3)
Intermediate (2-3)	81 (66.9)
High (4-5)	12 (9.9)
Unknown	1 (0.8)
Treatment	
IGRT 78 Gy in 39 fractions	121 (100)
Combinatorial ADT	0 (0)

Abbreviations: ADT = androgen deprivation therapy; GS = Gleason score; IGRT = image guided radiation therapy; ISUP = International Society of Urologic Pathology grading system for prostate cancer based on GS; IQR = interquartile range; NCCN = National Comprehensive Cancer Network.

* Percentages unless otherwise indicated.

† Patients were classified as unfavorable if they harbor any of 3 adverse features: (1) percentage of positive biopsy cores ≥50%; (2) primary Gleason grade 4; (3) 2 or 3 NCCN intermediate-risk factors (cT2b-c, GS 7, and prostate-specific antigen >10 ng/mL).

available online at https://dx.doi.org/10.1016/j.ijrobp.2018.08.030), even after adjustment for NCCN indices and subclassification, primary Gleason grade 4, and percentage of positive biopsy cores. This corresponded to a substantial improvement in accuracy for prediction of biochemical relapse: area under the curve (AUC) = 0.56 (NCCN only) versus 0.78 (GC only) versus 0.85 (NCCN + GC). Similarly, we observed improved prediction for early onset (5-year) metastatic recurrences: AUC = 0.54 (NCCN only) versus 0.86 (GC only) versus 0.89 (NCCN + GC) (Fig. 2). Therefore, our results expand on the existing literature and highlight the utility of the GC score as a clinical decision-making tool in addition to the NCCN criteria for selecting IR-PCa to receive combination ADT and IGRT (Fig. E2; available online at https://dx.doi.org/10.1016/j.ijrobp.2018.08.030).

Discussion

Here, we aimed to determine the clinical utility of a 22-gene GC in patients with IR-PCa treated with radical RT monotherapy and to build on the evidence highlighting the need to improve upon the current prognostication methods for localized prostate cancer. The present study is novel because it reports on the performance of the GC for predicting adverse outcomes (biochemical failures and lethal metastases) in an unpublished IR-PCa cohort treated with single modality DE-IGRT (78 Gy in 39 fractions) at a high-volume academic center. Of note, we observed that a substantial proportion of patients (60 of 87) were reclassified as GC low risk despite harboring unfavorable clinicopathologic risk factors. Importantly, the GC outperformed all other indices, including the NCCN subclassification, in predicting biochemical failure and metastasis occurrence after DE-IGRT, with an optimistic accuracy that exceeds 80%. This corresponded to our secondary observation of rates of restratification to high risk comparable to those with the GC test alone (12.4%) and the recent clinicogenomic classification system proposed by Spratt et al (9.9%).[14] Hence, our results underscore the clinical impact of incorporating genomic characterization into localized prostate cancer prognostic systems, allowing the identification of a substantial subgroup of IR-PCa patients who can be optimally treated by DE-RT without ADT.

On this note, it is known that IR-PCa represents a clinically heterogeneous subgroup, for which conventional clinicopathologic parameters of T-category, prostate-specific antigen, and GS are imprecise for risk stratification, thus commonly leading to under- and overtreatment. Hence, the NCCN recently updated its classification of IR-PCa by including additional diagnostic parameters to further stratify IR-PCa into favorable and unfavorable subgroups with disparate risks of metastasis and PCa-specific mortality.[5] Nonetheless, this subclassification scheme was developed in a heterogeneous cohort of men treated with DE-EBRT, most of whom received ADT. This may be consistent with clinical observations that men harboring unfavorable IR-PCa likely benefit from treatment intensification with addition of ADT to RT,[6,7,20,21] but the majority of patients included in these studies were not treated with contemporary escalated doses of RT. It therefore remains undefined whether the majority of unfavorable IR-PCa requires combined ADT for radiosensitization[2,22] and/or targeting occult metastases in the context of increased RT dose intensity. It is expected that the ongoing Radiation Therapy Oncology Group 0815 randomized controlled trial (Clinicaltrials.gov; NCT00936390) will determine the incremental benefit of ADT in the context of DE-IGRT, thus providing valuable information for this clinical conundrum in IR-PCa. All of this evidence

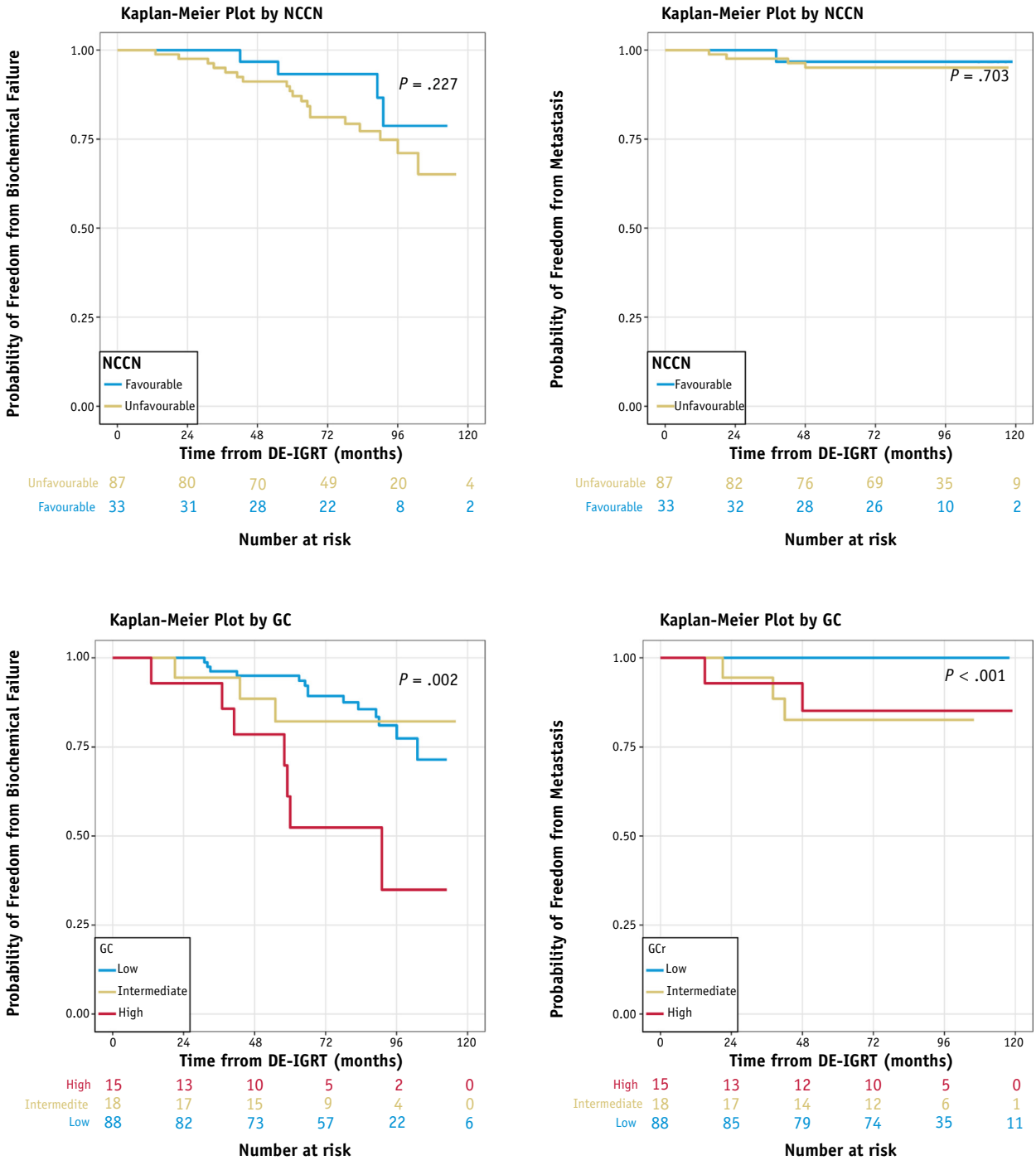

Fig. 1. (A) Kaplan-Meier plots stratified by NCCN IR-PCa subclassification for biochemical failure (left) and metastatic relapse (right). (B) Univariable analyses for biochemical (left) and metastatic (right) relapses for the different GC-risk categories. *Abbreviations:* GC = genomic classifier; IR-PCa = intermediate-risk prostate cancer; NCCN = National Comprehensive Cancer Network.

highlights the pressing need for more accurate, patient-specific, biology-based biomarkers to guide treatment individualization (de)intensification strategies.

Recently, a novel clinicogenomic model was proposed stressing the necessity of incorporating molecular biomarkers (GC) into clinical indices (NCCN classification) for accurate prediction of aggressive PCa.[14] Our results support the need for such a model; we observed that combinational NCCN + GC indices yield the strongest discrimination for favorable and unfavorable subtypes of IR-PCa (AUC for 5-year biochemical failure = 0.85 vs 0.78 [GC alone] vs 0.56 [NCCN alone]). Additionally, we propose the potential clinical utility of GC for personalizing treatment recommendations in men with IR-PCa. Men with GC low risk could be

Table 2 Association of conventional clinical indices, NCCN subclassification, and GC with biochemical failure

Models	Covariates	Univariable		Multivariable (24 events)	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
1	**Age (continuous)**	1.01 (0.93-1.09)	.895	1.00 (0.91-1.10)	.928
	Prediagnostic PSA (continuous)	1.37 (0.77-2.47)	.287	1.20 (0.62-2.32)	.587
	cT-category				
	T2b/c vs T1/T2a (ref)	1.26 (0.50-3.17)	.627	0.70 (0.22-2.21)	.544
	ISUP grade				
	3 vs 2 and 1 (ref)	1.96 (0.87-4.43)	.105	2.31 (0.96-5.60)	.063
	Percentage of positive biopsy cores				
	≥50 vs <50 (ref)	1.54 (0.65-3.63)	.326	1.50 (0.59-3.78)	.395
	GC score (continuous)*	***1.33 (1.08-1.66)***	***.009***	***1.36 (1.08-1.71)***	***.010***
2	**NCCN subclassification**				
	Unfavorable vs favorable (ref)	1.92 (0.65-5.65)	.235	1.63 (0.55-4.82)	.381
	GC score (continuous)*			***1.36 (1.09-1.71)***	***.007***
3	**ISUP grade**				
	3 vs 2 and 1 (ref)			2.0 (0.88-4.50)	.096
	GC score (continuous)*			***1.33 (1.08-1.64)***	***.008***

Abbreviations: GC = genomic classifier; ISUP = International Society of Urologic Pathology grading system for prostate cancer based on Gleason score; NCCN = National Comprehensive Cancer Network; ref = reference.
Texts were bold and italics when significant at 0.05 level ($P < 0.05$).
* Hazard ratios reported per 0.1 unit increase.

treated with DE-IGRT alone with expected excellent outcomes, whereas individuals harboring NCCN unfavorable disease coupled with GC high risk should be considered for combination ADT-RT.

A pertinent design aspect of our study relates to the molecular profiling of tumors that were isolated from diagnostic biopsies, which is crucial when considering the utility of a biomarker to inform treatment recommendations a priori. Notably, the impact of the spatial heterogeneity[8] on the prognostic accuracy of genomic biomarkers remains largely unquantified. Nevertheless, this work adds to other studies that have reported on biopsy-based genomic signatures that predict for aggressive localized PCa, although most of these studies used mixed cohorts of intermediate- and high-risk PCa that were predominantly treated with ADT-RT.[15,23,24] Our study is therefore informative; beyond prognostication it provides potentially actionable information by focusing solely on IR-PCa, for which current guidelines reflect the clinical challenge of DE-RT alone versus systemic (ADT) and/or local (brachytherapy boost) intensification.

Our study is not devoid of limitations. First, it is arguable that our study is underpowered given the modest

Table 3 Association of conventional clinical indices, NCCN subclassification, and GC with metastatic relapses

Models	Covariates	Univariable		Multivariable (5 events)	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
1	**Age (continuous)**	0.98 (0.84-1.17)	.790	1.14 (0.95-1.40)	.156
	Prediagnostic PSA (continuous)	1.09 (0.36-4.21)	.892	1.11 (0.17-9.28)	.912
	cT-category				
	T2b/c vs T1/T2a (ref)	1.30 (0.13-7.02)	.785	0.25 (0.00-3.04)	.316
	ISUP grade				
	3 vs 2 and 1 (ref)	***8.12 (1.50-81.0)***	***.014***	***7.92 (1.30-84.50)***	***.025***
	Percentage of positive biopsy cores				
	≥50 vs <50 (ref)	1.53 (0.24-9.92)	.634	0.83 (0.06-9.39)	.876
	GC score (continuous)*	***2.05 (1.24-4.23)***	***.003***	***2.07 (1.17-5.24)***	***.010***
2	**NCCN subclassification**				
	Unfavorable vs favorable (ref)	1.14 (0.21-11.41)	.885	0.74 (0.13-7.50)	.760
	GC score (continuous)*			***2.05 (1.24-4.24)***	***.004***
3	**ISUP grade**				
	3 vs 2 and 1 (ref)			***6.95 (1.25-70.13)***	***.026***
	GC score (continuous)*			***1.84 (1.18-3.57)***	***.006***

Abbreviations: GC = genomic classifier; ISUP = International Society of Urologic Pathology grading system for prostate cancer based on Gleason score; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; ref = reference.
Texts were bold and italics when significant at 0.05 level ($P < 0.05$).
* Hazard ratio reported per 0.1 unit increase

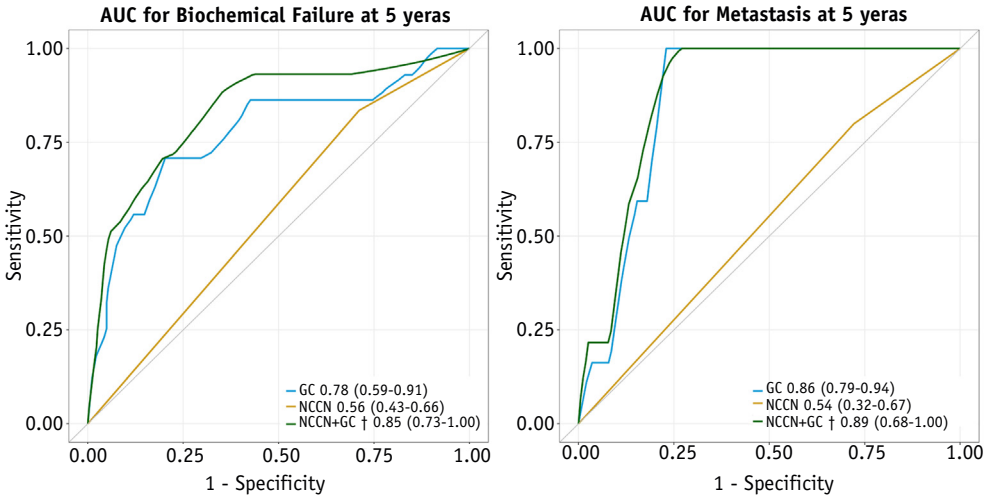

Fig. 2. Area under the receiver operating characteristic curve (AUC) for prediction of 5-year biochemical (left) and metastatic (right) relapses by the different clinical (NCCN) and genomic (GC and NCCN + GC) models. *Abbreviations:* GC = genomic classifier; NCCN = National Comprehensive Cancer Network. †Applied optimism correction.

sample size and consequently few metastatic events. Nonetheless, our patient cohort was identified from a prospective registry with stringent inclusion criteria of adequate diagnostic biopsy tissue for central pathology review and sampling, omission of concurrent ADT with RT, and contemporary RT dose intensity and technique of 78 Gy in 39 fractions delivered using IGRT. This reflects real life clinical practice, and the fact that the GC is robust for prognosticating these patients is compelling evidence for its routine clinical implementation in men with IR-PCa treated with RT. Next, although we acknowledge that the addition of ADT to RT for unfavorable IR-PCa disease is considered standard practice by several institutions, it remains debatable whether the reported benefits of the combinatorial approach are maintained in the context of RT dose-escalation. Presently, the European Organisation for Research and Treatment of Cancer 22991 phase 3 trial provides the main supportive evidence specific to this clinical conundrum.[4] However, it must be noted that the trial's cohort also consisted of 25% NCCN-defined high-risk patients, treatment schedules with minor dose escalation (ie, 70 Gy or 74 Gy in more than 75% of cases), and treatment delivered without image guidance; all elements could in part explain the poor outcomes in the EBRT-alone control arm. Therefore, at the time of the present study our practice for clinical management of IR-PCa remained largely unchanged, and the low rates of biochemical relapse and metastatic events observed support this approach. For example, the 5-year biochemical relapse−free rates in this series were 94% and 88% for the favorable and unfavorable subgroups, respectively, mirroring the 87% reported in the DE-RT arm from the Radiation Therapy Oncology Group 0126 trial in predominantly favorable IR-PCa.[25] Nevertheless, we cannot completely exclude the presence of selection bias within this cohort; in fact, during the last few years our practice has increasingly embraced the combination of DE-IGRT and short-term ADT, particularly in IR-PCa harboring unfavorable indices and/or other aggressive features such as intraductal and cribiform subpathologies.[26] Finally, although we have shown the potential utility of the GC test for identifying an unfavorable subgroup of men who likely require treatment intensification beyond DE-IGRT, this study is not positioned to determine the efficacy of combined ADT and DE-IGRT to overcome the adverse prognosis of patients with a GC high risk score.

Conclusions

We report on the robust prediction of biochemical failure and metastasis occurrence using a clinically available GC test in patients with IR-PCa who were treated with single-modality DE-IGRT. Our study supports the need to evaluate GC in a prospective fashion; we envisage that the clinicogenomic model could be used to personalize treatment intensification with combinatorial ADT and DE-IGRT for patients with IR-PCa.

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