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Performance of Clinicopathologic Models in Men with High Risk Localized Prostate Cancer: Impact of a 22-Gene Genomic Classifier

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Conflicts of Interest

Non-relevant conflicts of interest will be disclosed in the ICMJE forms.

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Abstract

Background: Prostate cancer exhibits biological and clinical heterogeneity even within established clinico-pathologic risk groups. The Decipher genomic classifier (GC) is a validated method to further risk-stratify disease in patients with prostate cancer, but its performance solely within NCCN high risk disease has not been undertaken to date.

Methods: A multi-institutional retrospective study of 405 men with high-risk prostate cancer who underwent primary treatment with radical prostatectomy (RP) or radiation therapy (RT) with androgen-deprivation therapy (ADT) at 11 centers from 1995 to 2005 was performed. Cox proportional hazards models were used to determine the hazard ratios for the development of metastatic disease based on clinico-pathologic variables, risk groups, and GC score. The area under the receiver operating characteristic curve (AUC) was determined for regression models without and with the GC score.

Results: Over a median follow-up of 82 months, 104 patients (26%) developed metastatic disease. On univariable analysis, increasing GC score was significantly associated with metastatic disease (hazard ratio [HR]: 1.34 per 0.1 unit increase, 95% confidence interval [CI]: 1.19–1.50, p<0.001), while age, serum PSA, biopsy GG, and clinical T-stage were not (all p>0.05). On multivariable analysis, GC score (HR: 1.33 per 0.1 unit increase, 95% CI: 1.19–1.48, p<0.001) and GC high-risk (vs. low-risk, HR: 2.95, 95% CI: 1.79–4.87, p<0.001) were significantly associated with metastasis. The addition of GC score to regression models based on NCCN risk group improved model AUC from 0.46 to 0.67, and CAPRA from 0.59 to 0.71.

Conclusions: Among men with high-risk prostate cancer, conventional clinico-pathologic data had poor discrimination to risk stratify development of metastatic disease. GC score was a significant and independent predictor of metastasis and may help identify men best suited for treatment intensification/de-escalation.

INTRODUCTION

Prostate cancer is the leading cause of cancer-associated morbidity in the world and the second-leading cause of cancer death in US men.[1] Approximately half of all prostate cancer deaths occur in men diagnosed with localized disease, the majority of which present with National Comprehensive Cancer Network (NCCN) high-risk cancer.[2] Even among the high-risk population, however, clinical outcomes vary widely,[3] and the vast majority of men will not develop metastatic disease or die of prostate cancer.[4] Thus, accurate, individualized risk stratification is necessary to better identify where treatment intensification or de-escalation can be personalized to optimize patient outcomes.

In the United States, the most common treatment for men with high-risk prostate cancer is radiotherapy (RT) with long-term androgen deprivation therapy (LT-ADT).[5] In recent years, the use of radical prostatectomy (RP) has increased,[6] often as part of a multi-modality approach including adjuvant or salvage RT. At the same time, clinical trials have demonstrated modest improvements in outcomes after treatment intensification, such as the addition of concurrent abiraterone or adjuvant chemotherapy to RT and LT-ADT,[7,8]

or the use of neoadjuvant chemotherapy with ADT prior to RP.[9,10] Thus, men harboring the highest risk, most biologically aggressive cancers appear to benefit from novel treatment intensification schemes, thereby providing the highest likelihood of long-term cure. Furthermore, if accurately identified, those with lower risk tumors could be spared the toxicity and cost of unnecessary treatment intensification.

Nevertheless, current risk stratification schemes are not able to accurately define subgroups of high-risk prostate cancer.[11] Additionally, the NCCN very high-risk classification includes only ~2% of men with localized prostate cancer and therefore fails to capture all patients destined to develop metastasis.[11] An increasing body of data suggests that genomic risk assessment tools are highly prognostic, irrespective of cancer stage, risk group, or treatment type.[12] For example, the 22-gene Decipher test appears to be superior to clinico-pathologic models in several settings, including low- and intermediate-risk localized disease, post-RP adjuvant therapy, biochemical recurrence, and, most recently, non-metastatic castration-resistant disease.[12–15] While a limited number of patients with high-risk prostate cancer have been included in previous studies,[12–15] we herein provide the first assessment of genomic classifier (GC) testing and clinico-pathologic risk groupings in an exclusively NCCN high-risk patient population.

PATIENTS AND METHODS

Study Cohort

Institutional Review Board approval was obtained at participating institutions prior to study initiation. The study cohort included patients diagnosed with NCCN high-risk and very high-risk prostate cancer who underwent GC testing. High-risk cancer was defined as: clinical stage T3a, or Grade Group (GG) 4–5, or PSA >20 ng/ml.[16] Because data regarding the number of biopsy cores with GG 4–5 cancer were not available, very high-risk (VHR) cancer was defined by clinical stage T3b-T4 or primary Gleason pattern 5 disease. Notably, the current NCCN definition of very high-risk cancer (i.e. clinical stage T3b-T4, or primary Gleason pattern 5, or >4 cores with GG 4–5) differs from the originally defined and recently validated definition (i.e. primary Gleason pattern 5, or >4 cores with GG 4–5, or multiple high-risk features).[4,17] Patients were treated at 11 centers between 1995 and 2005 (Supplementary Table 1 for details). Patients who received neoadjuvant ADT or had clinical evidence of nodal disease prior to RP were excluded. The final cohort contained 405 men in total, of which 151 underwent GC testing on the pre-treatment biopsy and 254 underwent GC testing on the RP specimen. Treatment details are shown in Table 1.

Study Variables and GC Score

Study variables included patient age, clinical T-stage, serum PSA, biopsy Grade Group (GG), and percentage of biopsy cores positive for cancer. CAPRA score (continuous scale, 0–10) and NCCN risk group (high-risk vs. very high-risk) were determined based on clinical variables. Biopsy tissue was graded at each institution by genitourinary pathologists in accordance with International Society of Urological Pathology guidelines.[18]

Specimen selection and processing was performed using a clinical-grade whole transcriptome RNA expression assay by Decipher Biosciences Laboratory (San Diego, CA, USA) as previously described.[19] For biopsy tissue, RNA was extracted using the biopsy core with the highest Gleason score and percentage tumor involvement. For RP specimens, cancer foci with the highest Gleason scores were selected. The GC score and risk groupings were generated from the Decipher PCa classifier assay as previously described.[19,20]

Statistical Analysis

The primary outcome was metastatic disease, defined by radiographic evidence of bone, viscera, or extra-pelvic lymph node metastasis on standard imaging with computed tomography or bone scan. Patient-level data were tabulated by number (percentage) and median (interquartile range, IQR) as appropriate. Comparisons of the biopsy-derived and RP-derived cohorts were made with the chi-squared and Mann-Whitney-Wilcoxon tests as appropriate. Cumulative incidence of metastatic disease was calculated for the study cohort stratified by clinico-pathologic variables and GC score.

Univariable and multivariable Cox proportional hazards models were used to determine the hazard ratios for metastasis based on clinico-pathologic variables and GC score. GC score was assessed using two approaches: 1) a continuous score ranging from 0 to 1, and 2) previously established low-, intermediate-, and high-risk categories based on threshold scores of 0.45 and 0.60.[21] The area under the receiver operating characteristic curve (AUC) was determined for regression models based on NCCN risk group and CAPRA score, without and with GC score. Confidence intervals for the C-index were computed using bootstrapping method, and the survival C-index of the combined models was estimated by bootstrapping with 500 resamples for optimism correction. Statistical analyses were performed in R v3.3, and all statistical tests were performed using a 5% significance level.

RESULTS

Cohort Characteristics

The median clinical follow-up was 82.1 months (IQR 55.1–119). The median age at diagnosis was 62 years (IQR 56–69), and median serum PSA was 15.2 ng/ml (IQR 6.37–25.8). Biopsy GG was 1–3 in 150 men (37%), 4–5 in 236 (58%), and unavailable in 19 (4.7%) (Table 1). The median GC score was 0.48 (IQR 0.30–0.65). Overall, 187 men (46%) were GC low-risk, 91 men (23%) were GC intermediate-risk, and 127 men (31%) were GC high-risk. GC score distribution was similar when analyzed on pre-treatment biopsy or RP (Supplementary Table 2).

Metastatic Outcomes

Metastatic disease was detected in 104 men (26%) during follow-up. As illustrated in Figure 1, the cumulative incidence of metastasis did not significantly differ across biopsy GG strata (p=0.69). The 5-year cumulative incidence of metastasis was 17.1%, 20.6%, and 15.3% in men with GG 1–3, GG 4, and GG 5, respectively. Similarly, the cumulative incidence of metastasis did not significantly differ after stratification based on clinical T-stage (p=0.59) or NCCN risk group (p=0.32, Fig. 1B–C). Figure 2 illustrates the cumulative incidence

curves for metastasis after stratification by GC score. The five-year cumulative incidence of metastasis was 9.4%, 16.7%, and 30.8% for GC low, intermediate, and high risk, respectively ($p<0.001$).

On univariable analysis, traditional clinico-pathologic risk factors including age, serum PSA, biopsy GG, and clinical T-stage were not significantly associated with metastatic disease (all $p>0.05$).

Furthermore, NCCN high versus very high-risk classification was not significantly associated with metastasis (HR 0.64, 95% CI 0.25–1.63; p=0.35). CAPRA score, however, conferred an increased hazard of metastasis (HR 1.34, 95% CI 1.00–1.40; p=0.044) per one-unit increase. Similarly, GC score was associated with an increased hazard for metastasis (HR 1.34 per 0.1 unit increase, 95% CI 1.19–1.50; $p<0.001$). When compared to the GC low-risk category, a high-risk GC score carried a hazard ratio of 2.93 for metastasis (95% CI 1.73–4.94; $p<0.001$).

In the multivariable model including age, PSA, biopsy GG, and clinical T-stage (Table 2), increasing GC score was the only factor significantly associated with metastasis (HR 1.33 per 0.1 unit, 95% CI 1.19–1.48; $p<0.001$). When GC score was treated as a categorical variable, GC high-risk was associated with a nearly three-fold increased hazard of metastasis compared to GC low-risk (HR 2.95 95% CI 1.79–4.87; $p<0.001$). GC intermediate-risk did not significantly differ from GC low-risk. In a second multivariable model incorporating NCCN risk group rather than each individual variable comprising risk group, GC was similarly associated with increased hazard of metastasis as both a continuous or categorical score, while NCCN very high-risk status did not significantly differ from high-risk status (HR 0.63, 95% CI 0.24–1.62, p=0.34). Similarly, in a third model including CAPRA as a continuous score and GC, CAPRA was not significantly associated with the development of metastasis (HR 1.13, 95% CI 0.97–1.31, p=0.12), whereas GC was associated in both the continuous and categorical models.

Time-dependent AUCs were derived to measure the ability of NCCN risk group and CAPRA score to discriminate which patients would subsequently develop metastatic disease (Figure 3A). At 5-years post-treatment (Figure 3B), a baseline model including only NCCN risk group showed poor discriminatory ability (AUC 0.46). In contrast, CAPRA had an AUC of 0.59. The addition of GC score to the NCCN risk group model improved the AUC to 0.67. Similarly, the addition of GC score to a baseline model including CAPRA score increased the model AUC to 0.71.

DISCUSSION

High-risk prostate cancer is clinically-defined to include men harboring biopsy Grade Group 4–5, clinical stage T3–4, or PSA ≥20 ng/mL.[16] This definition accounts for approximately <20% of men diagnosed with prostate cancer and represents a biologically diverse range of cancers.[22] Several investigators have previously demonstrated the heterogeneous clinical course of high-risk PCa following definitive treatment.[7,23,24] Accordingly, patients are offered a wide range of management options, ranging from potential RP monotherapy

to multimodal approaches. While traditional clinico-pathologic risk strata help to stratify localized prostate cancer patients,[4,17] the ability of these factors to sub-stratify patients in the high-risk group is limited.[11] Given the increasing morbidity and toxicity associated with treatment intensification, improved tools are needed to better identify those patients who could achieve cure with local therapy alone from those requiring a more aggressive, multimodal approach.

We evaluated the association of traditional clinico-pathologic risk factors and the expression-based GC score with metastatic outcomes in a cohort of patients with high-risk disease who underwent first-line treatment with RP or RT+ADT. Within this high-risk population, we found that Grade Group, clinical T-stage, and NCCN high/very high-risk status did not significantly differentiate patients based on likelihood of metastatic disease. Genomic risk categorization based on the GC score, however, was able to stratify by risk of metastasis. The five-year cumulative incidence of metastasis was 30.8% in GC high-risk as compared to 16.7% in GC intermediate-risk and 9.4% in GC low-risk (log-rank $p<0.001$). Furthermore, in a multivariable model adjusted for age, PSA, Grade Group, and clinical T-stage, increasing GC score was the only significant predictor of metastasis (continuous scale: HR 1.33 per 0.1 unit, 95% CI 1.19–1.48, $p<0.001$; GC high-risk vs. GC low-risk: HR 2.95, 95% CI 1.79–4.87, $p<0.001$). Thus, while the GC score was correlated with clinical factors, it appears to provide independent prognostic information beyond that of measured clinical variables. These findings suggest that pre-treatment genomic risk can sub-stratify the high-risk population by likelihood of metastasis and aid in tailoring management among individual patients.

While this study is the first to assess the GC test in an exclusively high-risk cohort, our findings build upon data observed in other patient populations. For example, in a cohort of mostly low- (40%) and intermediate-risk (47%) men, Klein et al determined that biopsy GC score was the only significant predictor of post-RP metastasis (HR 1.72, 95% CI 1.07–2.81; $p=0.02$) in a model adjusted for age, PSA, and biopsy grade.[19] In a multi-center study of 255 men with intermediate- to high-risk disease treated with RP or RT + ADT, Nguyen and colleagues similarly found that biopsy GC score was the only significant predictor of metastasis (HR 1.39, 95% CI 1.09–1.80; $p=0.009$) after adjusting for clinical variables and treatment.[25] Furthermore, Spratt et al demonstrated the utility of combining clinical and genomic data to improve risk stratification as compared to NCCN clinical risk grouping.[11] Among 756 men with NCCN low-, favorable-intermediate-, unfavorable-intermediate-, and high-risk cancer, the 10-year risk of metastasis was 7.3%, 9.2%, 38.0%, and 39.5%, respectively. Combining clinical risk groupings with GC score, the authors developed a three-tiered clinical-genomic risk stratification in which risk of metastasis was 0%, 25.9%, and 55.2%, respectively. These findings corroborate previous data validating the use of GC in predicting prostate cancer-specific mortality during long-term follow-up after RP.[26]

Other DNA-based alterations detectable in tissue, such as loss of PTEN and RB1, have similarly augmented prediction of oncologic outcomes.[27,28] Indeed, risk stratification combining clinico-pathologic factors with genomic risk appears to substantially improve prediction of meaningful clinical outcomes such as metastatic disease. While traditional risk factors are useful in stratifying the diverse population of men diagnosed with prostate

cancer, these factors appear to have limited value in further sub-stratifying patients within NCCN risk categories.[29] Acknowledging the wide range of potential outcomes in the high-risk population,[3] the high number of management options available,[16] and the extensive cost and morbidity associated with potentially unnecessary adjuvant treatments, these findings have important clinical implications. For one, clinical-genomic risk assessment prior to treatment is likely to be useful in selecting patients who may benefit from treatment de-intensification – such as omitting brachytherapy boost, shortening the duration of ADT in men undergoing RT, or identifying men most likely to achieve cure with RP alone. On the other hand, these data may better identify patients considering RP monotherapy who would almost certainly require adjuvant RT and ADT; thus allowing them to forego the morbidity of RP and pursue initial RT + ADT. With additional characterization and increased understanding of genomic risk, these tools may better identify a particular subset of patients likely to benefit from emerging treatment paradigms such post-RT chemotherapy.[7] Ultimately, our findings suggest that genomic data can provide pathways by which patients can be more accurately and confidently guided toward the optimal treatment approach for their specific cancer.

There are limitations of the current study worth noting. For one, GC testing was performed using biopsy tissue in some patients and RP tissue in others. Although GC scores in biopsy and surgical specimens have demonstrated high correlation,[30] it is possible this could impact our observations. Furthermore, there were limitations of the clinical data used in this analysis. Due to the fact that the number of GS 8–10 positive cores was not routinely collected, our definition of very high-risk cancer was not identical to the current NCCN definition, and only 35 patients met very high-risk criteria, thus limiting our study power. As noted, the current NCCN definition of very high-risk cancer differs from the originally defined and recently validated definition,[4,17] and therefore may not represent the optimal combination of clinical factors. For this reason, we assessed clinical factors both individually and as used in the preoperative CAPRA score. Notably, data regarding the extent of lymph node dissection with RP or nodal irradiation with RT were unavailable. Finally, metastatic disease was determined using standard of care imaging at the time of treatment. It is possible that novel imaging tools would have detected metastasis prior to treatment in some patients, altering their management and obviating the need for GC testing.

Within this multi-institutional cohort of men with NCCN high-risk prostate cancer, GC score successfully sub-stratified metastatic outcomes during follow-up, while traditional clinico-pathologic risk factors did not. For treatment decisions that are based on prognostic risk stratification, the use of GC has a superior performance than clinicopathologic methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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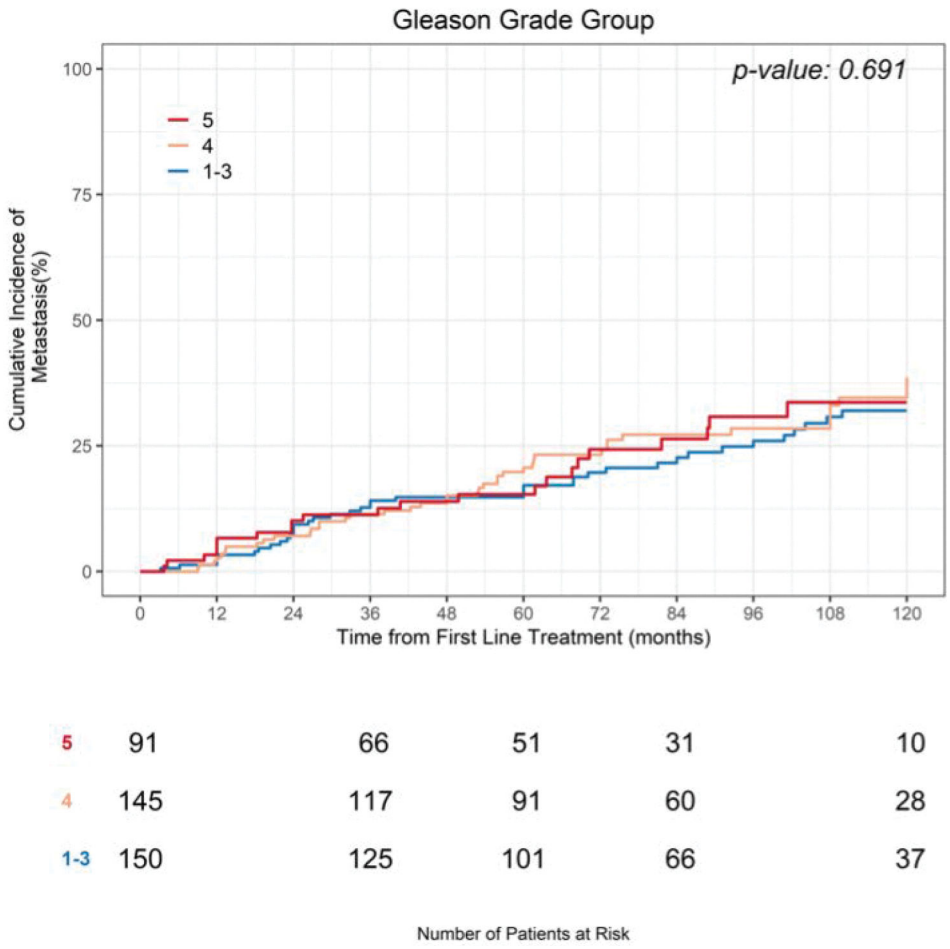
A)



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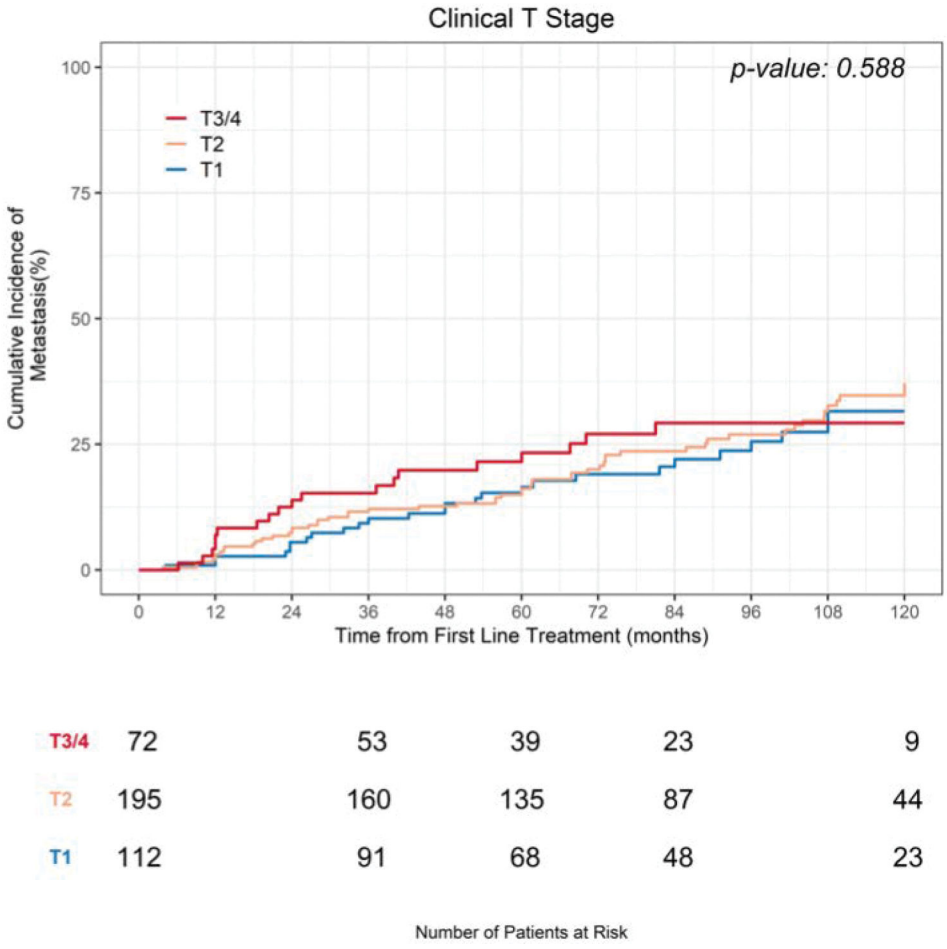


C)

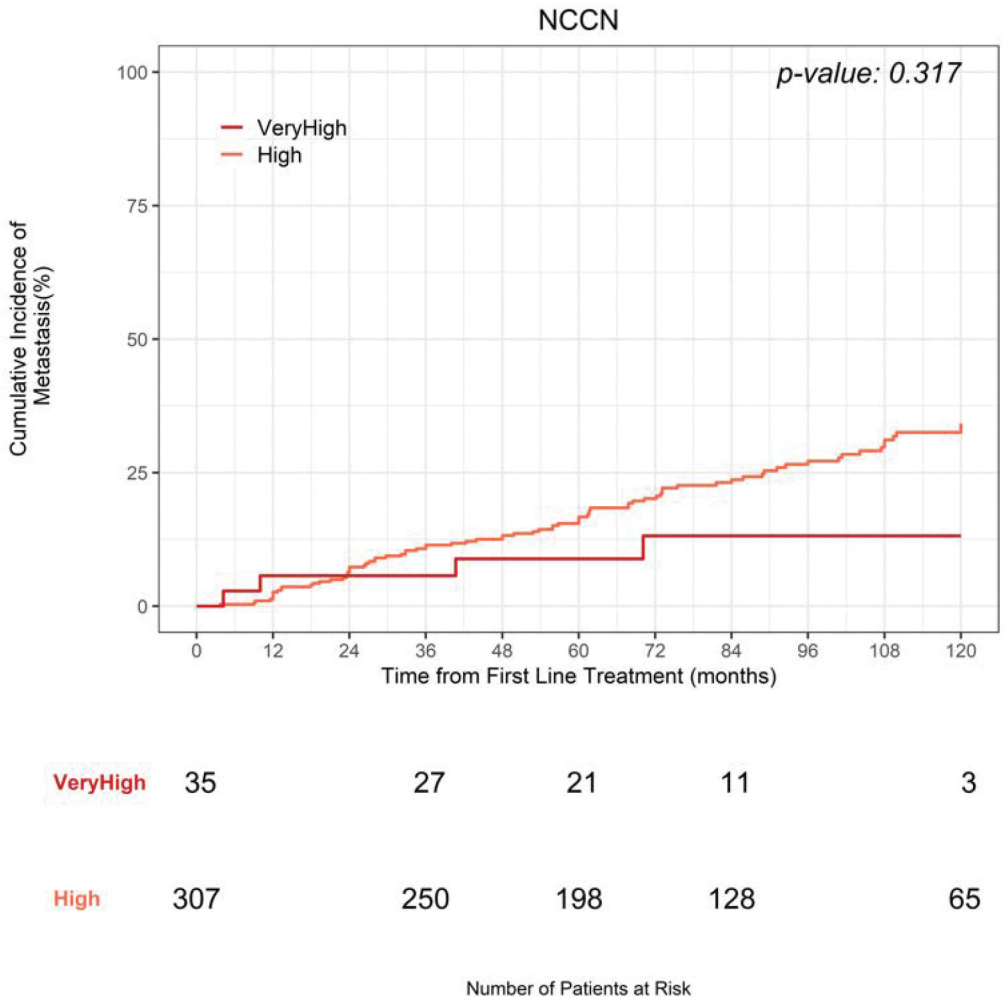


Fig. 1 -

Prognostic effect of clinical and pathologic variables on the cumulative incidence of metastases in men with high risk prostate cancer. Cumulative incidence curves of metastasis by (a) biopsy Grade Group, (b) clinical T-stage, and (c) National Comprehensive Cancer Network (NCCN) risk group.

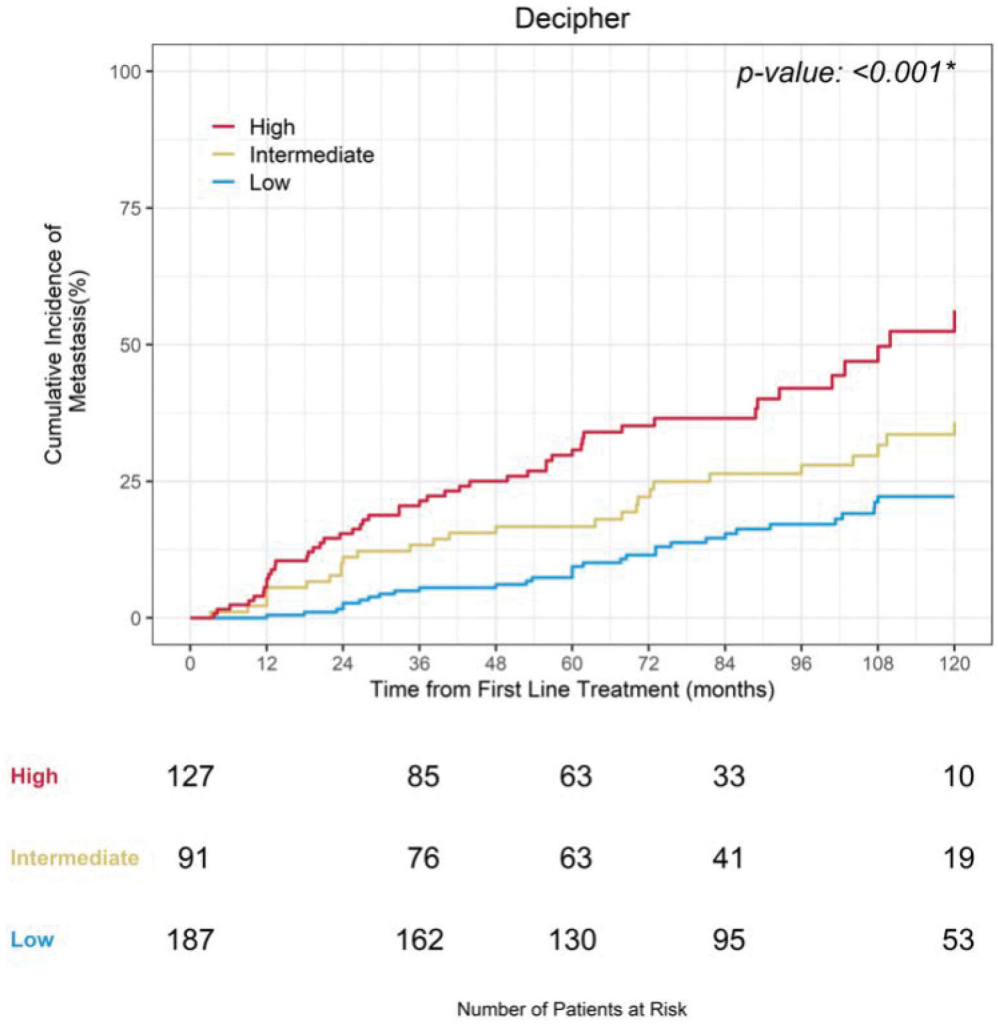
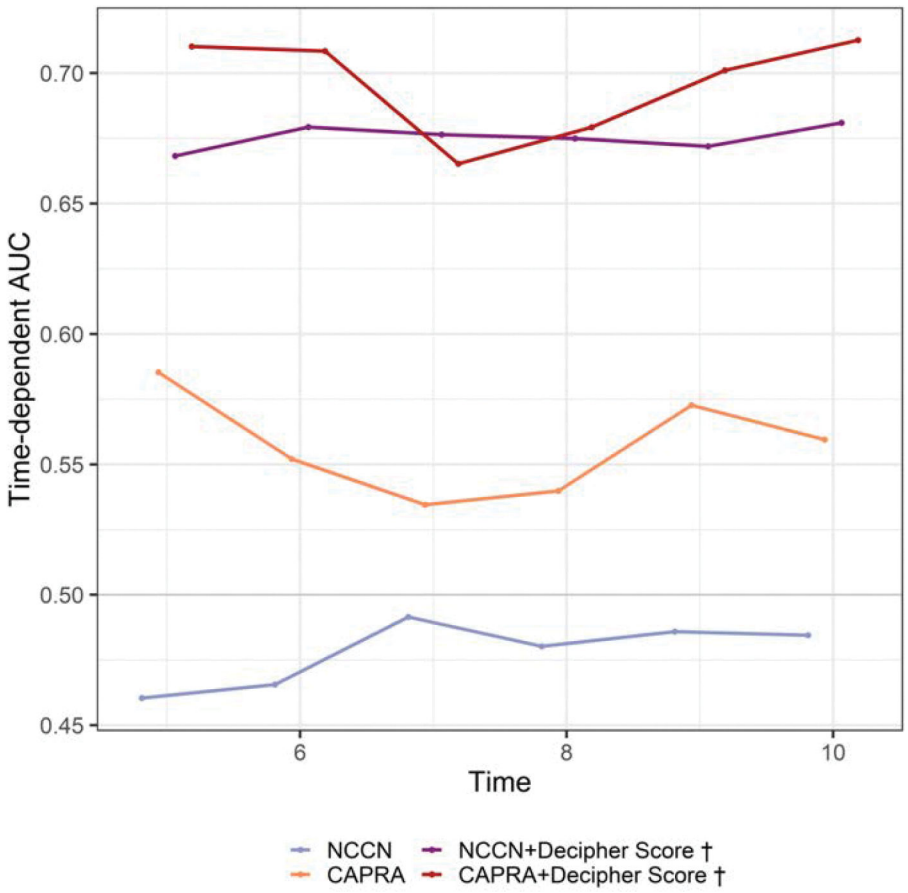


Fig. 2 -

Prognostic effect of Decipher on the cumulative incidence of metastases for men with high risk prostate cancer. Cumulative incidence curves of metastasis by Decipher low- (<0.45), intermediate- (0.45–0.60), and high-risk (>0.60) groups.

A)



B)

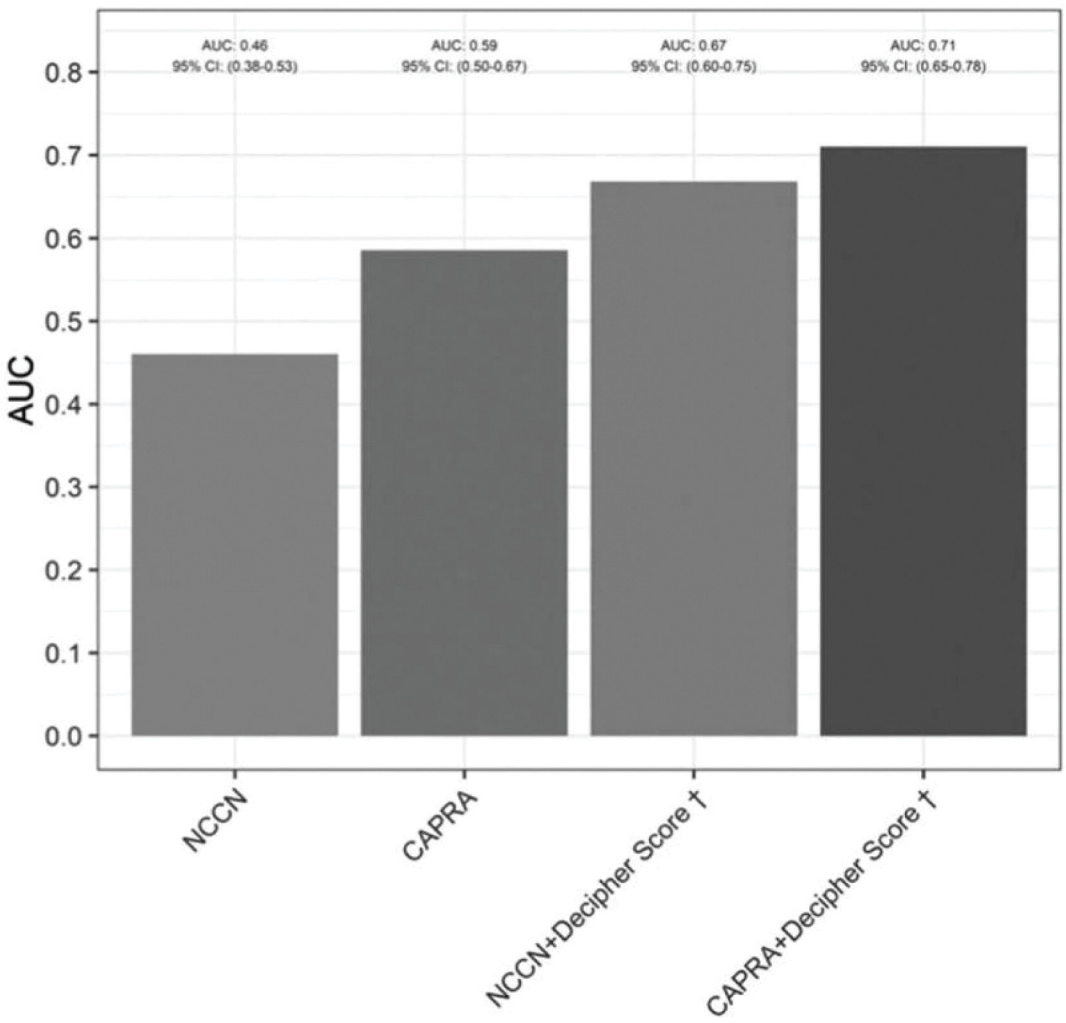


Fig. 3 -

Discriminatory performance of clinicopathologic models and Decipher to predict metastatic outcome. (A) Time-dependent and (B) five-year area under the receiver operating characteristic curve (AUC) for metastasis based on National Comprehensive Cancer Network (NCCN) and Cancer of the Prostate Risk Assessment (CAPRA) risk groups without and with inclusion of Decipher score.

Table 1.

Cohort characteristics

Variables	Study Cohort
No.	405 (100.0)
Age at diagnosis (yr)	
Median (Q1, Q3)	62 (56, 69)
PSA at diagnosis (ng/ml)	
Median (Q1, Q3)	15.2 (6.37, 25.8)
Grade Group (%)	
1	59 (14.6)
2	55 (13.6)
3	36 (8.9)
4	145 (35.8)
5	91 (22.5)
Unavailable	19 (4.7)
Percent positive cores (%)	
< 50%	82 (20.2)
≥ 50%	58 (14.3)
Unavailable	265 (65.4)
Clinical T-stage	
T1	112 (27.7)
T2	195 (48.1)
T3/4	72 (17.8)
Unavailable	26 (6.4)
NCCN Risk Group	
High risk	307 (75.8%)
Very high-risk	35 (8.6%)
Unavailable	63 (15.5%)
Follow-up time (yr)	
Median (Q1, Q3)	82.1 (55.1, 119)

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Variables	Study Cohort
Primary treatment	
RP	325 (80.2)
RT+/−ADT	80 (19.8)
Decipher risk category	
Low (0–0.45)	187 (46.2)
Intermediate (0.46–0.60)	91 (22.5)
High (0.61–1.0)	127 (31.4)

Table 2.

Univariable (UVA) and multivariable (MVA) models for prediction of metastasis

			UVA		MVA (Continuous)		MVA (Categorical)	
Model	**Variable**	**Levels**	**HR (95%CI)**	**P-Value**	**HR (95%CI)**	**P-Value**	**HR (95%CI)**	**P-Value**
Model 1	Age	(per 1 year)	0.97 (0.94–1.00)	0.052	0.97 (0.95–1.00)	0.060	0.97 (0.94–1.00)	0.029*
	PSA	(per 1 ng/ml)	1.00 (0.99–1.01)	0.710	1.00 (0.99–1.01)	0.721	1.00 (0.99–1.01)	0.597
	Grade Group	4 vs 1–3	1.67 (0.99–2.81)	0.053	1.33 (0.79–2.26)	0.284	1.57 (0.94–2.64)	0.084
		5 vs 1–3	1.35 (0.71–2.57)	0.364	1.12 (0.61–2.05)	0.714	1.19 (0.64–2.19)	0.586
	cT Stage	T2 vs T1	1.28 (0.80–2.04)	0.309	1.13 (0.70–1.81)	0.617	1.18 (0.74–1.89)	0.494
		T3/4 vs T1	1.15 (0.50–2.65)	0.744	0.94 (0.50–1.74)	0.836	1.09 (0.59–2.01)	0.793
	Decipher	(per 0.1 unit)	1.34 (1.19–1.50)	<0.001*	1.33 (1.19–1.48)	<0.001*		
	Decipher Risk (vs. Low)	Intermediate	1.61 (0.90–2.88)	0.109			1.43 (0.80–2.53)	0.224
		High	2.93 (1.73–4.94)	<0.001*			2.95 (1.79–4.87)	<0.001*
Model 2	NCCN Risk (vs. High)	Very High	0.64 (0.25–1.63)	0.346	0.63 (0.24–1.62)	0.338	0.59 (0.23–1.55)	0.286
	Decipher	(per 0.1 unit)	1.34 (1.19–1.50)	<0.001*	1.34 (1.19–1.50)	<0.001*		
	Decipher Risk (vs. Low)	Intermediate	1.61 (0.90–2.88)	0.109			1.56 (0.87–2.80)	0.132
		High	2.93 (1.73–4.94)	<0.001*			2.95 (1.75–4.98)	<0.001*
Model 3	CAPRA	(per 1 unit)	1.18 (1.00–1.40)	0.044*	1.13 (0.97–1.31)	0.122		
	CAPRA	6–9 vs 0–5	1.37 (0.87–2.14)	0.173			1.54 (1.01–2.34)	0.043*
	Decipher	(per 0.1 unit)	1.34 (1.19–1.50)	<0.001*	1.33 (1.19–1.48)	<0.001*		
	Decipher Risk (vs. Low)	Intermediate	1.61 (0.90–2.88)	0.109			1.47 (0.84–2.58)	0.177
		High	2.93 (1.73–4.94)	<0.001*			3.09 (1.88–5.06)	<0.001*

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