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ORIGINAL REPORT

Genomic Classifier Identifies Men With Adverse Pathology After Radical Prostatectomy Who Benefit From Adjuvant Radiation Therapy

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ABSTRACT

Purpose
The optimal timing of postoperative radiotherapy (RT) after radical prostatectomy (RP) is unclear. We hypothesized that a genomic classifier (GC) would provide prognostic and predictive insight into the development of clinical metastases in men receiving post-RP RT and inform decision making.

Patients and Methods
GC scores were calculated from 188 patients with pT3 or margin-positive prostate cancer, who received post-RP RT at Thomas Jefferson University and Mayo Clinic between 1990 and 2009. The primary end point was clinical metastasis. Prognostic accuracy of the models was tested using the concordance index for censored data and decision curve analysis. Cox regression analysis tested the relationship between GC and metastasis.

Results
The cumulative incidence of metastasis at 5 years after RT was 0%, 9%, and 29% for low, average, and high GC scores, respectively ($P = .002$). In multivariable analysis, GC and pre-RP prostate-specific antigen were independent predictors of metastasis (both $P < .01$). Within the low GC score (< 0.4), there were no differences in the cumulative incidence of metastasis comparing patients who received adjuvant or salvage RT ($P = .79$). However, for patients with higher GC scores (≥ 0.4), cumulative incidence of metastasis at 5 years was 6% for patients treated with adjuvant RT compared with 23% for patients treated with salvage RT ($P < .01$).

Conclusion
In patients treated with post-RP RT, GC is prognostic for the development of clinical metastasis beyond routine clinical and pathologic features. Although preliminary, patients with low GC scores are best treated with salvage RT, whereas those with high GC scores benefit from adjuvant therapy. These findings provide the first rational selection of timing for post-RP RT.

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INTRODUCTION

Despite the significant stage migration in prostate cancer (PCa) after the introduction of prostate-specific antigen (PSA) in clinical practice, a significant proportion of contemporary patients harbor adverse pathologic characteristics at radical prostatectomy (RP).[1] These individuals are frequently treated with postoperative radiotherapy (RT) alone or RT plus hormonal therapy.[2] However, the optimal timing of postprostatectomy RT is a subject of continuous debate. Advocates for adjuvant RT (ART) argue that this treatment modality might maximize cancer control outcomes. However, salvage RT (SRT) can minimize overtreatment while offering acceptable oncologic outcomes.

Multiple retrospective analyses have compared ART with SRT, with some studies demonstrating improvement in biochemical no evidence of disease (bNED)[3,4] favoring ART and others indicating that early SRT (triggered at a PSA between 0.3 and 0.5 ng/mL) does not compromise outcomes.[5] Given the even balance of the published literature, prospective randomized trials (Radiotherapy and Androgen Deprivation in Combination After Local Surgery [RADICALS],[6] French Genitourinary Tumor Group trial 17/0702,[7] and Radiotherapy—Adjuvant Versus Early Salvage [RAVES][8]) are under way comparing ART with SRT.

Because of the rarity of data in this field and the unresolved controversy between ART and SRT, we sought to integrate a novel biomarker test to

improve clinical decision making regarding post-RP RT. We hypothesized that the use of a validated PCa genomic classifier (GC) could distinguish between men who would benefit from ART and those in whom SRT would be the optimal approach.

PATIENTS AND METHODS

Patient Cohort

The GenomeDx PCa genomic database was used to extract the data of all patients with pT3 disease and/or positive surgical margins who received post-RP RT between 1990 and 2009. A total of 198 patients had available GC scores and clinical data for nomogram computation. Ten patients (5%) who received neoadjuvant hormonal therapy (n = 3) and/or had lymph node invasion (n = 6) or who received RT after metastatic disease onset (n = 1) were excluded. A total of 188 patients from Thomas Jefferson University (Philadelphia, PA; n = 137) and Mayo Clinic (Rochester, MN; n = 51) formed our analytic data set.[9,10] Patients were treated to a median dose of 66.6 Gy using conventional fractionation by either three-dimensional conformal RT or intensity-modulated RT techniques. Photons of 10 to 25 MV were used, with the clinical target volume delineated on computed tomography to include the prostatic fossa and periprostatic tissues. There was no statistical difference in use of intensity-modulated RT or pelvic fields or use of androgen-deprivation therapy in conjunction with RT between SRT and ART.[11,12]

The primary end point for the analysis was clinical metastasis (regional or distant) documented radiographically on computed tomography or bone scan. ART and SRT were defined by PSA levels of ≤ 0.2 and > 0.2 ng/mL before initiation of RT,[9] consistent with randomized clinical trials.[6,8] This study follows the REMARK criteria for evaluation of prognostic biomarkers.[13] The Thomas Jefferson University and Mayo Clinic institutional review boards reviewed and approved the research protocol under which the validation studies were conducted.

Specimen selection and processing have been described previously.[9,10] After microarray quality control using the Affymetrix Power Tools packages (Affymetrix, Santa Clara, CA),[14] probe set summarization and normalization were performed with the SCAN algorithm, which normalizes each batch individually by modeling and removing probe- and array-specific background noise using only data from within each array.[15]

Calculation of GC, Nomograms, and Combined Models

The expression values for the 22 prespecified biomarkers that constitute the GC were extracted from the normalized data matrix and entered into the locked random forests algorithm with tuning and weighting parameters defined as reported previously.[9,10,16] The GC read-out is a continuous risk score between 0 and 1, with higher scores indicating a greater probability of metastasis.[16] GC scores were rounded to two significant digits.

Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score was indirectly derived from a regression equation using seven variables.[17] Stephenson 5-year nomogram survival probability was calculated using eight clinicopathologic variables based on the locked Cox proportional hazards regression model.[18] The combined GC plus CAPRA-S and GC plus Stephenson models were trained for predicting the metastasis end point and locked on an independent data set as reported previously.[16] The training data set included 186 patients with 69 patients with metastatic disease. Overall, 47%, 49%, and 35% of patients had positive margins, extraprostatic extension, and seminal vesicle invasion, respectively.

Statistical Analyses

Age at RP, preoperative PSA level (log2 transformed), and time from RP to RT were considered continuous variables. Pathologic Gleason score (≤ 7 *v* > 7), extraprostatic extension (present *v* absent), seminal vesicle invasion (present *v* absent), surgical margin status (positive *v* negative), and treatment modality (ART *v* SRT) were considered categorical variables. In time-to-event analyses, event times were defined as the time from completion of RT to metastasis date.

The prognostic accuracy of the CAPRA-S, Stephenson nomogram, GC, and combined models was established according to time-dependent receiver operating characteristic curves for survival data using the nearest neighbor estimator described by Heagerty et al.[19] Cumulative incidence curves were constructed using Fine-Gray competing risks analysis to estimate the risk of metastasis over time.[20] As a result of the small number of events, penalized likelihood Cox regression methods (LASSO and Firth) were used for identification of the most prognostic risk factors to ensure the robustness of the analyses and avoid overestimation of the resulting hazard ratios (HRs).[21,22] Decision curve analysis was used to determine the net benefit derived from the use of the GC, CAPRA-S, GC plus CAPRA-S model, and GC plus Stephenson model.[23] The significance level was $P = .05$ for all statistical tests, and analyses were performed in R version 3.0 (http://www.r-project.org/).

RESULTS

The clinical characteristics of the study cohort are listed in Table 1. Seventy-two percent of men had extraprostatic extension, 35% had seminal vesicle invasion, and 78% had positive margins. Twenty-one percent of patients had a Gleason score of ≥ 8. Fifty-one percent of patients received ART (89% within 12 months of RP), and overall, patients received RT at a median of 5 months (range, 1 to 160 months)

Table 1. Demographics and Clinical Characteristics of Eligible Patients

Characteristic	Validation Cohort (N = 188)	
	No. of Patients	%
Patient age, years		
Median	61	
Range	42-78	
IQR (Q1-Q3)	56-66	
Preoperative PSA, ng/mL		
Median	7.8	
Range	0.4-80.4	
IQR (Q1-Q3)	5.3-12.3	
Pathologic Gleason score		
≤ 6	28	14.9
7 (3 + 4)	60	31.9
7 (4 + 3)	50	26.6
≥ 8	48	25.5
Unknown	2	1.1
Extraprostatic extension	136	72.3
Seminal vesicle invasion	65	34.6
Surgical margins	147	78.2
Pre-RT PSA, ng/mL		
Median	0.2	
Range	0-39	
IQR (Q1-Q3)	0.1-0.7	
RT modality		
Adjuvant RT	96	51.1
Salvage RT	89	47.3
Unknown	3	1.6
ADT	56	29.8
Time from RP to RT, months		
Median	5	
Range	1-159.7	
IQR (Q1-Q3)	3.6-15.3	

Abbreviations: ADT, androgen-deprivation therapy; IQR, interquartile range; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy; Q, quartile.

after RP. Thirty percent of patients received hormonal therapy with RT. The median follow-up times after RP and after RT were 10 and 8 years, respectively. Overall, 19 patients (10%) developed metastasis after post-RP RT, with a median time to metastasis of 3 years (interquartile range, 1 to 5 years; Table 1).

Using the CAPRA-S scoring model, the majority of the patients were categorized as either at average risk (50%) or high risk (45%) for disease progression (Appendix Fig A1A, online only). In contrast, the rates of men with previously described cut points for low (< 0.4), average (0.4 to 0.6), and high (> 0.6) GC scores were 39%, 41%, and 20%, respectively (Appendix Fig A1B). GC scores had a modest correlation with Gleason score (Spearman's $\rho = 0.26$; $P < .001$).

The survival concordance index (c-index) for predicting metastasis at 5 years after RT was 0.66 (95% CI, 0.56 to 0.78) for the CAPRA-S model, 0.83 (95% CI, 0.27 to 0.89) for the GC score, and 0.85 (95% CI, 0.79 to 0.93) for the CAPRA-S plus GC model (Fig 1A). Similar results were observed using the Stephenson nomogram (Appendix Fig A2, online only). Of the 19 patients who developed metastasis, 16 patients (84%) had average or high GC scores (GC ≥ 0.4), and two patients had the highest possible GC score (0.39) still categorized as low risk.

Consistent with the survival c-index, decision curve analysis showed that the models including GC (GC alone and GC plus CAPRA-S) were superior to clinicopathologic models (Fig 1B). Compared with scenarios where no prediction model would be used for a post-RP RT treatment decision (ie, treat all or treat none), the GC-based models had a higher net benefit than clinical models across a wide range of decision threshold probabilities (approximately 0% to 25% risk of metastasis). Furthermore, reclassification analysis shows that 71 patients (43%) with average- and high-risk CAPRA-S scores had their risk downgraded to GC low risk, and notably, 68 (96%) of these 71 patients remained metastasis free on study follow-up (Appendix Table A1, online only).

Univariable analysis demonstrated that GC, preoperative PSA levels, and RT modality were significant predictors of metastasis (Table 2). In multivariable analysis, only pre-RP PSA levels and GC were independent predictors of metastasis (Table 2). As a continuous variable, for every 10% increase in GC score, the HR for metastasis was 1.90 (95% CI, 1.31 to 2.75; $P < .001$). When analyzed as a categorical variable, high GC scores (> 0.6) had an HR of 9.58 ($P = .013$) compared with low GC scores (< 0.4) (Appendix Table A2, online only). Results of the multivariable analysis were confirmed using LASSO penalized regression for sparse data and rare events. Even with large values of the penalty parameter λ, GC had a nonzero hazard coefficient and was the first variable to enter the model, confirming its significance in predicting metastasis in multivariable analysis despite the few metastasis events in this cohort (Fig 1C). In a multivariable model that included GC and CAPRA-S, both of these variables were significant predictors of metastasis, with HRs of 1.69 (per 0.1-unit increase; $P < .001$) and 1.28 (per 1-unit increase; $P = .028$), respectively (Table 2).

Cumulative incidence plots depicted the estimated incidence of metastasis, after stratifying patients according to GC and CAPRA-S risk groups (Fig 2). The 5-year cumulative incidence rates of metastasis in patients with low, average, and high CAPRA-S scores were 13%, 2%, and 14%, respectively ($P = .04$). The 5-year cumulative incidence rates of metastasis in patients with low, average, and high GC scores were 0%, 9%, and 29%, respectively ($P = .002$).

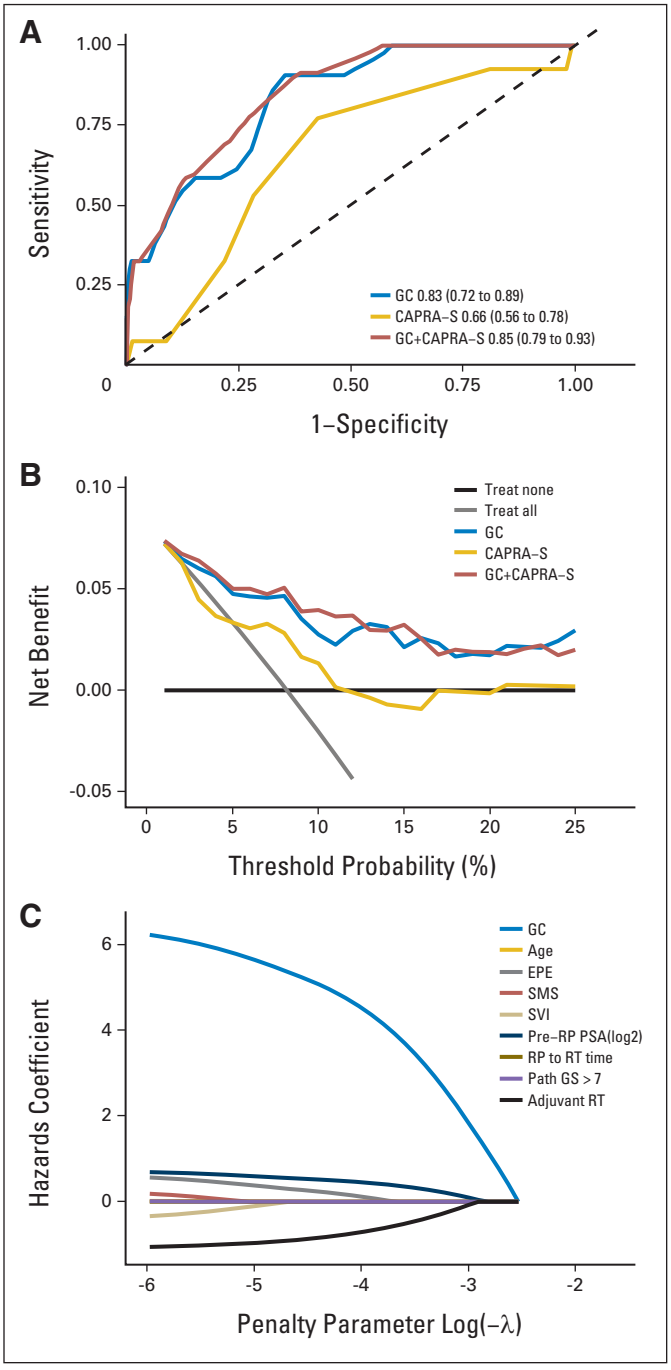

Fig 1. Discriminatory performance of the genomic classifier (GC) compared with clinical risk factors and Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score using different metrics. (A) GC has the highest survival concordance index compared with clinical models at 5 years after radiotherapy (RT). (B) Decision curve analysis for 5-year post-RT metastasis prediction shows that models including GC have the highest net benefit across 0% to 25% threshold probabilities. (C) Lasso hazards coefficient path of GC and clinical risk factors showing that GC is the first variable to enter the model as the penalty parameter is decreased. EPE, extraprostatic extension; GS, Gleason score; PSA, prostate-specific antigen; RP, radical prostatectomy; SMS, surgical margin status; SVI, seminal vesicle invasion.

Next, the prognostic models were evaluated for their ability to predict benefit from RT modality. Cumulative incidence plots for metastasis comparing ART with SRT were stratified by CAPRA-S and GC groups (Fig 3). The low and average CAPRA-S risk groups were

Table 2. Results of Cox* Proportional Hazards Analysis of GC (continuous), Clinical Risk Factors, and CAPRA-S

Model and Variable	UVA			MVA†		
	HR	95% CI	*P*	HR	95% CI	*P*
Model I						
Patient age, years	1.02	0.96 to 1.09	.5041	1.02	0.95 to 1.1	.5643
Log2 preoperative PSA, ng/mL	1.66	1.10 to 2.52	.0158	2.12	1.31 to 3.45	.0022
Pathologic Gleason score ≤ 7	Reference		1	Reference		1
Pathologic Gleason score > 7	2.36	0.89 to 6.00	.0837	1.08	0.33 to 3.22	.8889
Extraprostatic extension	2.43	0.75 to 12.28	.1489	1.67	0.45 to 9.05	.4648
Seminal vesicle invasion	1.46	0.55 to 3.71	.4343	0.65	0.20 to 2.01	.4561
Surgical margins	0.64	0.23 to 2.10	.424	1.31	0.43 to 4.62	.6397
Time from RP to RT, months	1.00	0.97 to 1.02	.9802	1.01	0.97 to 1.04	.7165
Adjuvant RT (reference: salvage RT)	0.29	0.09 to 0.89	.0219	0.37	0.11 to 1.05	.0621
GC‡	1.66	1.23 to 2.23	< .001	1.90	1.31 to 2.75	< .001
Model II						
CAPRA-S§	1.31	1.05 to 1.63	.0185	1.28	1.03 to 1.61	.0282
GC‡	1.61	1.20 to 2.15	< .001	1.69	1.24 to 2.31	< .001

Abbreviations: CAPRA-S, Cancer of the Prostate Risk Assessment Postsurgical; GC, genomic classifier; HR, hazard ratio; MVA, multivariable analysis; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy; UVA, univariable analysis.
*According to Firth's penalized likelihood method where CIs are obtained via profile penalized likelihood.
†In MVA, all available covariates were used and no variable selection was performed. For variable selection, LASSO was performed as shown in Figure 1C.
‡GC reported per 0.1-unit increase.
§CAPRA-S reported per 1-unit increase.

collapsed into one group, and the average and high GC score groups were similarly collapsed into one group as a result of limitations in sample size for this subset analysis. When comparing patients treated with ART versus SRT, the 5-year incidence of metastasis was 0% versus 7% ($P = .02$), respectively, for patients with CAPRA-S less than 5 (Fig 3A) and 7% versus 21% ($P = .1$), respectively, for patients with CAPRA-S ≥ 5 (Fig 3B). Stratified by GC, no differences in outcomes were observed comparing ART and SRT for patients with a GC score less than 0.4 (0% *v* 0%, respectively; $P = .7$; Fig 3C). In contrast, the results in patients with a GC score ≥ 0.4 were significant and favored ART, with 5-year metastasis incidence of 6% versus 23% for SRT ($P = .008$; Fig 3D).

A sensitivity analysis was performed considering different PSA level thresholds (ie, < 0.1, 0.1 to 0.5, and > 0.5 ng/mL) at RT initiation (Figs 4A and 4B). This analysis again showed that for patients in the low-risk GC group (< 0.4), no significant differences in cumulative incidence of metastasis were observed regardless of PSA level at RT ($P = .47$). In the high-risk GC group, for patients who received RT when PSA was less than 0.1 ng/mL (these patients by contemporary criteria would be considered to be true ART patients), the cumulative incidence of metastasis at 5 years was 0%, which is significantly better than the incidence of patients who received RT when PSA was between 0.1 and 0.5 ng/mL (ie, early SRT) or who received RT when PSA was greater than 0.5 ng/mL (ie, late SRT), who had a 12% and 26%

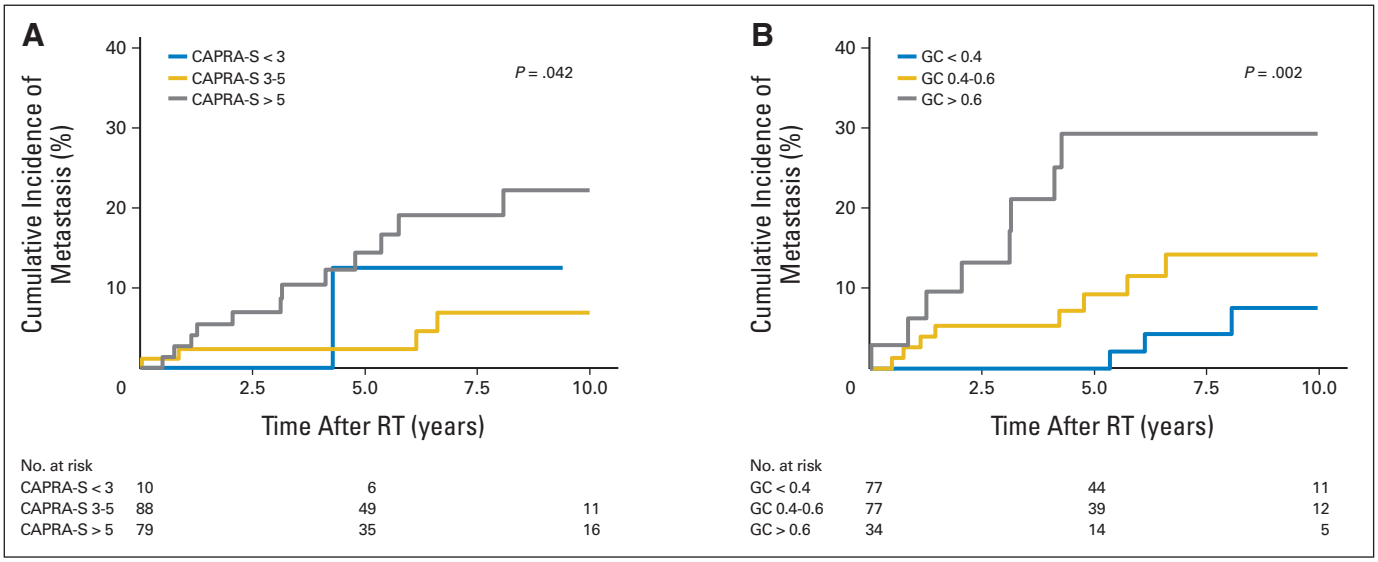

Fig 2. Cumulative incidence curves stratified by (A) Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score and (B) genomic classifier (GC) to evaluate their prognosis for postradiotherapy metastasis. RT, radiotherapy.

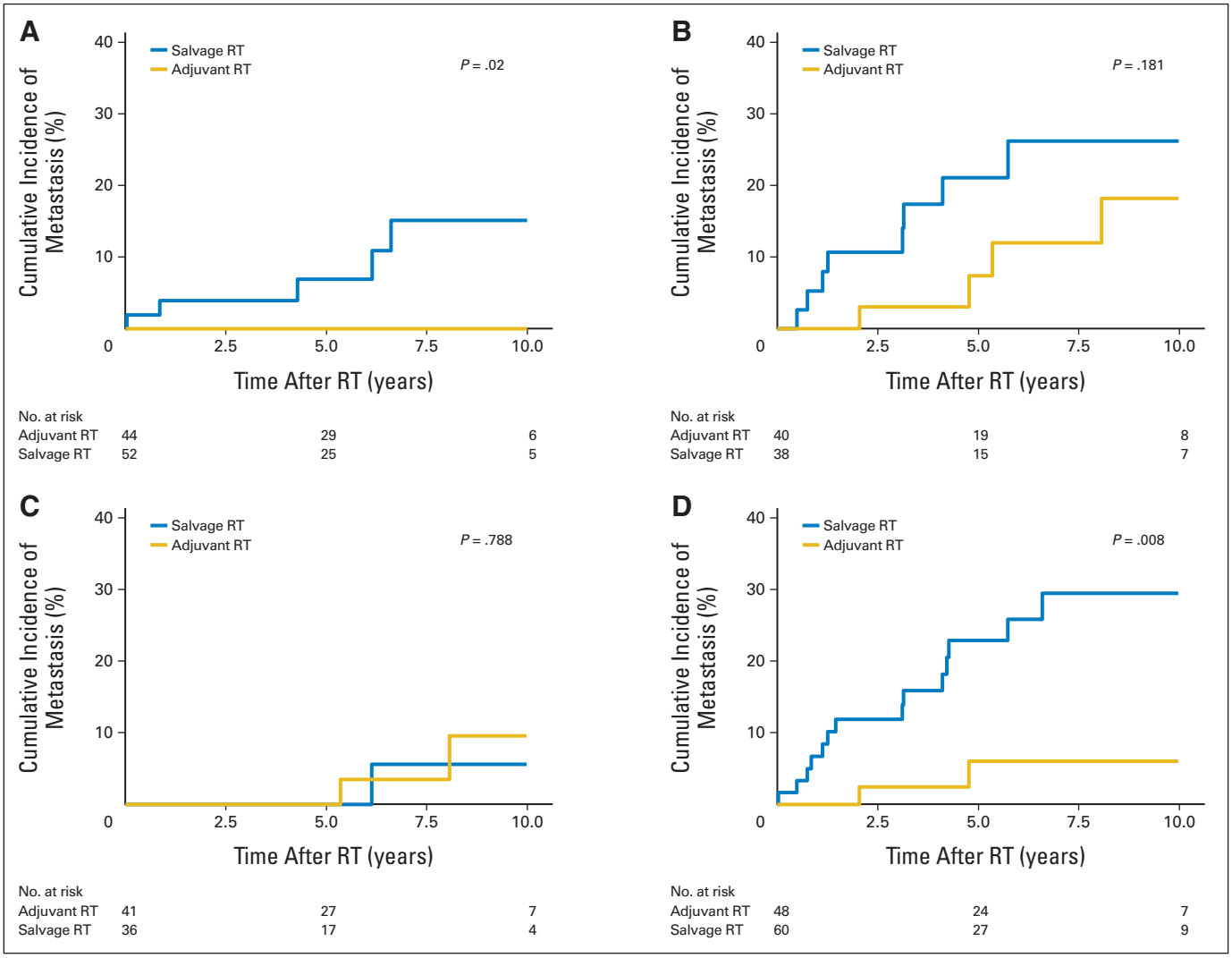

Fig 3. Cumulative incidence curves to evaluate benefit from adjuvant radiotherapy (RT) versus salvage RT stratified by (A and B) Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score and (C and D) genomic classifier (GC).

cumulative incidence of metastasis at 5 years after RT, respectively ($P = .02$). Finally, Cox proportional hazards demonstrated that patients with higher GC scores who received ART had an 80% reduction in risk (HR, 0.20; 95% CI, 0.04 to 0.90; $P < .04$) compared with patients who received SRT (Appendix Table A3, online only). No benefit for ART was observed over SRT in patients with a low GC score (HR, 0.76; 95% CI, 0.11 to 5.76; $P < .8$).

DISCUSSION

Postprostatectomy RT significantly reduces the risks of PSA progression and local recurrence and may reduce the risk of distant metastases and PCa-specific mortality.[24] However, there is a critical need within the genitourinary oncologic community to determine the optimal timing of postprostatectomy RT to avoid overtreatment and toxicities and realize the clinical benefits. Three prospective randomized trials comparing ART with initial observation for men with either pT3 disease or margin-positive (R1) resection (Southwest Oncology Group 8794,[25,26] European Organisation for Research and Treatment of Cancer 22911,[27,28] and ARO 96-02/AUO AP/09/95[29,30]) have demonstrated a benefit of ART in terms of bNED and local control at both 5- and 10-year follow-up. In addition, at 10 years, the Southwest Oncology Group trial demonstrated a benefit in overall survival and metastasis-free survival.[26] However, this was not recapitulated in the European Organisation for Research and Treatment of Cancer trial, and the ARO 96-02 trial was not powered for overall survival. In these trials, the 5-year bNED rate for the observation arm was approximately 50%, suggesting that adoption of ART for all men with positive-margin or pT3 disease would result in significant overtreatment. Furthermore, the use of ART has been shown to be associated with acute and late GI toxicity, urinary stricture, and incontinence,[31] all representing potential patient management and quality-of-life outcomes challenges.

The current American Urologic Association/American Society for Radiation Oncology consensus guidelines reflect the challenge of counseling and decision making in this setting.[32] Many

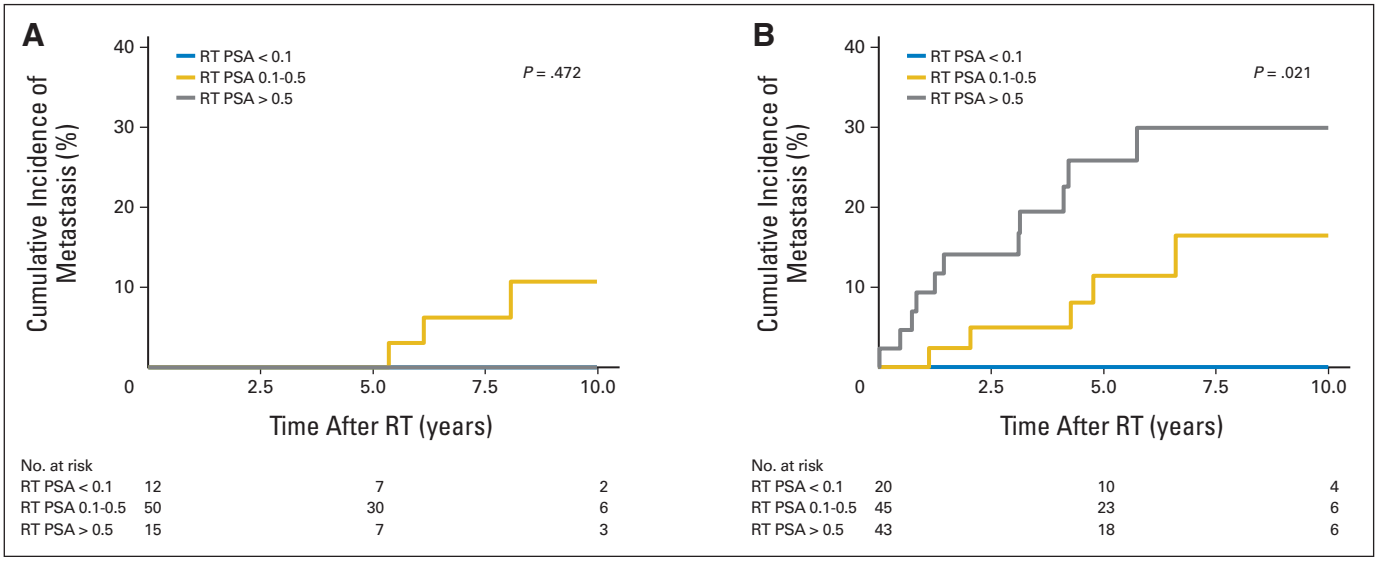

Fig 4. Cumulative incidence curves to evaluate benefit for three preradiotherapy prostate-specific antigen (PSA) levels (< 0.1, 0.1 to 0.5, and > 0.5 ng/mL) stratified by (A) low genomic classifier (GC) score (< 0.4) and (B) high GC score (≥ 0.4). RT, radiotherapy.

experts have advocated for the identification of novel biomarkers to tailor treatment decisions.[33,34] To that end, we used a multi-institutional data set to examine the prognostic and predictive ability of a GC to determine the potential benefit of ART and SRT. We demonstrate that the GC is highly prognostic in the setting of postprostatectomy RT and that the GC may be a predictive marker that can help determine which patients will benefit from ART as opposed to SRT. This supports the importance of local therapy in the setting of presumed occult metastatic disease.[35,36]

Within the literature, there are more than 100 published risk assessment tools,[37] yet few are validated instruments. The most commonly referenced include the Stephenson postoperative nomogram[18] and the CAPRA-S score.[17] Recently, decision curve analysis has demonstrated that CAPRA-S score appropriately identified patients in whom adjuvant therapy is most appropriate, and CAPRA-S has been shown to be robust for prediction of PCa-specific mortality.[38] In our study, first, we observed that GC downgraded risk in approximately 43% of CAPRA-S average- and high-risk patients to low risk GC, and 96% of these reclassified patients remained metastasis free on study follow-up. Accordingly, the c-index for predicting metastasis after RT was 0.66 for CAPRA-S but 0.83 for GC, with only a small gain to 0.85 for the combined model. Second, although we found that CAPRA-S retains significance in multivariable analysis with GC for predicting metastasis, it was observed that CAPRA-S score failed to discriminate patients who would benefit from ART. For patients with a less than 50% CAPRA-S risk of biochemical recurrence after RP,[35] ART was statistically associated with improved outcomes compared with SRT; however, for patients with a greater than 50% risk of biochemical recurrence by the CAPRA-S model, no significant differences were observed. This is juxtaposed to the utilization of GC, in which there was no difference noted between patients treated with ART or SRT regardless of pre-RT PSA levels for patients with low GC scores, whereas there was a statistically significant decrease in development of metastases in men with high GC scores who received ART.

Currently, ART is being used in approximately 10% of patients with at least one adverse pathologic feature (positive-margin or pT3 disease).[39-43] Given this low rate, some have questioned the extent to which preference-based and participatory decision making is occurring in routine clinical practice among patients and physicians.[44] This study provides intriguing evidence to assist in the nuanced discussion of postprostatectomy treatment. This study adhered to the prospective collection of specimens before outcome ascertainment,[45] and GC scores were determined with blinding to all clinical information.

There are a few limitations in this study. First, the data analyzed are retrospective, and the selection of ART as opposed to SRT varied among physicians and patients. Second, there were no concrete guidelines for the incorporation of androgen-deprivation therapy with postprostatectomy RT. Third, this study only included patients who received RT and thus could not identify a patient population in whom postprostatectomy RT could be withheld completely.

Despite these limitations, the findings of the study are particularly intriguing and provide a unique, more individualized approach in the management of postprostatectomy patients with adverse pathologic findings. Although a biomarker should not substitute for the shared patient-physician decision-making process, the integration of GC can provide additional insight into the aggressiveness of a man's PCa and more appropriately guide his postprostatectomy therapy selection. This study suggests that for men with a high GC score receiving SRT further intensification of therapy may be warranted; this is currently being examined in the Radiation Therapy Oncology Group 96-01 study, a prospective phase III randomized trial comparing SRT with SRT plus high-dose bicalutamide. Given that this cohort consists of high-risk patients by clinicopathologic nomograms and the utilization of a GC allowed for significant downstaging, this study has major ramifications in terms of both potential for overtreatment and substantial cost savings to the US health care system.[46] Thus, the GC is a valuable tool to aid in management of men with PCa undergoing prostatectomy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

Cancer of the Prostate Risk Assessment (CAPRA) score: a 0 to 10 score based on a multivariable Cox model that predicts biochemical and clinical (metastasis and mortality) end points after primary treatment for prostate cancer. A postsurgical version (CAPRA-S) offers improved prediction of the same end points after radical prostatectomy.

Cox proportional hazards regression model: a statistical model for regression analysis of censored survival data, examining the relationship of censored survival distribution to one or more covariates. This model produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

decision curve analysis: an approach to evaluating the discrimination and calibration of different prognostic tests or models. A decision curve plots net benefit for a given model across a range of threshold probabilities. Net benefit is calculated as true positives minus false positives, with the false-positive term weighted by the threshold probability. The threshold probability indicates the likelihood of a positive finding at which an intervention would be undertaken, given the results of the test or model.

prostate-specific antigen (PSA): a protein produced by cells of the prostate gland. The blood level of prostate-specific antigen (PSA) is used as a tumor marker for men who may be suspected of having prostate cancer. Most physicians consider 0 to 4.0 ng/mL to be the normal range. Levels of 4 to 10 and 10 to 20 ng/mL are considered slightly and moderately elevated, respectively. PSA levels have to be complemented with other tests to make a firm diagnosis of prostate cancer.

REMARK criteria: guidelines for reporting tumor marker studies, which include a statement of objectives and a description of patient population and treatments received, biologic materials, and assay methods. Criteria also include guidelines for reporting data, results, and discussion.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Genomic Classifier Identifies Men With Adverse Pathology After Radical Prostatectomy Who Benefit From Adjuvant Radiation Therapy

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Appendix

Table A1. Reclassification Between GC and CAPRA-S

	CAPRA-S Score (No. of patients)			Total Patients	
Model	< 3	3-5	> 5	No.	%
GC score					
< 0.4	2	42	29	73	41.2
Metastasis	0	1	2		
0.4-0.6	5	31	35	71	40.1
Metastasis	0	1	5		
> 0.6	3	15	15	33	18.6
Metastasis	1	2	5		
Total patients					
No.	10	88	79	177*	
%	5.6	49.7	44.6		

Abbreviations: CAPRA-S, Cancer of the Prostate Risk Assessment Postsurgical; GC, genomic classifier.
*Eleven patients with missing CAPRA-S scores were excluded from this analysis.

Table A2. Results of MVA Cox* Proportional Hazards Analysis of GC (categorical, < 0.4, 0.4-0.6, and > 0.6) and Clinical Risk Factors

Variable	HR	95% CI	*P*
Patient age, years	1.01	0.94 to 1.09	.7189
Log2 preoperative PSA, ng/mL	2.04	1.25 to 3.39	.0046
Pathologic Gleason score ≤ 7	Reference		1
Pathologic Gleason score > 7	1.67	0.54 to 4.98	.3621
Extraprostatic extension	1.54	0.41 to 8.32	.5464
Seminal vesicle invasion	0.61	0.18 to 1.96	.4139
Surgical margins	1.21	0.39 to 4.32	.7495
Time from RP to RT, months	1	0.96 to 1.03	.9014
Adjuvant RT (reference: salvage RT)	0.39	0.11 to 1.14	.0868
GC score			
< 0.4	Reference		1
0.4-0.6	2.29	0.55 to 11.11	.258
> 0.6	9.58	2.38 to 47.02	.0013

Abbreviations: GC, genomic classifier; HR, hazard ratio; MVA, multivariable analysis; PSA, prostate-specific antigen; RP, radical prostatectomy, RT, radiation therapy.
*Using Firth's penalized likelihood method.

Table A3. Results of Cox Proportional Hazards Analysis Evaluating Impact of RT Modality Within GC Categories

Model and RT Modality	HR	95% CI	*P*
Model I (GC < 0.4 subset)			
Salvage RT	Reference		1
Adjuvant RT	0.76	0.11 to 5.46	.787
Model II (GC ≥ 0.4 subset)			
Salvage RT	Reference		1
Adjuvant RT	0.20	0.04 to 0.90	.0357

Abbreviations: GC, genomic classifier; HR, hazards ratio; RT, radiation therapy.

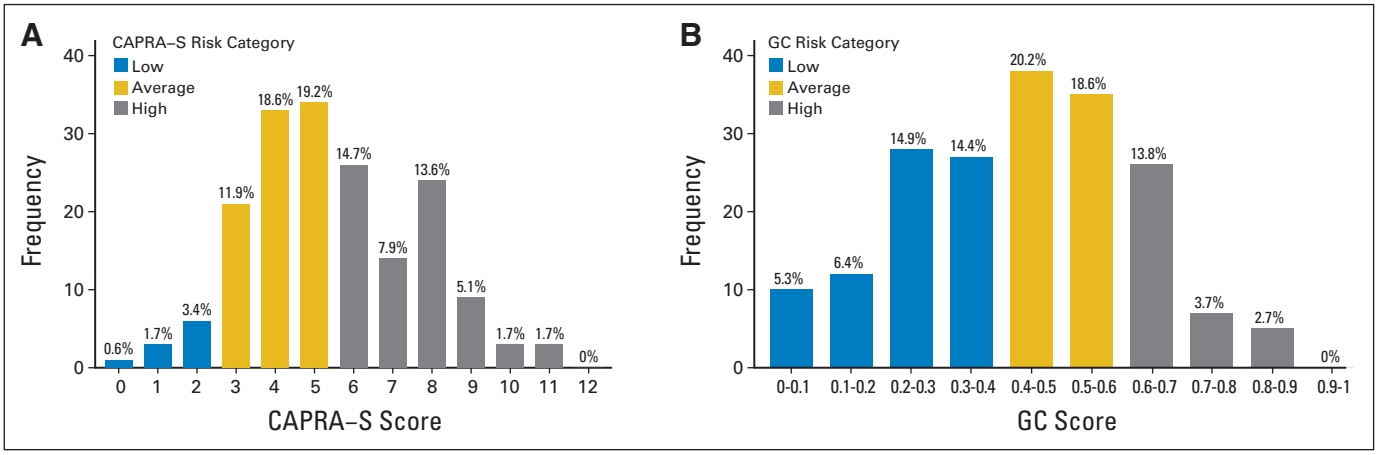

Fig A1. Risk score distribution of study patients based on (A) Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score and (B) genomic classifier (GC).

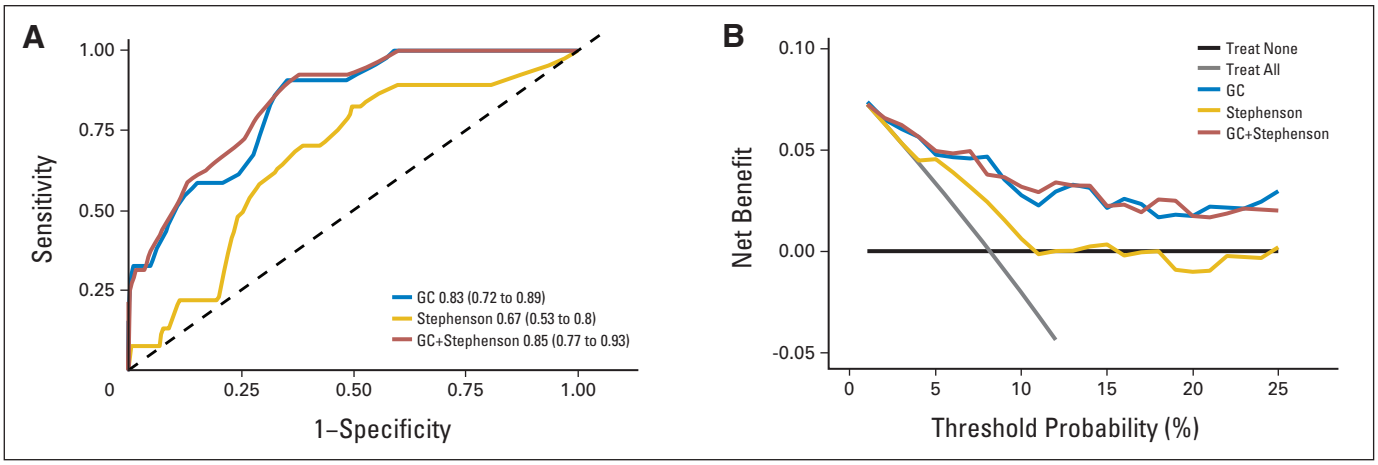

Fig A2. Discriminatory performance of genomic classifier (GC) compared with Stephenson nomogram. (A) GC has the highest survival concordance index compared with clinical models at 5 years after radiotherapy (RT). (B) Decision curve analysis for 5-year post-RT metastasis prediction shows that models including GC have the highest net benefit across 0% to 25% threshold probabilities.