Genomic Prostate Cancer Classifier Predicts Biochemical Failure and Metastases in Patients After Postoperative Radiation Therapy

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Abstract

Purpose—To test the hypothesis that a genomic classifier (GC) would predict biochemical failure (BF) and distant metastasis (DM) in men receiving radiation therapy (RT) after radical prostatectomy (RP).

Methods and Materials—Among patients who underwent post-RP RT, 139 were identified for pT3 or positive margin, who did not receive neoadjuvant hormones and had paraffin-embedded specimens. Ribonucleic acid was extracted from the highest Gleason grade focus and applied to a high-density-oligonucleotide microarray. Receiver operating characteristic, calibration, cumulative incidence, and Cox regression analyses were performed to assess GC performance for predicting BF and DM after post-RP RT in comparison with clinical nomograms.

Results—The area under the receiver operating characteristic curve of the Stephenson model was 0.70 for both BF and DM, with addition of GC significantly improving area under the receiver operating characteristic curve to 0.78 and 0.80, respectively. Stratified by GC risk groups, 8-year cumulative incidence was 21%, 48%, and 81% for BF (*P*<.0001) and for DM was 0, 12%, and 17% (*P*=.032) for low, intermediate, and high GC, respectively. In multivariable analysis, patients with high GC had a hazard ratio of 8.1 and 14.3 for BF and DM. In patients with intermediate or high GC, those irradiated with undetectable prostate-specific antigen (PSA ≤ 0.2 ng/mL) had median BF survival of >8 years, compared with <4 years for patients with detectable

PSA (>0.2 ng/mL) before initiation of RT. At 8 years, the DM cumulative incidence for patients with high GC and RT with undetectable PSA was 3%, compared with 23% with detectable PSA (*P*=.03). No outcome differences were observed for low GC between the treatment groups.

Conclusion—The GC predicted BF and metastasis after post-RP irradiation. Patients with lower GC risk may benefit from delayed RT, as opposed to those with higher GC; however, this needs prospective validation. Genomic-based models may be useful for improved decision-making for treatment of high-risk prostate cancer.

Introduction

Every year, approximately 233,000 men are diagnosed with prostate cancer (PCa) in the United States, and more than 29,000 men die from this disease annually (1). The vast majority present with clinically localized disease, and many undergo radical prostatectomy (RP) as their primary treatment. Although RP is performed with curative intent, a proportion of these patients will develop PCa recurrence, particularly those with adverse pathologic features, defined as positive surgical margin, extraprostatic extension, seminal vesicle involvement (SVI), or detectable post-prostatectomy prostate-specific antigen (PSA) (2). Recently, joint consensus guidelines from the American Urologic Association and the American Society for Radiation Oncology (3) advocated for postprostatectomy adjuvant radiation in patients at risk for recurrence or with evidence of progression based on detectable PSA or clinical progression. However, the guidelines stressed the importance of a "thoughtful discussion" and a multidisciplinary approach to balance risks and benefits, reflecting the underlying controversy within the field.

One of the main concerns with postprostatectomy radiation therapy (RT) is that outcomes can vary, and many men will be subjected to unnecessary adjuvant therapy. In the 3 prospective, randomized clinical trials examining adjuvant RT (defined as treatment at the time of undetectable PSA) (4–7), approximately 50% of patients randomized to observation never developed biochemical failure (BF), even though some patients had detectable PSA after RP. Thus, some clinicians would have advocated for salvage RT as a more selective approach rather than adjuvant RT. At present there is not yet level 1 evidence to support the hypothesis that adjuvant and early salvage RT are equivalent. Further, with salvage RT, 6-year BF-free survival is approximately 40%, and patients with BF have a 60% probability of developing distant metastasis (DM) and 20% probability of PCa-specific death within 10 years (8). Thus, it is clear that even among a high-risk patient population based on standard clinical features, there remain a significant proportion of patients who may benefit from additional local therapy, whereas others may require systemic therapy. On the other hand, studies have shown that there also exist a significant proportion of patients for whom the disease progression is indolent and who derive little benefit from post-RP RT (8, 9).

Novel biomarkers that can improve our prognostic tools and inform decision making are acutely needed. One such potential platform is the Decipher® genomic classifier (GC) (GenomeDx Biosciences, San Diego, CA) that uses a whole-transcriptome microarray assay from formalin-fixed, paraffin-embedded PCa specimens. This signature was developed and validated as a predictor for clinical metastases after RP in a cohort of men with adverse

features (10). Further, it was shown to more accurately predict metastases than individual clinical variables or nomograms (11). Thus, we hypothesized that incorporation of the GC in clinical models would more accurately predict BF and DM in men receiving post-RP RT.

Methods and Materials

The Thomas Jefferson University institutional review board reviewed and approved the research protocol under which this validation study was conducted. The study met the PRoBE (12) and REMARK (13) criteria for prospective-blinded evaluation and analysis of a prognostic biomarker.

Patient cohort

The cohort comprised 143 patients with pT3 or margin-positive disease, who may have elevated post-RP PSA, and who underwent post-RP RT at Kimmel Cancer Center, Thomas Jefferson University between 1999 and 2009. Four patients who received neoadjuvant hormone therapy were excluded from the analysis. The GC scores were available for 139 patients only (Fig. e1, available online). Accounting for sample loss, there were no significant differences in the cohort with available GC data in comparison with the original selected cohort (data not shown). The radiation techniques including clinical target division definition, planning target volume generation, RT techniques, doses, and volumes have been described previously (14). Further, the use of hormone therapy and irradiation of pelvic lymph nodes was performed at the discretion of the treating radiation oncologist.

Specimen selection and processing

After histopathologic review of formalin-fixed, paraffin-embedded (FFPE) tumor blocks from each case by 2 expert genitourinary pathologists, the tumor block with the index lesion was selected for specimen processing. The index lesion was identified as the prostatectomy FFPE block with the highest pathologic Gleason grade, regardless of its volume. Two [x] 0.6-mm diameter tissue biopsy punch tool cores were sampled to enrich for tumor cells from the highest Gleason grade in the index lesion and placed in a microfuge tube for RNA extraction. The RNA extraction and microarray expression data generation were as previously described (10). After microarray quality control using the Affymetrix Power Tools packages (Santa Clara, CA) (15), probeset summarization and normalization were performed by the SCAN algorithm (16), 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 scores and nomogram scores

The 22-marker GC was applied to the microarray expression data for each patient sample as previously described (10). Cut points for the GC were estimated using receiver operating characteristic curve–based methods described previously (11). Cancer of the prostate risk assessment post-surgical (CAPRA-S) scores were calculated as described by Cooper-berg et al (17), and Stephenson 5-year survival probabilities were calculated using the online prediction tool (18).

Statistical analyses

Statistical analyses were performed in R, version 3.0, and all statistical tests were 2-sided using a 5% significance level. As previously described, for men who achieved an undetectable PSA level after surgery, BF was defined as a PSA 0.4 ng/mL with a subsequent confirmation. For all other patients, including those with a detectable pre-RT PSA, BF was defined as 3 increases in PSA measured at least 6 weeks apart, considering the first PSA rise dated as the BF; or androgen deprivation therapy due to PSA rise (14). Undetectable PSA and detectable PSA were defined as PSA levels of 0.2 and >0.2 ng/mL immediately before initiation of RT, respectively. Metastatic failure was defined as DM documented in clinical notes and imaging reports. In time-to-event analyses, event times were defined as the time from RT completion date to BF or DM date.

The χ^2, Wilcoxon, or Fisher exact test were used to test for association between categoric variables. Area under receiver operating characteristic curves (AUC), calibration, and Hosmer-Lemeshow goodness of fit, strip plots, univariable, and multivariable (MVA) Cox proportional hazard models were used to compare the GC-based and clinical-only models for predicting BF or DM after RT. The LASSO method for the Cox model was used for identification of the most predictive variables as described previously (19). Cumulative incidence curves were constructed using Fine-Gray competing risks analysis (20) to estimate the risk of BF or DM while accounting for censoring and death due to other causes.

Results

A total of 143 evaluable patients had available archival FFPE blocks for genome-wide expression analysis. Genomic classifier scores were generated for 139 patients (97%) (Fig. e1). Eighty-four percent had Gleason score 7 or above; 27% with Gleason 8–10. Eighty-two percent of men had extraprostatic extension, 38% had seminal vesicle invasion, and 75% had positive margins. Fifty-three percent of patients had radiation initiated when PSA was 0.2 ng/mL, and 21% received radiation with hormonal therapy. The median follow-up times after RP and after RT were 11.8 and 7.4 years, respectively. After RT, 54 patients (39%) experienced BF, and 10 (7%) developed DM on follow-up (Table 1).

The distribution of men among low (<0.4), intermediate (0.4–0.6), and high (>0.6) GC risk categories was 41%, 38%, and 22%, respectively (Fig. e2). Nearly all patients who developed DM on follow up (n=10) had intermediate or high GC scores (ie, 0.4), except for 1 patient with a borderline GC score (0.395). The GC scores increased with higher Gleason score and tumor stage (Fig. e3). Genomic classifier has a modest correlation to Gleason scores (r^2=0.29, P=.0004) and tumor stage (r^2=0.15, P=.07). The agreement between observed BF and GC scores demonstrates virtually perfect calibration of GC for predicting BF, with a slope of 1.1 and a Hosmer-Lemeshow P value of .77 (Fig. e4A). We did not observe as good calibration for the post-RT BF endpoint with the Stephenson model (Fig. e4B). Too few events were available to evaluate calibration for the DM endpoint.

Receive operator characteristic curve analysis was used to determine whether GC could improve prediction of outcome as compared with commonly used clinical risk prediction models for discrimination of BF and DM events (Fig. 2A, B). The AUC for the post-RP

Stephenson nomogram was 0.70 (95% confidence interval [CI] 0.61–0.79) and 0.70 (95% CI 0.49–0.90) for BF and DM endpoints, respectively. For CAPRA-S, the AUC was 0.67 (95% CI 0.58–0.77) and 0.65 (0.44–0.86) for BF and DM endpoints, respectively. Note that neither clinical nomogram was significantly superior to chance in predicting DM because the 95% CI included the AUC of 0.5 for a random model. The AUC for the GC score was 0.75 (95% CI 0.67–0.84) and 0.78 (95% CI 0.64–0.91) for BF and DM endpoints, respectively. Combining the GC with the Stephenson nomogram improved the AUC to 0.78 (95% CI 0.69–0.86) and 0.80 (95% CI 0.68–0.93) for BF and DM, respectively (Fig. 1). A similar improvement in AUC was noted for combining GC with CAPRA-S.

Decision curve analysis was used to determine the clinical utility of the gain in AUC for the GC-based models (Fig. e5). Compared with scenarios in which no prediction model would be used for a postoperative 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 20%–75% risk of BF).

Cumulative incidence plots for the probability of BF and DM show significance for 3 previously reported GC score risk groups (Fig. 2). The 4-year cumulative incidence of BF in patients with low, intermediate, and high GC scores was 13%, 31%, and 49%, respectively (Fig. 2A). By 8 years after RT the difference in BF incidence rates became more pronounced, with cumulative incidence rates of 21%, 48%, and 81% for low, intermediate, and high GC score, respectively ($P<.0001$). The 8-year cumulative incidence rates of DM were 0, 12%, and 17% for the GC score groups. The incidence rates were signficant ($P=.032$) despite the small number of DM events on follow-up in this cohort (Fig. 2B).

Univariable analysis demonstrated that GC and a number of clinical factors such as pre-RP PSA level, seminal vesicle involvement, Gleason score, timing of RT (ie, undetectable vs detectable PSA), radiation dose, and concomitant hormone therapy were all significant predictors of BF (Tables e1 and e2). Only GC and pre-RP PSA level were also significant for DM. In MVA analysis GC, pre-RP PSA level, pathologic Gleason score, and PSA level prior to RT remained significant predictors of BF (Table 2). Again, only GC and pre-RP PSA level were significant for DM. The hazard ratio (HR) for intermediate and high GC was 2.9 and 8.1 in comparison with the low GC risk group (Table 2). The HR estimates for the DM endpoint were only significant for high GC (HR 14.3, $P=.005$, although because of a small number of events it has a wide confidence interval) (21). Further, we validated the findings from the multiple regression model using penalized regression to ensure that the significance of GC was not an artifact of few metastasis events in the MVA analysis. For both BF and DM, GC was the top variable with a non-zero coefficient, confirming that GC is the most significant variable and that the MVA analysis was robust (Fig. e6).

Exploratory analyses were performed to determine whether GC could predict benefit between those treated with RT with either undetectable or detectable PSA. We did not observe the 2 RT groups to differ significantly for any clinical or treatment variable aside from more concomitant hormone therapy and a higher proportion of African Americans in the detectable PSA group (Table e4). The median time from RP to initiation of RT was 4.21 months (interquartile range, 3.4–5.9) and 6.8 months (interquartile range, 3.9–25.8) for

undetectable and detectable PSA groups, respectively. Within each GC score group, for patients with BF GC was higher than for patients who did not experience BF, regardless of when RT was initiated (Fig. e7). Cumulative incidence plots for BF and DM, comparing undetectable with detectable PSA RT groups, were stratified by GC risk (Fig. 3). The intermediate and high GC score groups were collapsed into 1 group owing to limitations in sample size for this subset analysis. Within the low GC score group (GC <0.4) there was no difference in cumulative incidence of BF (Fig. 3A) or DM (Fig. 3B) for patients who had RT with undetectable or detectable PSA. However, for the group with GC ≥0.4, a 27% absolute difference in BF was observed at 8 years, with a median 4-year PSA-free survival advantage for patients who received RT with undetectable PSA compared with those with detectable PSA (Fig. 3A). Patients with GC ≥0.4 who had detectable PSA when RT was initiated had a DM cumulative incidence of 23% by 8 years, compared with just 3% for patients with undetectable PSA (Fig. 3B; *P*=.03). Similar results were obtained for both BF and DM endpoints in a sensitivity analysis when considering different PSA level thresholds (eg, ≤0.2, 0.21–1, >1.0 ng/mL) at RT initiation (Fig. e8). Finally, in MVA analysis we were able to estimate the hazards at any time point for BF after completion of RT and found that patients with GC ≥0.4 who had RT with detectable PSA had an HR of 2.2 (*P*=.01) in comparison with patients with GC ≥0.4 who had RT with undetectable PSA (Table 3). The same trend was observed for the DM endpoint, with an HR of 7.1 (*P*=.07). For GC low risk patients, no significant differences in hazards were observed for either endpoint when comparing RT initiated with undetectable and detectable PSA.

Discussion

Despite the publication of the American Urologic Association–American Society for Radiation Oncology consensus guidelines and 3 phase 3 prospective trials demonstrating the benefit of adjuvant therapy as opposed to observation, both in terms of biochemical progression–free survival as well as overall survival (Southwest Oncology Group), there remains controversy regarding the administration of post-prostatectomy radiation. Two critical factors are that only 50% of patients with adverse pathologic features treated with surgery alone will develop BF, and even among those patients with a persistently elevated PSA after prostatectomy, approximately 10% may never develop clinical metastases (22). Given the possibility of overtreatment, many clinicians are hesitant to initiate additional therapy (23). Currently, 4 prospective randomized clinical trials—Radiotherapy and Androgen Deprivation in Combination After Local Surgery (RADICALS), Radiotherapy Adjuvant versus Early Salvage (RAVES), GETUG-17, and European Organization for Research and Treatment of Cancer 22,043–30,031—are investigating the therapeutic benefit of early salvage RT with or without androgen deprivation therapy compared with adjuvant RT.

This study provides critical insight into disease aggressiveness, which can have major ramifications for the interpretation of these forthcoming trials. Herein we provide the first validation of the GC score in the postprostatectomy RT setting. We demonstrated that within a group of patients with high-risk features for BF and development of DM, the GC score was able to differentiate outcomes. The GC score improved risk stratification above known clinical classifiers, specifically in terms of development of DM. Moreover, our data suggest

that for patients with low GC scores outcomes were not different for men receiving adjuvant versus salvage RT; for those men with intermediate- or high-risk GC the timing of RT initiation in terms of PSA levels significantly altered BF and DM survival outcomes.

Given the high cumulative incidence of BF and DM in particular, for the high GC score patient group, this is a patient population in whom exploration of intensification of therapy would be warranted. In an unselected patient population, postprostatectomy radiation combined with anti-androgen therapy has been demonstrated to improve freedom from BF as well as reduce the incidence of metastatic PCa (24) in comparison with radiation monotherapy. A subsequent phase 2 trial examining adjuvant docetaxel after androgen deprivation and RT for high-risk postprostatectomy patients is closed, with results expected within the next several years. With the plethora of new agents approved for metastatic castrate-resistant PCa (25–30) on the basis of improvements in overall survival, there are a variety of combinations that can be examined clinically. As such, defining those patients most at risk for local treatment failure is critical because many of these therapies have potential morbidity associated with them.

There are several limitations in the present study. First, there were few DM noted in this patient population. As such, full analysis of DM as an endpoint was limited. Further, this is a retrospective analysis from a single institution, and this data set only included patients receiving RT, and as such, examining whether outcomes from patients treated with observation alone would mimic those treated with RT, particularly for those patients with low GC score, is beyond the scope of this analysis. In addition, some patients received early adjuvant RT, whereas others received later salvage therapy, according to both physician as well as patient preference. The use of androgen deprivation therapy was not universal and reflected inherent biases among the treating physicians. However, this does reflect current treatment practices.

The data presented in this study confirm and extend the prior publications demonstrating the predictive capability and utility of the GC score (10, 11) beyond clinicopathologic parameters. The use of a genomic signature has been demonstrated to alter clinical decision making in approximately 50% of cases (31), indicating the potential broad clinical impact. Further, both GC score and clinical factors independently associated with BF and DM in MVA analysis, implying that genomic risk classifiers can be incorporated with added value into clinical care. Furthermore, when translating genomic risk classifiers into clinical practice, it is important that the added information be supplemented with traditional clinical parameters to guide decision making. It is expected that low-risk GC scores in patients with adverse pathology could be used to guide treatment decisions for possibly delayed or deferred irradiation when risk of failure is low. This may benefit patients incontinent of urine, who require additional time to heal after RP or those in whom daily radiation may be burdensome. Given the increasing incidence and costs of PCa treatments (32), avoidance of unnecessary or inadequate treatment would have major implications for the healthcare system and limit the potential overtreatment of patients who will not recur or progress. These observations are particularly salient given the ongoing randomized controlled trials of adjuvant versus early salvage radiation therapy because our results demonstrate 2 distinct groups of patients, who are currently not stratified in the trial designs.

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Supplementary Material

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Acknowledgments

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Summary

One of the main concerns with postprostatectomy RT is that outcomes can vary, resulting in inappropriate treatment. We assessed a validated genomic classifier (GC) to distinguish outcomes in men with high-risk prostate cancer. The GC was able to predict biochemical failure and distant metastasis after RT; significant differences between adjuvant and salvage RT were noted for those with intermediate or high GC scores but not for those with low GC scores.
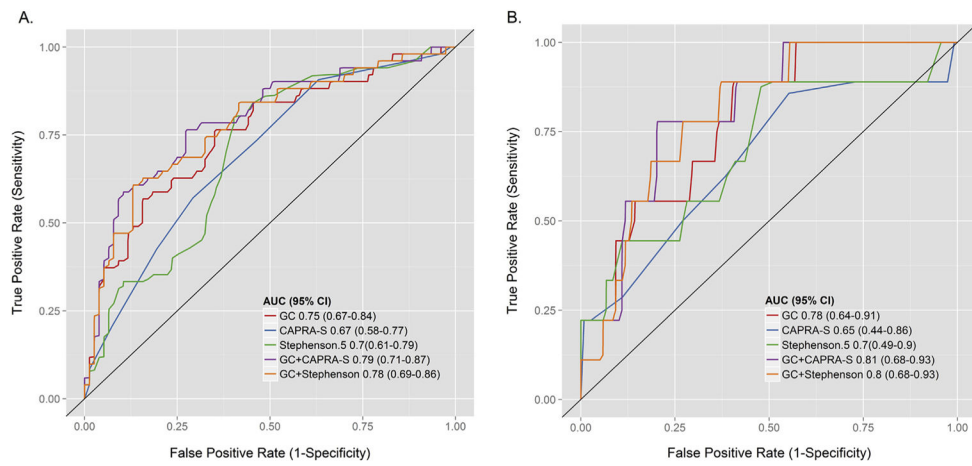
Fig. 1.

Area under the receiver operating characteristic curve (AUC): comparison of genomic classifier (GC)-based and clinical-only risk models for predicting biochemical failure (A) and distant metastasis (B) after postoperative radiation therapy. CAPRA-S = cancer of the prostate risk assessment post-surgical score; CI = confidence interval.
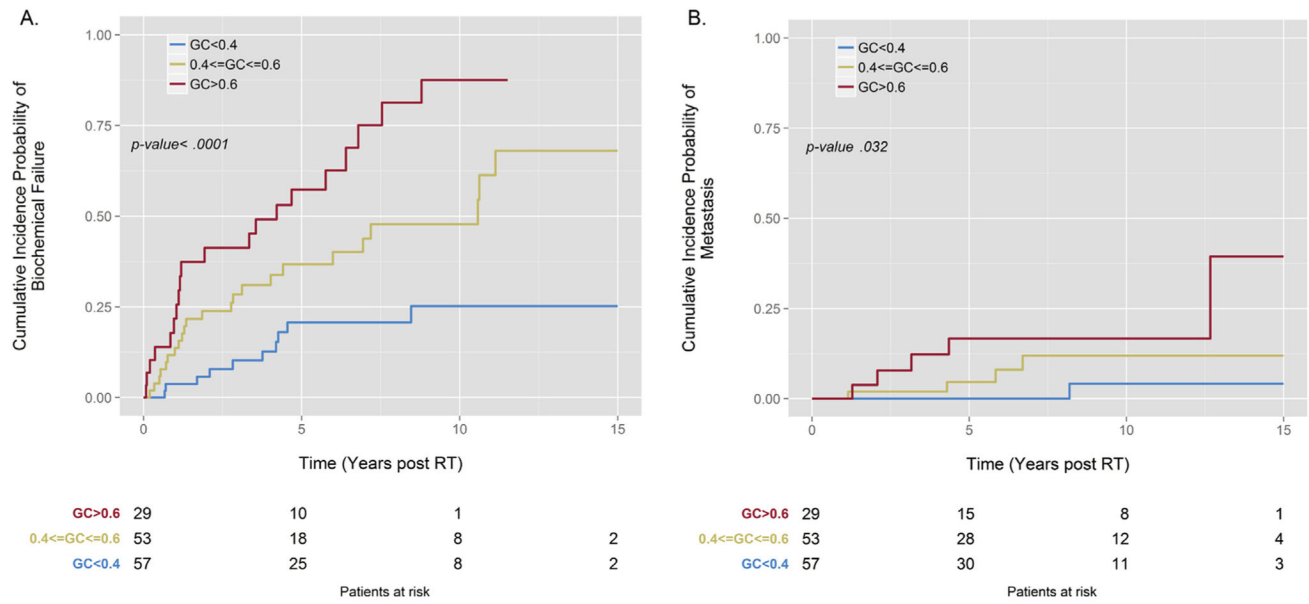
Fig. 2.
Cumulative incidence plots of biochemical failure (A) and distant metastasis (B) for low-, intermediate-, and high-risk genomic classifier (GC) score groups. Cut points were reported previously (29).
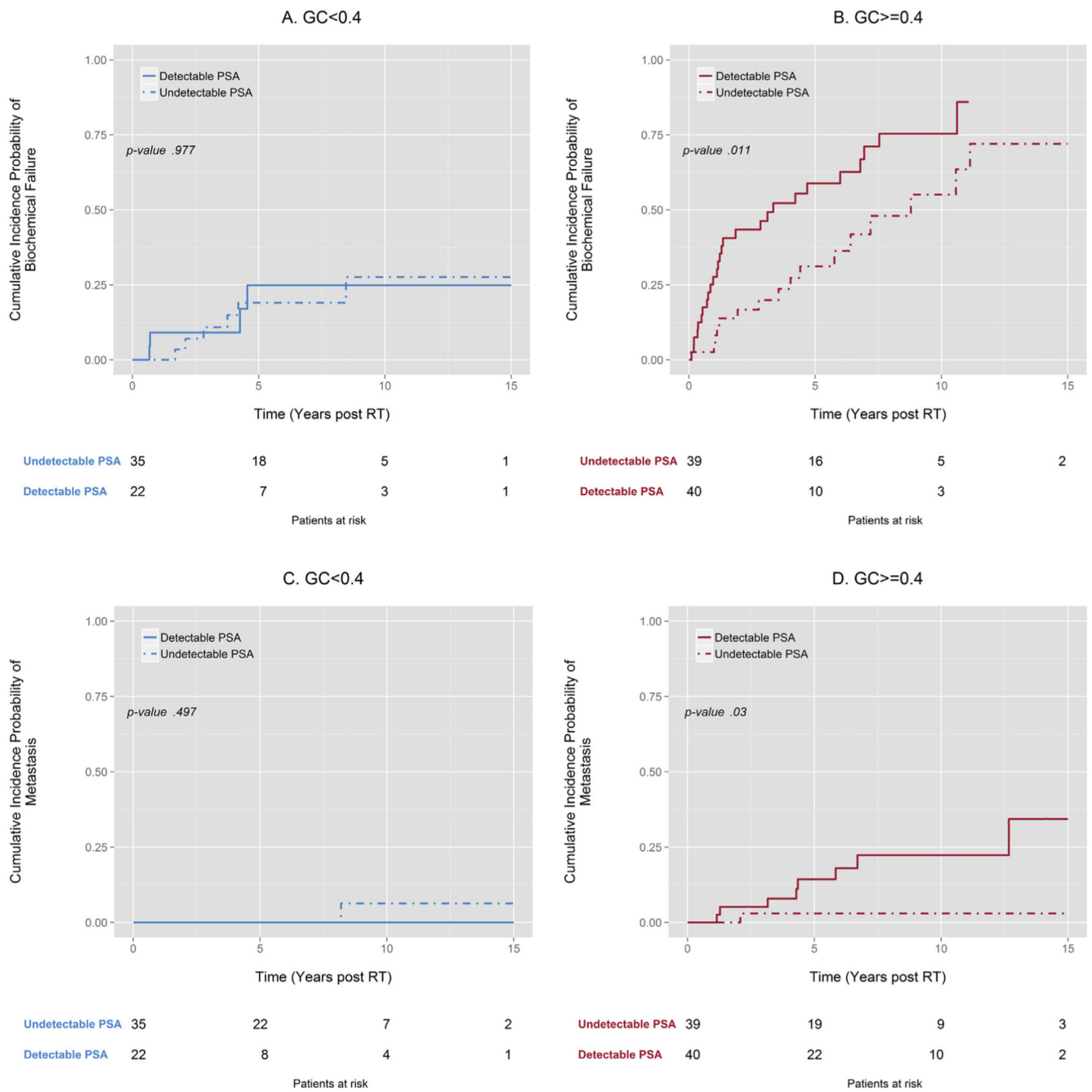
Fig. 3.
Cumulative incidence plots of biochemical failure and distant metastasis comparing patients treated with radiation therapy (RT) when prostate-specific antigen (PSA) was undetectable (A, C) and detectable (B, D), as stratified by genomic classifier (GC) score risk groups.

Table 1

Patient characteristics

Clinicopathologic variable	All	No biochemical failure (column %)	Biochemical failure[*] (column %)	P
Total N	139	85	54	
Age (y)				.93[†]
Median	60	60	61	
Range	(40–76)	(40–76)	(47–76)	
Race				.13[‡]
Caucasian	118 (84.9)	68 (80)	50 (93)	
Black	18 (13.0)	14 (17)	4 (7)	
Hispanic	3 (2.2)	3 (3)	0	
Pre-RP PSA (ng/mL)				.03[§]
<10	90 (64.7)	61 (72)	29 (53)	
10–20	27 (19.4)	14 (16)	13 (24)	
>20	15 (10.8)	6 (7)	9 (17)	
Unknown	7 (5.0)	4 (5)	3 (6)	
EPE				.18[†]
Positive	114 (82.0)	66 (78)	48 (89)	
Unknown	1 (0.7)	1 (1)	0	
SVI				.16[†]
Positive	53 (38.1)	28 (33)	25 (46)	
Margin				1[†]
Positive	105 (75.5)	64 (75)	41 (76)	
Gleason score				.03[‡]
6	21 (15.1)	19 (22)	2 (4)	
7	79 (56.9)	49 (58)	30 (56)	
8–10	38 (27.3)	16 (19)	22 (40)	
Unknown	1 (0.7)	1 (1)	0	
Pre-RT PSA (ng/mL)				.008[‡]
0.2	74 (53.0)	51 (60)	23 (43)	
>0.2–1	36 (26.0)	22 (26)	14 (26)	
>1–5	18 (13.0)	7 (8)	11 (20)	
> 5	8 (5.8)	2 (2)	6 (11)	
Unknown	3 (2.2)	3 (4)	0	
Time from RP to RT (mo)				.51[†]
Median	4.57	4.53	4.64	
Range	(1.08–159.67)	(1.77–159.67)	(1.08–60.91)	
Dose				1[†]
Median	66.6	66.6	66.6	
Range	(45–72)	(45–72)	(60–70.2)	

Clinicopathologic variable	All	No biochemical failure (column %)	Biochemical failure[*] (column %)	P
Field				.60[†]
Fossa only	110 (79.1)	69 (81)	41 (76)	
Whole pelvic	20 (20.9)	16 (19)	13 (24)	
ADT				.025[†]
Positive	29 (20.9)	12 (14)	17 (32)	

Abbreviations: ADT = androgen deprivation therapy; EPE = extraprostatic extension; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy; SM = surgical margin; SVI = seminal vesicle involvement.

[*]
Only 10 patients developed distant metastasis among patients with biochemical failure.

[†]Using Pearson χ^2 test.

[‡]Using Fisher exact test.

[§]Using Wilcoxon rank sum test.

Table 2

Multivariable Cox proportional hazards analysis of risk factors for postoperative radiation treatment biochemical failure and distant metastasis

Risk factor	Biochemical failure		Distant metastasis*	
	HR (95% CI)	*P*	HR (95% CI)	*P*
GC Intermediate (Ref: GC < 0.4)	2.88 (1.21–6.85)	.02	2.15 (0.18–39.48)	.55
GC High (Ref: GC < 0.4)	8.13 (3.40–19.46)	<.0001	14.28 (2.13–210.38)	.005
Age at RP	1.02 (0.96–1.07)	.57	1.01 (0.90–1.15)	.9
Caucasian Race (Ref: AAM/Hispanic)	2.31 (0.73–7.31)	.16	0.39 (0.05–5.34)	.42
(Pre-RP PSA) ($\log_2$)	1.49 (1.06–2.10)	.02	2.69 (1.33–5.65)	.007
EPE (Ref: Negative)	2.04 (0.73–5.66)	.17	2.72 (0.21–505)	.53
SVI (Ref: Negative)	1.08 (0.50–2.32)	.85	0.54 (0.07–2.96)	.49
SM (Ref: Negative)	0.68 (0.31–1.46)	.32	2 (0.28–18.45)	.49
Pathologic Gleason score (Ref: 7)	2.21 (1.07–4.56)	.03	2.13 (0.30–14.99)	.4
Detectable PSA (Ref: Undetectable PSA)	3.23 (1.49–6.98)	.003	0.92 (0.08–10.42)	.91
Time between RP and RT (mo)	0.98 (0.96–1.01)	.17	1.03 (0.97–1.09)	.23
Radiation dose	1.05 (0.91–1.22)	.49	1.24 (0.83–1.92)	.28
Pelvis radiation (Ref: Fossa only)	0.61 (0.25–1.48)	.28	2.1 (0.31–15.93)	.44
Concomitant hormone therapy (Ref: None)	1.14 (0.52–2.49)	.74	1.44 (0.26–7.24)	.66

Abbreviations: AAM = African American men; CI = confidence interval; GC = genomic classifier; HR = hazard ratio; Ref = referent. Other abbreviations as in Table 1.

*
Firth's penalized likelihood method was used due to low number of metastatic events.

Table 3

Multivariable Cox proportional hazards analysis of risk prediction models for postoperative radiation treatment biochemical failure and distant metastasis

Risk factor	Multivariable analysis (BF)		Multivariable analysis (DM)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Detectable PSA (Ref: Undetectable PSA)				
GC low-risk subset (<0.4)	2 (0.56–7.12)	.29	NA[*]	NA
GC high-risk subset (0.4)	2.24 (1.19–4.22)	.01	7.12 (0.89–57.09)	.07

Abbreviation: NA = not applicable. Other abbreviations as in Tables 1 and 2.

[*] Cox regression model does not converge, owing to low number of events (events = 1 out of 10).