PROGNOSTIC UTILITY OF CCP SCORE IN MEN WITH PROSTATE CANCER AFTER PRIMARY EBRT

Stephen Freedland,[1] Leah Gerber,[1] Julia Reid,[2] William Welbourn,[2] Eliso Tikishvili,[2] Jimmy Park,[2] Adib Younus,[2] Alexander Gutin,[2] Zaina Sangale,[2] Jerry S. Lanchbury,[2] Joseph K. Salama,[3] and Steven Stone[2]

1. Department of Surgery, Durham VA Medical Center, and Departments of Surgery (Urology) and Pathology, Duke University School of Medicine. Durham NC **2.** Myriad Genetics, Inc., Salt Lake City, UT

3. Department of Radiation Oncology, Durham VA and Department of Radiation Oncology, Duke University

BACKGROUND

Accurate risk stratification improves clinical decision making for men with localized prostate cancer. The CCP score, a prognostic RNA signature based on the average expression level of 31 cell cycle progression (CCP) genes, was developed to aid and improve clinical decision making. Previously, the CCP score was shown to be predictive of biochemical recurrence (BCR) after prostatectomy, and prostate cancer specific mortality in men undergoing observation.[1,2] However, the value of CCP score in men who received primary external beam radiation therapy (EBRT) is untested.

METHODS

The CCP score was derived retrospectively from the diagnostic biopsy specimens of men diagnosed with prostate cancer at the Durham VA Medical Center (DVAMC) from 1991 to 2006. All patients who were diagnosed with localized prostate cancer, were treated with definitive EBRT at DVAMC, and had available biopsy tissue were included in this study. Approximately half of the cohort was African-American. Outcome was time from EBRT to BCR using Phoenix definition, and median follow-up for patients without BCR was 4.8 years. Patient data were censored at 5-years of follow-up and 19 patients (13%) had BCR.

RESULTS

The median CCP score was 0.12 (IQR -0.43 to 0.66).

In univariable analysis, CCP score was a significant prognostic variable (p-value = 0.0017). The hazard ratio (HR) for BCR was 2.55 (95% CI (1.43, 4.55)) for a one-unit increase in CCP score (equivalent to a doubling of gene expression, Table 2 and Figure 1).

In a multivariable analysis that included Gleason score, PSA, percent positive cores, and androgen deprivation therapy (ADT) the HR for CCP remained significant (HR per CCP unit 2.11 (95% CI (1.05, 4.25), p-value = 0.034), indicating that CCP provides prognostic information that is not provided by standard clinical parameters (Table 3).

With 10-year censoring, the score was associated with prostate cancer specific mortality (HR per CCP unit = 3.77 95% CI (1.37, 10.4), p-value = 0.013).

There was no evidence for interaction between CCP and any clinical variable, including ethnicity.

TABLE 1. SUMMARY OF CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF COHORT.

Characteristic	N	Summary measure
CCP score, median (IQR)	141	0.12 (-0.43. 0.66)
Age, years at diagnosis, median (IQR)	141	66 (60, 71)
Ethnicity† (%)		
African-American	81	57.4
Other	60	42.6
Baseline PSA‡ (ng/ml), median (IQR)	140	8.04 (5.45, 13.47)
Clinical stage (%)		
T1	72	60.0
T2	44	36.7
T3	4	3.3
Gleason score (%)		
<7	54	38.3
7	70	49.6
>7	17	12.1
Concurrent hormone use (%)		
No	74	52.5
Yes	67	47.5
Percent positive cores, median (IQR)	134	45 (24,67)
Year of biopsy, median (IQR)	141	2004 (2001, 2005)
Modified D'Amico risk (%)		
Low	38	27.3
Intermediate	72	51.8
High	29	20.9
Radiation Dose (Gy), median (IQR)	116	74 (71, 74)

Abbreviations: CCP= cell cycle progression; IQR = interquartile range; PSA = prostate specific antigen; AUA = American Urological Association; Gy = gray.
† Data were collected upon 81 African-Americans, 58 Whites, and 2 patients of "Other" ethnicity. We dichotomized ethnicity, to avoid statistical modeling issues resulting from data sparseness. ‡ Maximum baseline PSA was 87.7 ng/ml.

TABLE 2. SUMMARY OF UNIVARIABLE ANALYSIS

Covariate	Number of events	Hazard ratio (95% CI)	χ^2 (df)	p-value
CCP score	19	2.55 (1.43, 4.55)	9.81 (1)	0.0017
Age, years at diagnosis	19	1.06 (0.99,1.13)	2.74 (1)	0.098
Ethnicity				
African-American	11	1.00 (ref)	4.0×10^{-4} (1)	0.984
Other	8	0.99 (0.40, 2.47)		
log(1+PSA)	19	2.72 (1.57, 4.71)	11.9 (1)	0.00057
Clinical stage				
T1	4	1.00 (ref)	10.1 (2)	0.0066
T2	9	3.53 (1.09, 11.5)		
T3	2	19.08 (3.43, 106.2)		
Gleason score				
<7	3	1.00 (ref)	5.95 (2)	0.051
7	13	3.87 (1.10, 13.6)		
>7	3	3.67 (0.74, 18.2)		
Concurrent hormone use				
No	8	1.00 (ref)	1.17 (1)	0.280
Yes	11	1.65 (0.66, 4.11)		
Percent positive cores	17	6.24 (1.05, 36.9)	4.02 (1)	0.045
Year of biopsy	19	0.90 (0.79, 1.03)	2.15 (1)	0.142
Modified D'Amico risk		1.00 (ref)		
Low	1	6.20 (0.79, 48.6)	8.49 (2)	0.014
Intermediate	10	11.12 (1.37, 90.5)		
High	7			
Radiation dose	15	0.98 (0.94, 1.02)	0.84 (1)	0.358

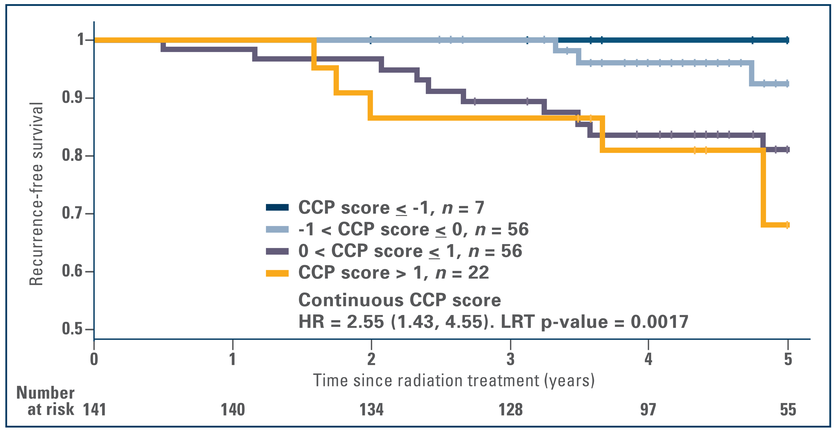
Abbreviations: CCP = cell cycle progression; CI = confidence interval; χ^2= chi-square; df = degrees of freedom; PSA = prostate specific antigen; AUA = American Urological Association; Gy = gray; ref = reference category

TABLE 3. MULTIVARIABLE COX MODEL

Covariate	Hazard ratio (95% CI)	χ^2 (df)	p-value
CCP score	2.11 (1.05, 4.25)	4.48 (1)	0.034
log(1+ PSA)	1.77 (0.90, 3.48)	2.93 (1)	0.087
Gleason score			
<7	1.00 (ref)	3.25 (2)	0.197
7	3.73 (0.76, 18.2)		
>7	2.71 (0.42, 17.5)		
Percent positive cores	1.11 (0.13, 9.19)	0.01 (1)	0.920
Concurrent hormone use			
No	1.00 (ref)	0.05 (1)	0.826
Yes	1.14 (0.35, 3.78)		

Abbreviations: CCP = cell cycle progression; CI = confidence interval; χ^2 = chi-square; df = degrees of freedom; PSA = prostate specific antigen; ref = reference category;
[a]N = 134, with 17 events

FIGURE 1. KAPLAN-MEIER FOR 5-YEAR RECURRENCE FREE SURVIVAL ILLUSTRATING THE EFFECT OF A ONE-UNIT INCREASE IN CCP SCORE (ALSO EQUIVALENT TO A DOUBLING IN GENE EXPRESSION LEVELS



CONCLUSIONS

CCP score was significantly associated with outcome after EBRT, and provided prognostic information beyond what was available from clinical parameters.

If validated in a larger cohort, CCP score could be used to select high-risk men undergoing EBRT who may need combination therapy for their clinically localized prostate cancer.

REFERENCES

1. Cuzick et al. *Lancet Oncol* 2011; 12(3): 245-55.
2. Cuzick et al. *Br J Cancer* 2012; 106(6): 1095-9.