# Abstract #247: Cell Cycle Progression Score and PTEN as Prognostic Factors for Metastasis in Intermediate- and High-Risk Prostate Cancer Overall and in Men who also Received Salvage Radiotherapy

Bruce J Trock[1], Saradha Rajamani[2], Igor Vidal[3], Stephanie A. Glavaris[3], Tracy Jones[3], Misop Han[1], Alan W. Partin[1], Todd Cohen[2]
Steven Stone[2], Angelo M. De Marzo[3]

1. Johns Hopkins School of Medicine Dept. of Urology 2. Myriad Genetics, Inc. 3. Johns Hopkins School of Medicine Dept. of Pathology

Twitter: @brucetrock, @brady_urology
Facebook: Brady Urology at Johns Hopkins
Web: urology.jhu.edu



## BACKGROUND

The cell cycle progression (CCP) score is an RNA-based classifier comprised of 31 genes normalized to 15 housekeeping genes. The cell cycle risk (CCR) score is a locked algorithm that combines CCP and CAPRA-S with regression-derived weights.

CCP and PTEN have never been evaluated together as prognostic markers for risk of metastasis in a radical prostatectomy (RP) case-cohort study of men with NCCN intermediate- and high-risk **(IR-HR)** prostate cancer (PCa), nor in a cohort of IR-HR patients who also received salvage radiation (SRT) alone or with androgen deprivation (SRT+ADT).

This study evaluated CCP score and PTEN for their association with metastasis-free survival (MFS) in both settings.

## METHODS

**Case-cohort study**: 209 John Hopkins IR-HR patients with RP 2007-2015. The subcohort consists of 174 men, including 6 with metastasis, and 35 additional metastasis patients not in the subcohort comprised the cases.

FFPE tissue sections from RP were sent to Myriad Genetics for RNA extraction and expression analysis to calculate the CCP score, and PTEN was analyzed by immunohistochemistry..

MFS was analyzed using Cox proportional hazards regression weighted for the case-cohort design. Model performance was evaluated with pseudo-likelihood ratio test.

**Cohort study of SRT & SRT+ADT**: 172 Johns Hopkins IR-HR patients with RP 2007-2015, including 153 controls and 19 metastasis cases. FFPE tissue sections analyzed as above.

MFS was analyzed with Kaplan-Meier curves and standard Cox proportional hazards regression. Model performance was evaluated with likelihood ratio test and concordance index.

### Table 1: Clinical characteristics of IR-HR case-chort

| Variable | Cases (n=35) | Subcohort (n=174) | p-value |
|---|---|---|---|
| NCCN high risk, n (%) | 18 (51) | 30 (17) | <.0001 |
| CAPRA-S, median (IQR) | 7 (5-9) | 2 (1-6) | <.0001 |
| CCP Score, median (IQR) | 0.8 (0.4, 1.7) | 0.1 (-0.2, 0.5) | <.0001 |
| CCR Score, median (IQR) | 3.4 (2.6, 3.7) | 0.9 (0.4, 1.7) | <.0001 |
| PTEN loss, n (%) | 13 (37) | 20 (11) | .0002 |
| Gleason grade group 4-5, n (%) | 24 (69) | 24 (14) | 0.151 |

## RESULTS: CASE-COHORT STUDY

In univariate analyses, CCP, HR=4.9 (95% CI 2.2, 10.9 and CAPRA-S, HR=2.3 (95% CI 1.7, 3.1) were significantly associated with metastasis; the association with PTEN was not significant.

CCR was also significant, HR=7.2 (3.8, 13.4), p<.0001.

In multivariable analyses, CCP and CAPRA-S remained significant. Adding CCP to CAPRA-S significantly improved the model, pseudo-likelihood chi-square, 20.0, p<.0001.

Adding PTEN did not further improve the model, pseudo-likelihood chi-square, 2.9, p=.09.

### Table 2: Multivariable models of MFS in IR-HR case-cohort study.

| Model | HR (95% CI) | p-value |
|---|---|---|
| **a. CCP and CAPRA-S** | | |
| CCP (per unit) | 4.5 (1.7, 11.9) | .003 |
| CAPRA-S (per 1 unit increase) | 2.0 (1.5, 2.7)) | <.0001 |
| **b. CCP, CAPRA-S, and PTEN** | | |
| CCP (per unit) | 3.6 (1.2, 11.0) | .023 |
| CAPRA-S (per 1 unit increase) | 2.1 (1.5, 2.8) | <.0001 |
| PTEN (loss vs. intact) | 2.0 (0.5, 8.6) | 0.362 |

## RESULTS: SALVAGE RADIOTHERAPY COHORT

In univariate analyses, CCP, HR=2.0 (95% CI 1.3, 3.1) and CAPRA-S, HR=1.4 (95% CI 1.1, 1.7) were significantly associated with metastasis; the association with PTEN was not significant.

CCR was also significant, HR=1.9 (1.3, 2.6), p<.0001.

In multivariable analyses, CCP and CAPRA-S remained significant. Adding CCP to CAPRA-S significantly improved the model, concordance index (c-index) increased from 0.734 to 0.803.

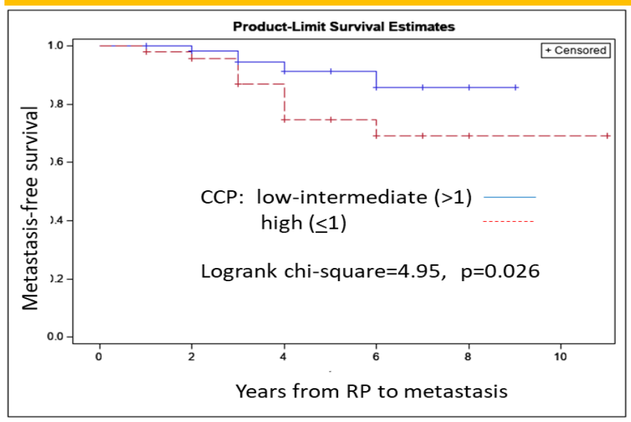
Adding PTEN did not significantly mprove the model, pseudo-likelihood chi-square, 1.7, p=.19, c-index increased from 0.803 to 0.811.

There was no significant difference in MFS between patients who received SRT+ADT vs. SRT, HR=0.8 (95% CI 0.3, 2.1), p=.703

### Table 4: Multivariable models of MFS in IR-HR salvage radiotherapy cohort study.

| Model | HR (95% CI) | p-value | Model C-index |
|---|---|---|---|
| **a. CCP and CAPRA-S** | | | |
| CCP (per unit) | 1.9 (1.2, 2.8) | .003 | 0.803 |
| CAPRA-S (per 1 unit increase) | 1.4 (1.1, 1.7) | .004 | |
| **b. CCP, CAPRA-S, and PTEN** | | | |
| CCP (per unit) | 1.7 (1.1, 2.7) | .012 | 0.811 |
| CAPRA-S (per 1 unit increase) | 1.3 (1.1, 1.6) | .008 | |
| PTEN (loss vs. intact) | 1.9 (0.7, 4.9) | .186 | |

### FIG. 1: Kaplan-Meier curve of CCP high risk (>1) vs. low-intermiate risk (≤1)




## CONCLUSIONS

- This is the first evaluation of CCP and PTEN to predict metastasis in IR-HR PCa patients, and the first in IR-HR patients receiving salvage radiotherapy
- CCP strongly predicts metastasis in men with IR-HR PCa generally, and in IR-HR patients who received salvage radiotherapy, even after adjusting for CAPRA-S. PTEN was not significant after adjusting for CCP and CAPRA-S
- CCR, a locked algorithm combining CCP and CAPRA-S also strongly predicts metastasis
- Given this is a single-institution retrospective study, it should be replicated in another center with a more diverse population