Evaluating cell cycle progression score as a prognostic marker for non-muscle invasive bladder cancer (NMIBC)

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BACKGROUND

- Accurate grading and staging from transurethral resection of bladder tumors (TURBT) is vital for appropriate clinical management.
- Non-muscle-invasive bladder cancer (NMIBC) can recur or progress with higher grade and/or stage progression to MIBC, requiring radical intervention with poorer prognosis.
- Further, grade and stage may change in 20-50% of TURBTs following re-review by expert GU pathologists.
- Objective measures of stage and grade might offer additional and/or improved risk stratification; therefore, we evaluated a molecular RNA signature as a prognostic marker for NMIBC.

METHODS

COHORT

- Patients were diagnosed with NMIBC at the University of Minnesota (UM) or Spectrum Health System (SHS) from 2005-2012.
- The combined cohort consisted of 293 patients (UM n=152, SHS n=141).

MOLECULAR TESTING

- Cell Cycle Progression (CCP) score was determined from the average expression of 46 genes (31 CCP genes and 15 housekeeping genes) for patients with available formalin−fixed paraffin embedded diagnostic TURBT.
- CCP score was calculated as the average of the CCP gene expression normalized by the average expression of the housekeeping genes.

STATISTICAL ANALYSIS

- Study outcome was time from NMIBC diagnosis to progression, defined as either metastasis or cystectomy procedure.
- Median follow-up for patients who did not experience a progression event was 6.0 years (IQR: 3.4, 7.7) for the combined cohort (Table 1).
- Association with outcomes was evaluated by Cox proportional hazards survival analysis and likelihood ratio tests.
- All analyses were stratified by cohort.

Table 1. Patient Demographics for Combined Cohorts

	N	Median (IQR) or %
Age at diagnosis	293	70 (61, 77)
Follow-up (years)*	239	6.0 (3.4, 7.7)
Gender		
Male	221	75.4%
Female	72	24.6%
Grade		
High	139	47.8%
Low	152	52.2%
Stage		
T1	78	26.6%
Ta	209	71.3%
IS	6	2.0%
Progression		
Yes	54	18.4%
No	239	81.6%

*Follow-up time for non-events

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RESULTS

- CCP score was associated with progression in univariate analysis [hazard ratio 1.42 (95% CI 1.19, 1.68), p=4.3x10^{-5}] (Table 2).
- Tumor grade and stage also were highly prognostic.

Table 2. Univariate Analysis in Combined Cohorts N=293 (54 Events)

	N	Hazard Ratio (95% CI)	p-value
CCP score	293	1.42 (1.19, 1.68)	4.3x10^{-5}
Grade (N=291)			
High	141	5.12 (2.63, 9.96)	5.9x10^{-8}
Low	150	*Ref*	
Stage (N=287)			
T1	78	4.05 (2.33, 7.02)	7.15x10^{-7}
Ta	209	*Ref*	

Table 3. Multivariate Analysis in Combined Cohorts N=293 (54 Events)

	N	Hazard Ratio (95% CI)	p-value
CCP score	285	1.13 (0.88, 1.45)	0.32
Grade (N=285)			
High	141	2.55 (1.06, 6.16)	0.032
Low	150	*Ref*	
Stage (N=285)			
T1	79	2.13 (1.08, 4.20)	0.027
Ta	206	*Ref*	

Table 4. Multivariate Analysis in Ta Subset N=207 (22 Events)

	N	Hazard Ratio (95% CI)	p-value
CCP score	207	1.43 (0.99, 2.06)	0.056
Grade (N=207)			
High	69	2.88 (0.87, 9.56)	0.079
Low	138	*Ref*	

- CCP score was strongly associated with stage (T1 vs. Ta p<10^{-6}) (Figure 1) and grade (high vs. low p<10^{-14}) in both cohorts.
- As a result, CCP score did not provide independent prognostic information in multivariable analysis after adjusting for stage and grade in the entire cohort (p=0.32) (Table 3).
- However, there was a significant interaction between stage and CCP score (p=0.0017), justifying an exploratory analysis of CCP score in Ta disease (Figure 3).
- In this subset, CCP score trended toward significance (p=0.056) after adjusting for grade (Table 4).

Figure 1. Disease Progression According to CCP Score and Stage

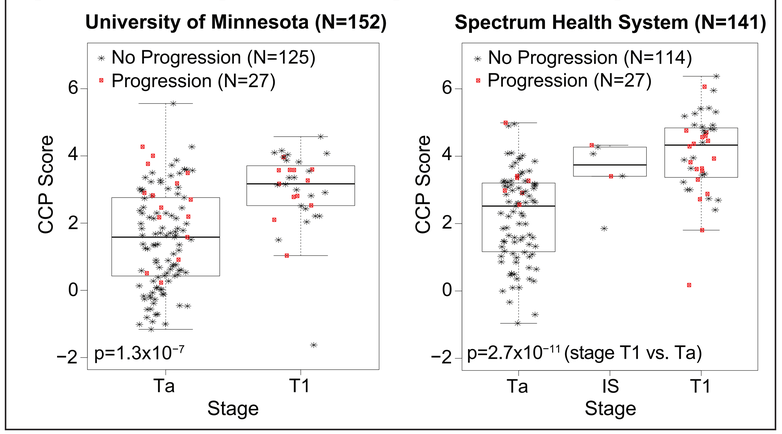


Figure 2. Kaplan-Meier Plot by Median CCP Score for Combined Cohorts

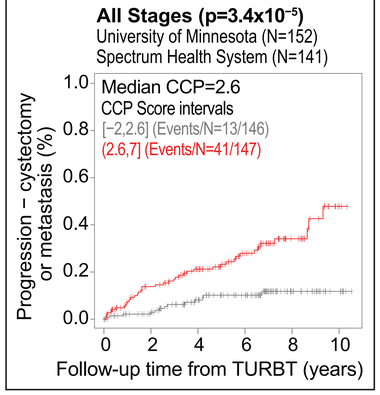
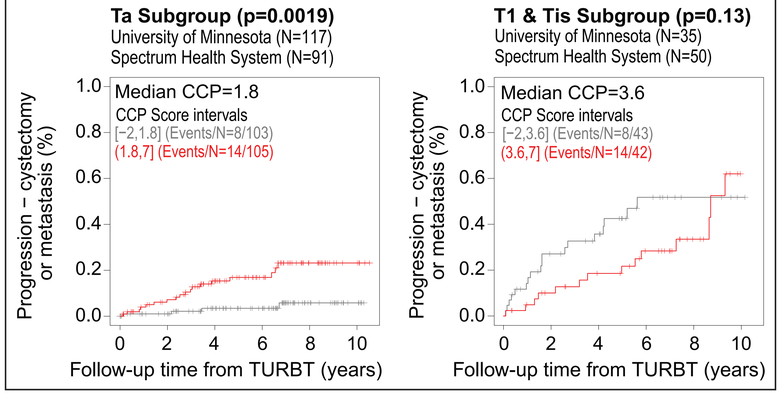


Figure 3. Kaplan-Meier Plot by Median CCP Score and Stage for Combined Cohorts



CONCLUSIONS

- In NMIBC, CCP score was highly correlated with tumor stage and grade and could serve as a quantitative measure of these clinical parameters.
- CCP score may also provide prognostic information regarding risk of progression to cystectomy or metastasis, particularly in patients with Ta disease, but this requires additional validation.

PLEASE EMAIL CHRISTOPHER WEIGHT (CJWEIGHT@UMN.EDU) WITH ANY QUESTIONS OR COMMENTS