VALIDATION OF A CELL CYCLE PROGRESSION SCORE FOR FIVE-YEAR MORTALITY RISK IN PATIENTS WITH STAGE I LUNG ADENOCARCINOMA

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BACKGROUND

- Although surgery is the standard treatment for patients with early stage (I-IIIA) lung cancer [1], survival rates remain relatively low.
- There is evidence that some patients may benefit from post-surgical chemotherapy; however, identification of patients who would benefit from adjuvant chemotherapy is under investigation [2,3].
- A 46-gene panel assessing cell cycle progression (CCP) gene expression has been developed for pathologic stage I and II lung adenocarcinoma patients [4,5].

OBJECTIVE

- The aim of this study was to validate the CCP gene signature (CCP score) and a Prognostic Score [(PS) combination of CCP and pathological stage] (IA or IB) that identify stage I non-small cell lung cancer patients with a higher risk of cancer-related death after surgical resection.

METHODS

PATIENTS

- A set of 1200 consecutively treated patients at the Memorial Sloan Kettering Cancer Center was identified.
- Patients were included in the study if they had NSCLC with adenocarcinoma histology, Stage I disease using 7th edition International Association for the Study of Lung Cancer criteria and a complete resection of the primary lung tumor. Patients who recurred and then received chemotherapy and/or radiation were acceptable.

GENE EXPRESSION TESTING

- Formalin-fixed paraffin-embedded surgical tumor samples were analyzed for the expression levels of 31 CCP genes and 15 house-keeping genes by quantitative RT-PCR [6].
- The CCP score is an un-weighted average of 31 cell cycle genes normalized by the average of 15 house-keeping genes.
- The formula for the prognostic score (PS) is 20*(0.33*CCP + 0.52*stage) + 15, where CCP score is rounded to the nearest tenth, and stage is treated as a numerical variable (stage IA = 1, stage IB = 2). The PS was rounded to the nearest integer.

STATISTICAL ANALYSIS

- Primary endpoint: 5-year lung cancer mortality (death from lung cancer within 5 years of surgery).
- The linear association of the CCP score and prognostic score with 5-year lung cancer mortality was evaluated with Cox proportional hazards regression.
- A PS threshold was used to define a binary variable for patients who have a “low” PS (< 28) or a “high” PS (≥ 28), as previously established [5].
- The log-rank test was employed to evaluate whether the 5-year lung cancer survival was significantly more favorable for patients in the low prognostic score group than in the high prognostic score group.

RESULTS

- 1137/1200 patients were evaluable based on available follow-up status and adequate tumor tissue quality to generate a CCP score.
- Demographic and other baseline characteristics for these evaluable patients are shown in Table 1.
- The baseline characteristic of morphology grade is derived from predominant histologic subtype (Table 2).

TABLE 2. PREDOMINANT HISTOLOGY AND MORPHOLOGY GRADE

Predominant Histologic Subtype	n (%)	Morphology Grade	n (%)
Lepidic	121 (10.6)	Low	160 (14.1)
Adenocarcinoma in situ (AIS)	1 (0.1)		
Minimally invasive adenocarcinoma (MIA)	38 (3.3)		
Acinar	464 (40.8)	Intermediate	712 (62.6)
Papillary	248 (21.8)		
Micropapillary	65 (5.7)	High	265 (23.3)
Solid with mucin production	153 (13.5)		
Invasive mucinous adenocarcinoma*	39 (3.4)		
Colloidal adenocarcinoma*	8 (0.7)		

TABLE 1. PATIENT CLINICAL CHARACTERISTICS AND MULTIVARIATE COX PROPORTIONAL HAZARDS REGRESSION ANALYSIS

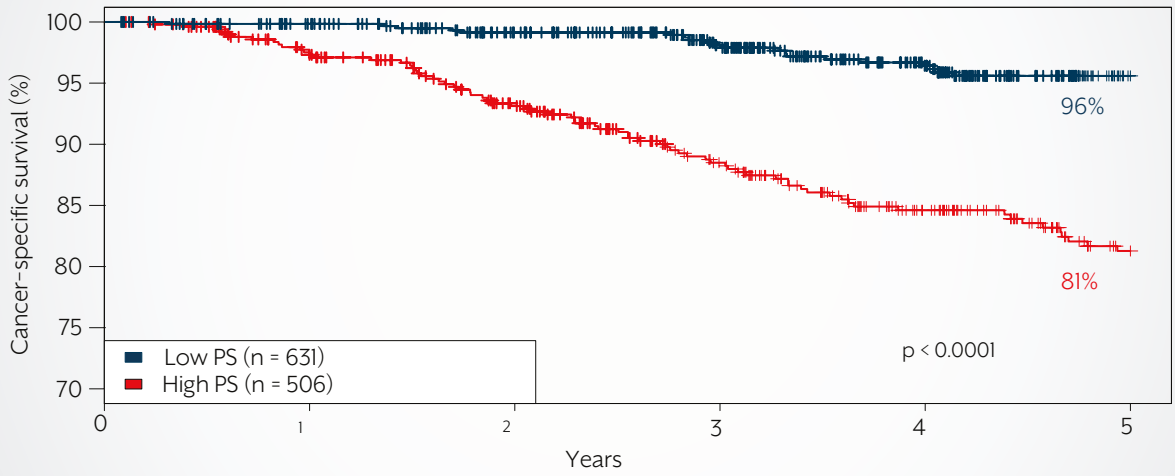
			CCP Score		Prognostic Score	
Characteristic	**Statistic/ Category**	**Evaluable Analysis Set (N=1,137)**	**Hazard Ratio* (95% CI)**	**p-value**	**Hazard Ratio* (95% CI)**	**p-value**
			1.54 (1.10, 2.15)	0.011	1.76 (1.14, 2.72)	0.011
Age at diagnosis (years)	n	1,137	1.03 (1.01, 1.06)	0.007	1.03 (1.01, 1.06)	0.007
	Mean (SD)	68.2 (10.00)				
	Median	69				
	Min, Max	23, 96				
Gender	Male	440 (38.7%)	1	0.188	1	0.188
	Female	697 (61.3%)	0.76 (0.50, 1.15)		0.76 (0.50, 1.15)	
Smoking Status	Never	200 (17.6%)	1	0.649	1	0.646
	Former	775 (68.2%)	1.35 (0.70, 2.94)		1.35 (0.70, 2.95)	
	Current	162 (14.2%)	1.46 (0.62, 3.63)		1.47 (0.62, 3.63)	
Tumor size (cm)	n	1,137	1.54 (1.17, 2.01)	0.003	1.54 (1.17, 2.00)	0.003
	Mean (SD)	2.2 (0.97)				
	Median	2.0				
	Min, Max	0.3, 5.0				
Pathological Stage	IA	810 (71.2%)	1	0.748	1	0.196
	IB	327 (28.8%)	0.88 (0.40, 1.92)		0.56 (0.23, 1.35)	
Pleural invasion	PLX/PL0	953 (83.8%)	1	0.138	1	0.140
	PL1	164 (14.4%)	1.81 (0.86, 3.81)		1.81 (0.86, 3.81)	
	PL2	20 (1.8%)	2.54 (0.87, 6.60)		2.53 (0.86, 6.57)	
Lymphatic invasion	Absent	769 (67.6%)	1	0.013	1	0.012
	Present	368 (32.4%)	1.79 (1.13, 2.86)		1.80 (1.14, 2.86)	
Vascular invasion	Absent	830 (73.0%)	1	0.055	1	0.055
	Present	307 (27.0%)	1.58 (0.99, 2.51)		1.58 (0.99, 2.51)	
Surgical procedure	Lobectomy/ Bilobectomy/ Pneumonectomy	851 (74.8%)	1	<0.0001	1	<0.0001
	Segmentectomy	98 (8.6%)	3.23 (1.59, 6.13)		3.23 (1.59, 6.12)	
	Wedge	188 (16.5%)	4.55 (2.71, 7.56)		4.54 (2.70, 7.54)	
Morphology grade	Low	160 (14.1%)	1	0.012	1	0.012
	Intermediate	712 (62.6%)	2.18 (0.77, 9.10)		2.18 (0.77, 9.11)	
	High	265 (23.3%)	3.78 (1.28, 16.16)		3.79 (1.29, 16.21)	

Abbr: Max = maximum, Min = minimum, SD = standard deviation, CI = confidence interval.
**Hazard ratios for CCP score and Prognostic score are per the interquartile range of each score, respectively.*

RESULTS -CONTINUED-

- In the multivariate analysis, the CCP score was an independent significant prognostic marker (p = 0.011) of 5-year lung cancer mortality with a hazard ratio (HR) of 1.54 (95% CI = [1.10, 2.15]) (Table 1).
- Other significant variables included age at diagnosis (p = 0.007), tumor size (p = 0.003), lymphatic invasion (p = 0.013), surgical procedure (p < 0.0001) and morphology grade (p = 0.012) (Table 1).
- In a separate multivariate analysis, the prognostic score was an independent significant prognostic marker (p = 0.011) of 5-year lung cancer mortality with a hazard ratio (HR) of 1.76 (95% CI = [1.14, 2.72]) (Table 1).
- Other significant variables included age at diagnosis (p = 0.007), tumor size (p = 0.003), lymphatic invasion (p = 0.012), surgical procedure (p < 0.0001) and morphology grade (p = 0.012) (Table 1).
- The 5-year lung cancer survival rate was 96% for low prognostic score patients and 81% for high prognostic score patients (Figure 1).
  - The difference in survival rates between these two groups was significant (p < 0.0001).

FIGURE 1. 5-YEAR LUNG CANCER SURVIVAL BASED ON A PROGNOSTIC SCORE THRESHOLD



CONCLUSIONS

- This study validates both the CCP score and PS as independent prognostic markers of lung cancer death in patients with Stage I lung adenocarcinoma treated with surgery.
- The CCP score and PS provide quantitative risk information above that captured by current NCCN high risk features.
- Patients with a high PS had nearly five times the rate of disease-related mortality than patients with a low PS (19% vs. 4%).
- Patients with resected stage I lung adenocarcinoma and a high CCP score and PS may be candidates for adjuvant therapy to reduce cancer related mortality.

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