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Validation of a Molecular and Pathological Model for Five-Year Mortality Risk in Patients with Early Stage Lung Adenocarcinoma

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Introduction: The aim of this study was to validate a molecular expression signature [cell cycle progression (CCP) score] that identifies patients with a higher risk of cancer-related death after surgical resection of early stage (I-II) lung adenocarcinoma in a large patient cohort and evaluate the effectiveness of combining CCP score and pathological stage for predicting lung cancer mortality.

Methods: Formalin-fixed paraffin-embedded surgical tumor samples from 650 patients diagnosed with stage I and II adenocarcinoma who underwent definitive surgical treatment without adjuvant chemotherapy were analyzed for 31 proliferation genes by quantitative real-time polymerase chain reaction. The prognostic discrimination of the expression score was assessed by Cox proportional hazards analysis using 5-year lung cancer-specific death as primary outcome.

Results: The CCP score was a significant predictor of lung cancer-specific mortality above clinical covariates [hazard ratio (HR) = 1.46 per interquartile range (95% confidence interval = 1.12–1.90; $p = 0.0050$)]. The prognostic score, a combination of CCP score and pathological stage, was a more significant indicator of lung cancer mortality risk than pathological stage in the full cohort (HR = 2.01; $p = 2.8 \times 10^{-11}$) and in stage I patients (HR = 1.67; $p = 0.00027$). Using the 85th percentile of the prognostic score as a threshold, there was a significant difference in lung cancer survival between low-risk and high-risk patient groups ($p = 3.8 \times 10^{-7}$).

Conclusions: This study validates the CCP score and the prognostic score as independent predictors of lung cancer death in patients with early stage lung adenocarcinoma treated with surgery alone. Patients with resected stage I lung adenocarcinoma and a high prognostic score may be candidates for adjuvant therapy to reduce cancer-related mortality.

Key Words: Carcinoma, Nonsmall cell lung cancer, Real-time polymerase chain reaction, Risk stratification.

(*J Thorac Oncol.* 2015;10: 67–73)

Lung cancer is one of the most common cancers in the United States and Europe and the leading cause of cancer death for both men and women in the United States, with approximately 160,000 patient deaths per year. Nonsmall cell lung cancer (NSCLC) comprises 85% of lung cancer cases of which up to 40% have adenocarcinoma histology. Patients diagnosed with stage I and II adenocarcinoma (localized disease) have 5-year overall mortality rates ranging from 30% in stage IA, 50% in stage IB disease, and up to 66% in stage II.[1,2]

The results of the Lung Adjuvant Cisplatin Evaluation meta-analysis established surgical resection followed by adjuvant chemotherapy with a cisplatin doublet as standard of care in patients with stage II and III disease.[3–5] However, this analysis failed to demonstrate a significant benefit for patients with stage IA and IB disease. A separate study, CALGB 9633, comprised of patients with stage IB disease, demonstrated a statistically significant survival advantage for patients with tumors ≥4 cm who received adjuvant therapy.[6] The significant mortality rate from lung cancer at 5 years for patients with stage I disease

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despite complete surgical resection suggests that some patients may benefit from adjuvant chemotherapy although molecular markers to identify those patients are lacking.[1,7]

Defining the population at high risk of recurrence will allow for rational clinical trials that will determine the best therapies for these patients. There is a particularly acute need currently for developing such a strategy as the recent introduction of low-dose computed tomographic scans or other screening modalities for high-risk populations will lead to increased numbers of patients with early stage disease.[8] The ability to identify those patients with a high rate of recurrence, for whom adjuvant chemotherapy might provide benefit, is crucial in reducing the mortality from NSCLC. The fundamental role of this strategy is to identify which patients with early stage lung adenocarcinoma should be subjected to the risk of adjuvant therapy and which are unlikely to benefit from it.

Molecular signatures have been developed to assist in defining the risk of death with early stage disease.[9–12] However, a recent review highlighted the unsolved issues in the development and analysis of gene signatures in general, and lung cancer signatures in particular.[13] Very few of these signatures have been rigorously tested in combination with pathological variables, and even fewer have been applied to formalin-fixed clinical samples. Currently, no gene signatures have been included in clinical practice guidelines for the treatment of early stage resectable lung cancer.

We previously described the development and validation of an RNA expression signature based on cell cycle progression (CCP) genes to predict death from lung cancer.[14] In that analysis, the CCP score was a highly significant, independent predictor of cancer-specific mortality in adenocarcinomas in three independent datasets. Pathological stage remained an independent prognostic factor besides the CCP score, which prompted us to model a combined prognostic score of CCP and pathological stage based on the data in the CCP validation study. The combined score integrated molecular and clinical data to obtain a superior predictor of outcome than either variable alone.

The purpose of this study was to further validate the association of CCP with 5-year lung cancer mortality after adjusting for clinical parameters. We also sought to investigate the prognostic score as a predictor of 5-year lung cancer mortality risk and to establish a cut point for classifying patients into low- and high-risk groups. This study validates the CCP and prognostic score as robust molecular markers that predict death from early stage adenocarcinoma and provide useful information to determine which patients need to be considered for additional therapy to improve survival.

MATERIALS AND METHODS

Patients

Samples for this study were collected from consecutive population cohorts surgically treated at Brigham and Women's Hospital (BWH; Boston, MA) and the Royal Infirmary of Edinburgh (RIE; Edinburgh, United Kingdom) with appropriate Institutional Review Board approvals. Inclusion criteria were patients with NSCLC with adenocarcinoma histology, stage I-II disease according to 7th edition International Association for the Study of Lung Cancer (IASLC) guidelines, complete resection of the primary tumor, no treatment with radiation or chemotherapy before surgery, no adjuvant treatment with radiation or chemotherapy within 12 weeks of surgery, and at least 1-month of follow up. Patients diagnosed with previous lung cancer or synchronous lung cancers were excluded. Adenocarcinoma subtypes were assessed in the BWH cohort and are provided in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/JTO/A710). To ascertain the primary outcome measure of death from lung cancer, clinical records or death records and ICD-10 codes were retrieved and reviewed. The secondary outcome measure was overall survival.

BWH provided 655 samples. Twelve samples were excluded based on little/no tumor or incorrect tumor pathology. The majority of samples (641/655) generated passing molecular scores but only 474 samples matched the above selection criteria, had complete clinical data and passing molecular scores. All samples were reviewed by a pulmonary pathologist to confirm diagnosis and tumor content before being sent for molecular analysis. Of 205 eligible samples from the RIE, 190 (92.6%) had passing molecular scores and 176 samples conformed to all inclusion criteria and had full clinical data. This study was conducted and reported according to REMARK guidelines.[15] All samples were rendered non-identifiable so that all laboratory analysis was blinded to any clinical or pathological data.

Expression Assay

All assay procedures were fully developed before initiation of the validation study and implemented in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory. Experimental details of the CCP score have been described.[14] Briefly, tumor tissue was marked on a hematoxylin and eosin-stained section of formalin-fixed paraffin-embedded (FFPE) samples by a pathologist and two 5 to 10 μm sections of tumor tissues were excised by macro-dissection. Tissue was pooled and total RNA extracted with the FFPE miRNEasy Kit (Qiagen, Valencia, CA). RNA yield was determined using a Nanodrop 2000 Spectrophotometer (ThermoScientific, Waltham, MA) and RNA quality was assessed by the expression as described in the passing criteria below; 500 ng of total RNA were DNase-treated (Sigma-Aldrich, St. Louis, MO) and reverse transcribed with the High Capacity cDNA Archive Kit (Life Sciences, Foster City, CA). For pre-amplification, 60 ng of RNA-equivalent cDNA and a multiplex of all gene primers were setup in triplicate polymerase chain reaction (PCR) reactions. After 14 cycles, preamplified material was diluted 1:20 and used to inoculate custom Taqman Low Density arrays (Life Technologies, Grand Island, NY). Expression levels of 15 housekeeping genes and 31 cell cycle target genes were quantified as Ct values at a predefined threshold. Passing criteria for calculation of CCP scores included amplification of a minimum of 13 housekeeping genes and 22 cell cycle genes with measurable raw Ct values and a standard deviation of less than 0.5 between CCP scores from the three replicates for each sample. A list of genes that constitute the CCP score is provided in Supplemental Table 2 (Supplemental Digital Content 1, http://links.lww.com/JTO/A710).

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Determination of the CCP Score and the Prognostic Score

Details of the selection and verification of the CCP score in lung adenocarcinoma have been previously published.[14] In summary, the CCP score is the unweighted average of 31 cell cycle genes normalized by the average of 15 housekeeping genes. Each unit of the CCP score represents a twofold change in mRNA expression. The algorithm for the prognostic score was developed in an independent training cohort and fully defined before analysis. Details on the derivation of the coefficients in the prognostic score are provided in the Supplemental Methods (Supplemental Digital Content 1, http://links.lww.com/JTO/A710). In summary, the coefficients for the CCP score and pathological stage were determined from a Cox proportional hazard (PH) model of the CCP score and pathological stage in three cohorts from the CCP validation study.[14] The resulting score is scaled and shifted to yield the final equation which is prognostic score = 20 × (0.33 × CCP + 0.52 × Stage) + 15 where the CCP score was rounded to the nearest 10th and the prognostic score was rounded to the nearest integer. Calculation of the prognostic score was fixed before the analysis presented here.

Statistical Analysis

Statistical analysis was performed only after all patient clinical data and expression data had been independently completed. Primary outcome for all analyses was death from lung cancer within 5 years of surgery. Follow-up times started on the date of surgery. Patients who were lost to follow up, died from other causes, or died from unknown causes without evidence of lung cancer recurrence were censored at the last observation. Deaths attributed to lung cancer, and deaths due to unknown causes after lung cancer recurrence were considered events. All patients were censored at 5 years.

The contribution of the CCP score and clinical variables to the prediction of outcome was assessed in univariate and multivariate models using Cox PH regression. Gender and pleural invasion were modeled as binary variables. Age, tumor size (rounded to the nearest millimeter), the CCP score, and the prognostic score were included as quantitative covariates. Pathological stage and cohort were handled as four-level (IA, IB, IIA, and IIB) and two-level (BWH and RIE) categorical variables, respectively. Cox PH p-values were based on the chi-squared test statistics from partial likelihood models. Analyses were conducted using R version 2.15.1.[16] A p-value less than 0.05 was considered a significant result. All reported p-values are two-sided. Hazard ratios (HR) for CCP and prognostic score are reported per interquartile range.

Univariate Cox PH analysis tested the association of the prognostic score with 5-year lung cancer mortality. We estimated the risk of lung cancer death within 5 years of resection, as a function of the prognostic score, according to this univariate model; 95% confidence intervals (CI) for risk estimates were calculated based on the log hazard. To evaluate the significance of the prognostic score compared with pathological stage alone, a bivariate model of prognostic score and stage was compared with a model with pathological stage alone.

We predefined a threshold for categorizing low and high risk as the 85th percentile of the prognostic score in stage IA patients. This threshold was chosen based on literature showing that approximately 15% of stage IA patients died from lung cancer within 5 years.[14,17–21] Patients at or below the cut point were classified as low risk; patients with prognostic score above were high risk. Using the Mantel–Cox log-rank test, with the prognostic score coded as a binary variable, we tested the hypothesis that the rate of 5-year lung cancer mortality would be significantly less in the low prognostic score group than in the high prognostic score group.

RESULTS

To validate the CCP score and the prognostic score as predictors of outcome in lung adenocarcinoma, we assembled a cohort of surgically treated, chemotherapy and radiation-naive stage I and II patients. The validation set included 650 patients from two datasets: 474 patients from the BWH and 176 patients from the RIE. Patient clinical and pathological features are shown in Table 1. The 5-year lung cancer survival rate was 73% with a median follow up of 5.5 years for patients who did not die of lung cancer.

Validation of the CCP Score as an Independent Predictor of Cancer-specific Mortality

The primary goal of the study was to validate the CCP score as an independent prognostic marker in the presence of clinicopathological parameters, thus justifying its combination with pathological stage in the prognostic score. In this analysis, the CCP score was a significant predictor of 5-year lung cancer-specific mortality after adjustment for clinical variables (Table 2). The CCP score was highly significant in univariate analysis [HR = 1.79 (95% CI = 1.42–2.27; $p = 1.1 \times 10^{-6}$)]. Age ($p = 0.0097$), gender (with decreased mortality for female patients; $p = 0.0091$), pathological stage ($p = 7.7 \times 10^{-9}$), and tumor size ($p = 1.1 \times 10^{-5}$) were also significant factors in

TABLE 1. Patient Clinical and Pathological Characteristics

		BWH $N = 474$ n (%)	RIE $N = 176$ n (%)
Age at diagnosis (Median ± SD)		67 ± 11	68 ± 10
Gender	Male	172 (36)	69 (39)
	Female	302 (64)	107 (61)
Tumor size	<3 cm	394 (83)	76 (43)
	≥3 cm	80 (17)	100 (57)
Stage	IA	309 (65)	36 (20)
	IB	142 (30)	53 (30)
	IIA	15 (3)	62 (35)
	IIB	8 (2)	25 (14)
Pleural invasion[a]	Yes	114 (24)	64 (36)
	No	343 (72)	112 (64)
Disease-related death at 5 yrs	Yes	92 (19)	60 (34)
	No	382 (81)	116 (66)

[a]Pleural invasion data not available for 17 patients.

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TABLE 2. Univariate and Multivariate Cox Proportional Hazards Analysis of CCP Score and Other Parameters in all Patients[c]

	Univariate		Multivariate	
	HR (95% CI)	***p* Value**	**HR (95% CI)**	***p* Value**
CCP[a]	1.79 (1.42–2.27)	1.1×10^{-6}	1.46 (1.12–1.90)	0.0050
Age	1.02 (1.00–1.04)	0.0097	1.02 (1.01–1.04)	0.010
Gender		0.0091		0.064
Male	1		1	
Female	0.65 (0.47–0.90)		0.73 (0.53–1.02)	
Stage		7.7×10^{-9}		0.0023
IA	1		1	
IB	1.65 (1.11–2.44)		1.72 (1.00–2.96)	
IIA	3.79 (2.47–5.75)		3.47 (1.84–6.5)	
IIB	3.30 (1.76–5.77)		3.42 (1.28–8.62)	
Tumor size[b]	1.20 (1.11–1.29)	1.1×10^{-5}	1.01 (0.88–1.15)	0.93
Pleural invasion	1.30 (0.91–1.82)	0.14	0.83 (0.53–1.29)	0.41
Cohort		0.00092		0.47
BWH	1		1	
RIE	1.76 (1.26–2.43)		0.86 (0.56–1.3)	

[a]Hazard ratio per interquartile range of the CCP score.
[b]Hazard ratio per cm, rounded to the nearest mm.
[c]Events/*N* = 147/633 for multivariate analysis, and univariate analysis of pleural invasion. Other univariate analyses had Events/*N* = 152/650.

predicting the risk of cancer-related death. There was a significant difference in mortality between the two patient cohorts ($p = 0.00092$). This difference was expected given the larger proportion of stage II patients in the RIE dataset; there was no longer a significant difference after adjusting for stage. In multivariate analysis, the CCP score was an independent risk factor for lung cancer mortality ($p = 0.0050$) with a HR of 1.46 (95% CI = 1.12–1.90). Apart from the CCP score, only stage ($p = 0.0023$) and age ($p = 0.010$) remained significant predictors of disease-specific mortality in multivariate analysis. Results for overall survival were comparable with the addition of age remaining a significant predictor in multivariate analysis (Supplemental Table 4, Supplemental Digital Content 1, http://links.lww.com/JTO/A710).

Similar results were obtained when the analysis was restricted to stage I patients. CCP score, age, gender, pathological stage, tumor size, and pleural invasion were significant in univariate analysis (Table 3). In multivariate analysis

TABLE 3. Univariate and Multivariate Cox PH Analysis of CCP Score and Other Parameters in Stage IA-IB Patients[b]

	Univariate		Multivariate	
	HR (95% CI)	**p Value**	**HR (95% CI)**	**p Value**
CCP[a]	1.63 (1.21–2.20)	0.0013	1.56 (1.12–2.18)	0.0087
Age	1.03 (1.01–1.05)	0.0014	1.03 (1.01–1.05)	0.0087
Gender		0.073		0.13
Male	1		1	
Female	0.69 (0.47–1.03)		0.73 (0.49–1.1)	
Stage		0.012		0.98
IA	1		1	
IB	1.65 (1.12–2.44)		1.01 (0.42–2.38)	
Tumor size	1.24 (1.02–1.48)	0.031	1.15 (0.86–1.53)	0.33
Pleural invasion		0.033		0.41
No	1		1	
Yes	1.59 (1.04–2.39)		1.38 (0.65–3.03)	
Cohort		0.58		0.56
BWH	1		1	
RIE	1.15 (0.69–1.84)		0.86 (0.49–1.43)	

[a]HR for CCP is per interquartile rang of the CCP score in stage IA-IB patients.
[b]Events/*N* = 96/523 for multivariate analysis, and univariate analysis of pleural invasion. Other univariate analyses had Events/*N* = 101/540.

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of stage I patients, only the CCP score [HR = 1.56 (95% CI = 1.12–2.18; $p = 0.0087$)] and age ($p = 0.0087$) were independent prognostic factors.

Validation of the Prognostic Score

We next examined the prognostic significance of the prognostic score, specifically the added prognostic value over pathological stage alone. For this analysis, we employed a bivariate Cox PH model with stage and the prognostic score. As shown in Table 4, stage alone is a highly significant predictor of disease-specific mortality ($p = 7.7 \times 10^{-9}$). However, the value of the prognostic score in univariate analysis exceeds that of stage by two orders of magnitude [HR = 2.01 (95% CI = 1.64–2.45; $p = 2.8 \times 10^{-11}$)] reflecting the prognostic information added by the CCP component. This is also manifested in bivariate analysis, where the prognostic score remains highly significant [HR = 1.86 (95% CI = 1.16–2.97; $p = 0.0093$)] after adjustment for pathological stage, indicating that the molecular part of the prognostic score substantially improves its prognostic value compared with stage alone. The lack of significance for pathological stage in the bivariate analysis indicates that the coefficients in the calculation of the prognostic score are appropriate.

In a subanalysis of stage I patients, the prognostic score was a more significant predictor of outcome [HR = 1.67 (95% CI = 1.27–2.20; $p = 0.00027$)] than pathological stage [HR = 1.65 (95% CI = 1.12–2.44; $p = 0.012$)]. In multivariate analysis, the prognostic score added significant prognostic discrimination over pathological stage alone [HR = 1.74 (95% CI = 1.16–2.61; $p = 0.0080$)].

Risk Stratification by the Prognostic Score

The predicted 5-year risk of lung cancer-specific death across the range of prognostic score is shown in Figure 1. There is also a wide range of prognostic score within each stage category and substantial overlap of scores from different stages (Figure 1). To demonstrate the effect on patient prognosis of adding the CCP score to pathological stage, we compared the predicted 5-year risk of disease-specific death by stage alone against the prediction obtained from the prognostic score (Supplemental Figure 1, Supplemental Digital Conetnt 2, http://links.lww.com/JTO/A711). Within each stage category, the prognostic score provides additional discrimination, changing some risk estimates up to threefold. On the basis of the analysis of CALGB 9633, dichotomized tumor size can be used as a prognostic factor in stage IB patients.[6] However, in this dataset, tumor size was not a significant prognostic factor in stage IB patients [HR = 0.56 (95% CI = 0.28–1.29; $p = 0.16$)]. In contrast, the CCP score does add prognostic discrimination in stage 1B patients [HR = 1.53 (95% CI = 1.01–2.33; $p = 0.044$)].

When the predefined threshold was applied to the total validation cohort, the cohort separated into almost equal groups of patients (low prognostic score, $N = 328$; high prognostic score, $N = 322$). Figure 2 shows the Kaplan–Meier-based survival estimates of low- and high-risk patient groups based on prognostic score category. Five-year cancer-specific survival in the low-risk group was 82% versus 65% in the high-risk group. The difference in survival between the low and high patient groups was highly significant ($p = 3.8 \times 10^{-7}$). Similar results were obtained in stage I patients ($N = 540$); 60.7% of stage I patients fell into the low-risk group with 5-year cancer-specific survival of 82%. For the 39.3% of high-risk stage I patients, 5-year survival was 72% ($p = 0.0057$).

DISCUSSION

These results validate CCP as an independent predictor of death from lung adenocarcinoma. In addition, the study validates the prognostic score as a predictor of survival in early stage, surgically resected lung adenocarcinoma. The prognostic score combines the CCP score, a highly quantitative molecular assessment of tumor proliferation, with pathological stage, the current standard prognostic tool in NSCLC. This approach acknowledges the cooperative nature of molecular and clinical variables.

TABLE 4. Prognostic Value of the Prognostic Score and Stage in Univariate and Bivariate Models for Total and Stage I Patients

	Univariate			Bivariate		
Total Cohort	**HR**	**(95% CI)**	***p* Value**	**HR**	**(95% CI)**	***p* Value**
Prognostic score[a]	2.01	(1.64–2.45)	2.8×10^{-11}	1.86	(1.16–2.97)	0.0093
Stage			7.7×10^{-9}			0.38
IA	1			1		
IB	1.65	(1.11–2.44)		1.03	(0.61–1.75)	
IIA	3.79	(2.47–5.75)		1.45	(0.62–3.35)	
IIB	3.30	(1.76–5.77)		0.92	(0.29–2.82)	
	Univariate			**Bivariate**		
Stage I patients	**HR**	**(95% CI)**	***p* Value**	**HR**	**(95% CI)**	***p* Value**
Prognostic score[a]	1.67	(1.27–2.20)	0.00027	1.74	(1.16–2.61)	0.0080
Stage			0.012			0.80
IA	1			1		
IB	1.65	(1.12–2.44)		0.93	(0.52–1.66)	

[a]Hazard ratio is reported per interquartile range of the prognostic score.

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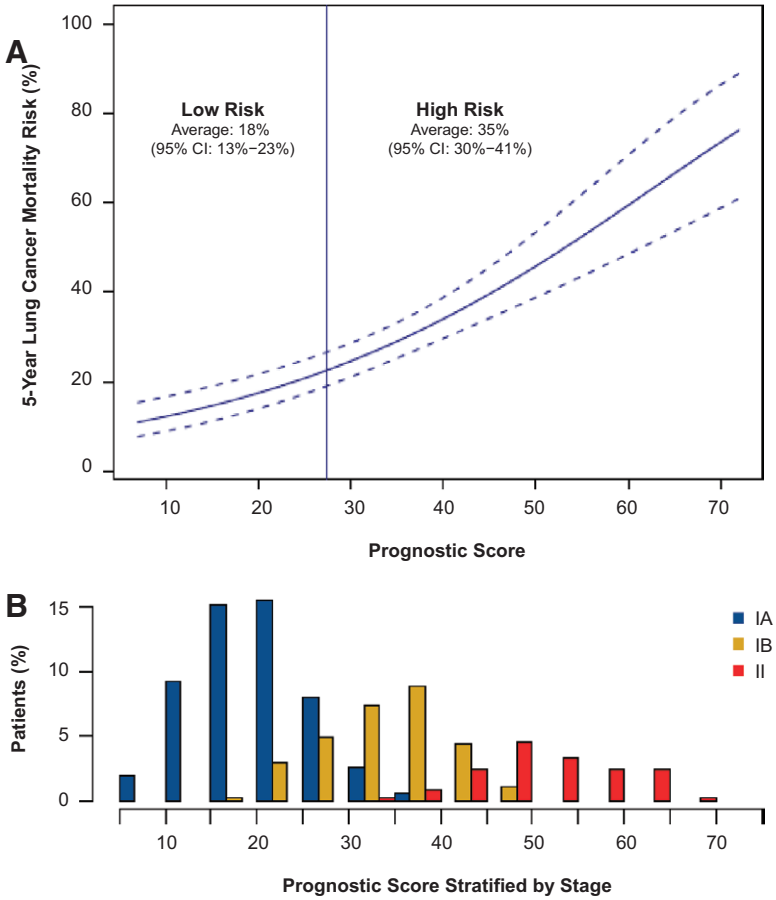

FIGURE 1. Risk estimates based on the prognostic score and the distribution of prognostic score by stage. *A,* Five-year cancer-specific survival estimates were derived from a Cox PH model using the continuous combined prognostic score. The vertical line represents the predefined threshold at the 85th percentile of the prognostic score in stage IA patients. Average risk estimates for the low- and high-risk groups are given in the inset. *B,* The prognostic score distribution for patients of different stages shows the overlap of prognostic scores between stage groups. Low prognostic score stage IB patients are grouping with stage IA and high prognostic score stage IB patients extend into stage II patients.

Many signatures can be shown to add discrimination above that provided by clinical variables. Yet, clinical parameters remain independently prognostic such that the best discrimination is obtained by combining both.[7,9] The added prognostic value of the molecular component is obtained by examining the information from the combined score within each level of the best prognostic clinical variable. Specifically, the prognostic score adds discrimination within each of the early pathological stages. For example, patients with stage IA disease based on stage alone would have a 15% probability of death at 5 years from his/her disease. A prognostic score of 47 in this same patient would translate to a 42% risk of death from lung cancer at 5 years and may warrant a discussion of risks/benefits of adjuvant chemotherapy and/or enrollment into a clinical trial of adjuvant therapy.

There were multiple strengths of this study including (1) a large patient cohort with associated statistical power, (2) a homogenous patient population of stage I and II patients without adjuvant treatment, (3) a predefined prognostic score and predefined cut-offs for risk categories, (4) specimens collected from two independent centers in the United States and Europe, and (5) a validated, quantitative polymerase chain reaction-based platform suitable for the analysis of routine clinical FFPE specimens. One potential limitation is the exclusion of known prognostic pathological features such as tumor grade/differentiation and the presence of lymphovascular invasion from the analysis. It is possible that this assay is statistically independent from these features, but even if it recapitulates them, the test still provides valuable information by quantifying these descriptive features and combining the data into a more accessible format.

This test provides prognostic information to the patient and their physician that can be used in making decisions on treatment including whether to have adjuvant chemotherapy, plan a more rigorous follow up, or participate in clinical trials. This test also provides a way for clinicians conducting chemotherapy trials in homogeneous high-risk patient cohorts to quantify effective adjuvant therapy regimens in these patients with stage IA and IB lung adenocarcinoma. It has been suggested that prospective studies to establish chemotherapy benefit in high-risk individuals could potentially demonstrate full clinical utility of the prognostic score. However, these studies are currently not feasible due to the required study size and extended follow-up times necessary for endpoints. In lieu of a prospective study, chemotherapy benefit and risk of death from therapy, as reported in the LACE studies, can be used to calculate benefit in the low - and high-risk populations as determined by the prognostic score. We expect the high-risk population to receive a significant absolute benefit to chemotherapy, whereas the low-risk population will receive little to no absolute benefit to chemotherapy and may have an increase in risk of death due to treatment.

In summary, our study shows independent validation of a previously described CCP signature to predict death from early stage adenocarcinoma. The prognostic score, utilizing stage, and CCP, can classify patients into low and high-risk

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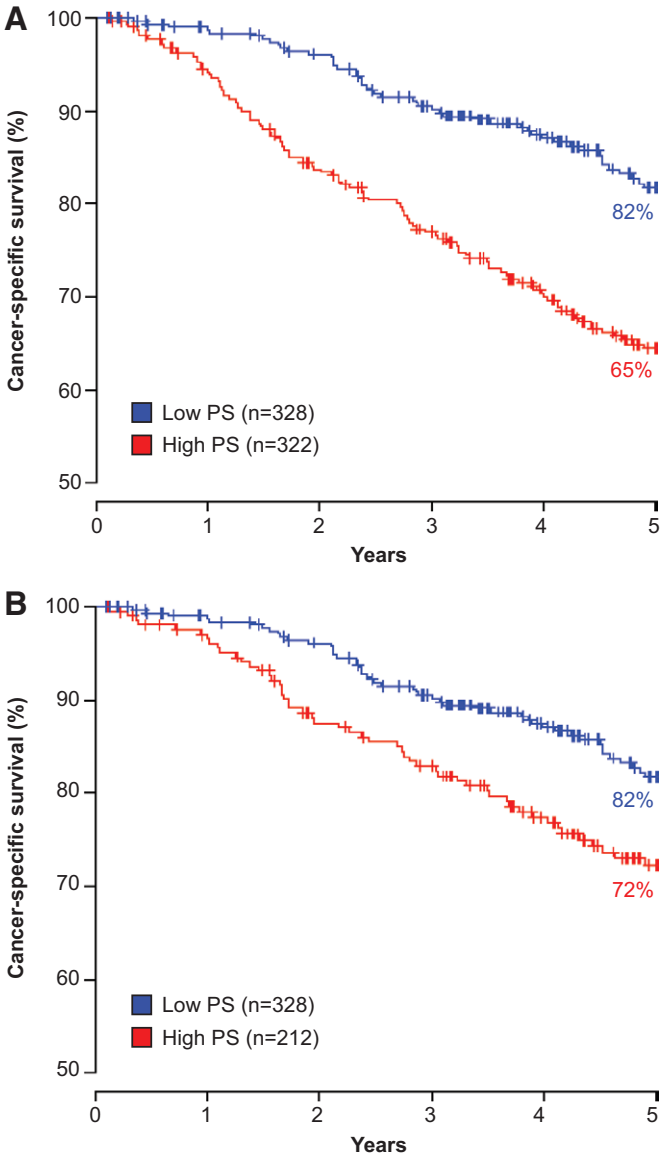

FIGURE 2. Likelihood of lung cancer survival based on prognostic score category for (*A*) the total cohort and (*B*) stage I patients. Kaplan-Meier survival estimates were derived for low prognostic score and high prognostic score patient groups based on the predefined prognostic score threshold.

categories to allow for improved treatment selection. The high prognostic score group had an average mortality risk that was nearly twofold higher than the low prognostic score group. With the expected increase in diagnosis of early stage lung cancer due to adoption of screening modalities, the prognostic score can be used to identify a subset of early stage patients who have a high risk for recurrence and for whom adjuvant chemotherapy may be more effective.

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