

# PROGNOSTIC MULTI-GENE MOLECULAR ASSAY MIGHT IMPROVE IDENTIFICATION OF PATHOLOGIC STAGE IB LUNG ADENOCARCINOMA PATIENTS AT RISK FOR RECURRENCE

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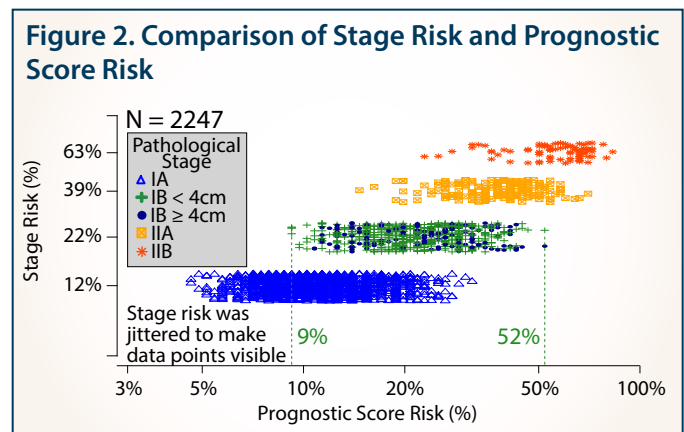
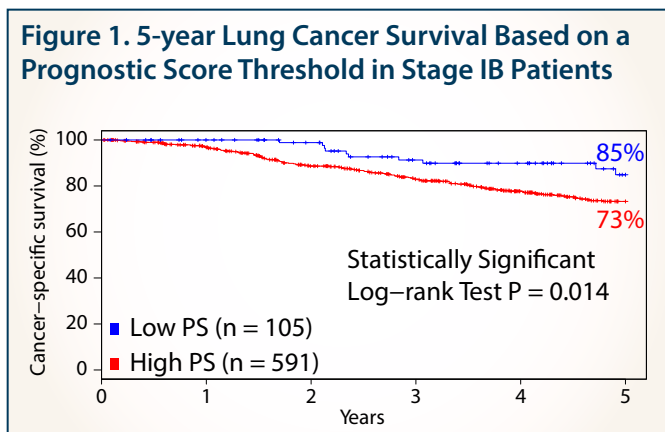
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# Introduction

- Adjuvant chemotherapy improves survival for some patients with NSCLC and is recommended for consideration by NCCN guidelines<sup>1</sup> for pathologic stage IB patients presenting certain high risk features.
- A validated, 46-gene panel measuring cell cycle progression (CCP) gene expression has been shown to stratify lung cancer specific, post-resection mortality risk in pathologic stage I and II NSCLC adenocarcinoma independently of pathologic staging<sup>2</sup> and high risk features.<sup>3</sup>
- For example, in a large cohort (n=696) of patients with stage IB lung adenocarcinoma,<sup>2,4</sup> the 5-year mortality risk was substantially and significantly different for high and low risk groups (Figure 1).
- Additionally, there is a wide distribution of prognostic score risk for all stages, especially Stage IA and IB (Figure 2). Notably, the distribution of risk for stage IB patients with tumors < 4cm and those with tumors ≥ 4cm is nearly identical.
- The aim of this study was to compare stage IB patient risk as assessed by cell cycle progression and prognostic score (PS), a combination of CCP score and pathologic stage, versus NCCN high risk factors.



# Patients and Methods

- Formalin-fixed paraffin-embedded (FFPE) surgical tumor samples from 279 patients with stage IB lung adenocarcinoma, who underwent definitive surgical treatment were stratified to high or low risk groups by analysis of the molecular assay and the remaining NCCN high risk features of poorly differentiated tumor, vascular invasion, wedge resection, tumor size > 4 cm, visceral pleural involvement, and incomplete lymph node evaluation.

# Methods

## Cell Cycle Progression (CCP) Score

- RNA is extracted from FFPE lung resection samples and the gene expression of 31 CCP genes was measured by qRT-PCR.
- The expression of the CCP genes is normalized by 15 housekeeper genes to produce a numerical CCP score.

## Prognostic Score

- Prognostic score was the linear combination of the CCP score and pathologic stage, with an offset to keep all scores above zero.
  - $PS = 20 \times (0.33 \times CCP \text{ score} + 0.52 \times \text{stage}) + 15$
- Stage was used as a numerical variable (1=IA, 2=IB, 3=IIA, 4=IIB).
- Previous studies have determined that patients with a  $PS \geq 28$  are high risk and patients with a  $PS < 28$  are low risk.

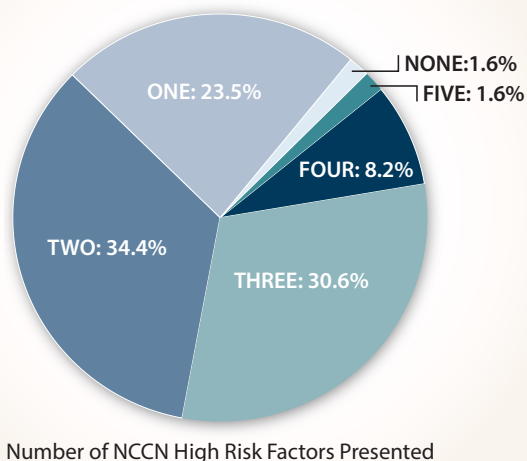
# Results

- Patient clinical characteristics are summarized in Table 1.
- Of the 279 patients with stage IB, 183 (65.6%) were designated high risk by their prognostic score.
- Figure 3 illustrates that among patients with a high prognostic score:
  - 3 (1.6%) presented with no NCCN high risk features.
  - 43 (23.5%) presented with only 1 high risk feature.
  - 63 (34.4%) presented with 2 high risk features.
  - 56 (30.6%) presented with 3 high risk features.
  - 15 (8.2%) presented with 4 high risk features.
  - 3 (1.6%) presented with 5 high risk features.
  - No patients presented with all 6 high risk features.

**Table 2. NCCN High Risk Factors<sup>1</sup>**

■ Poorly differentiated tumor (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors])
■ Vascular invasion
■ Wedge resection
■ Tumor size > 4 cm
■ Visceral pleural involvement
■ Incomplete lymph node evaluation

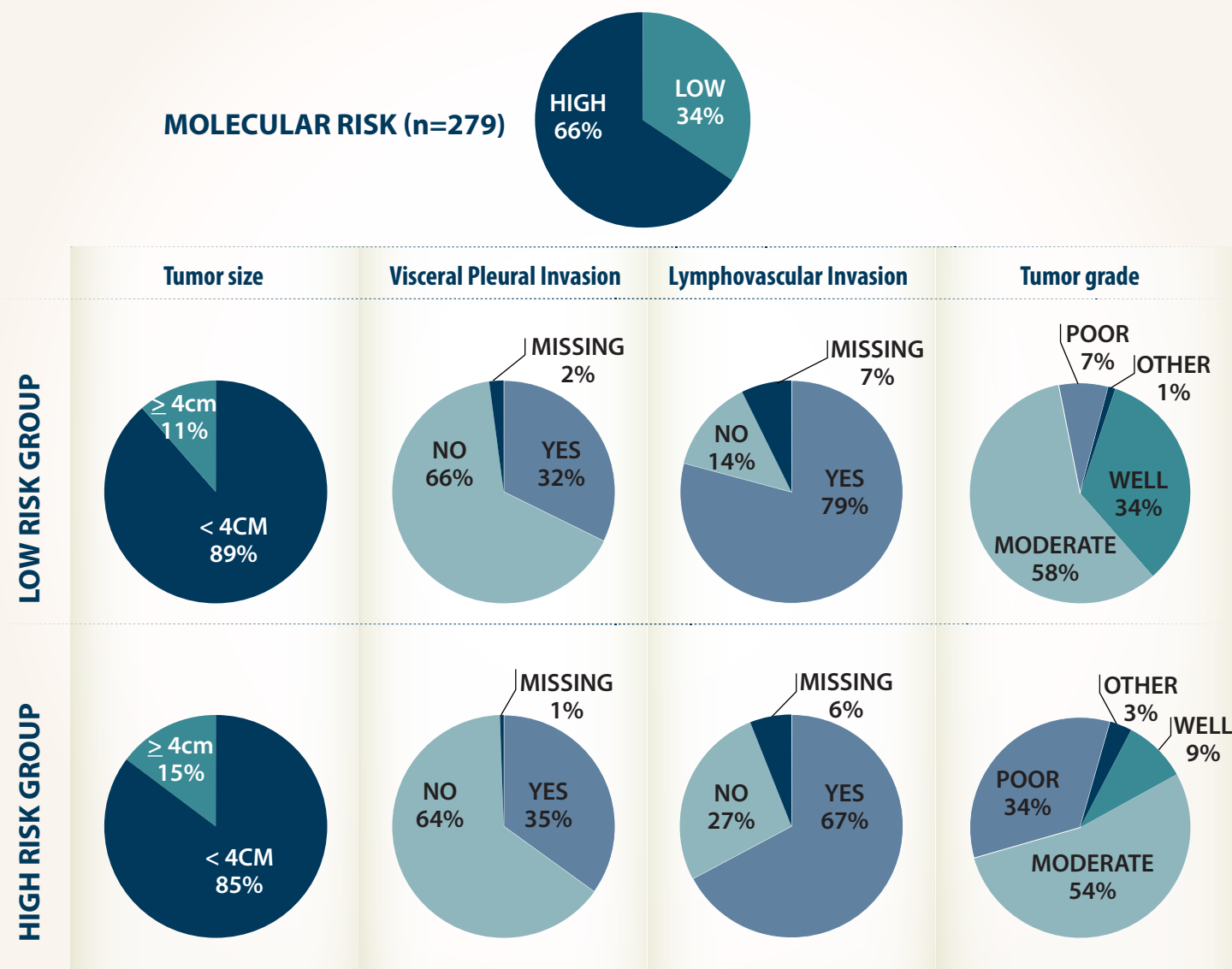
**Figure 3. Presentation of NCCN High Risk Factors in Patients with High Prognostic Score**



**Table 1. Stage IB Patient Clinical Characteristics by Prognostic Score Threshold**

Characteristic	Statistic/Category	Low PS (N=96)	High PS (N=183)	All Patients (N=279)	
Age at diagnosis (years)	N	83	173	256	
	Mean (SD)	71.1 (9.10)	67.7 (9.46)	68.8 (9.47)	
	Median	73	68	70	
	Min, Max	44, 88	32, 92	32, 92	
Gender	Female	62 (64.6%)	109 (59.6%)	171 (61.3%)	
	Male	34 (35.4%)	74 (40.4%)	108 (38.7%)	
Tumor size (cm)	N	96	183	279	
	Mean (SD)	2.8 (1.11)	3.1 (1.04)	3.0 (1.07)	
	Median	3.0	3.2	3.1	
	Min, Max	0.8, 5.0	0.7, 6.5	0.7, 6.5	
Tumor size	< 4 cm	85 (88.5%)	156 (85.2%)	241 (86.4%)	
	≥ 4 cm	11 (11.5%)	27 (14.8%)	38 (13.6%)	
Pleural invasion	Absent	31 (32.3%)	64 (35.0%)	95 (34.1%)	
	Present	63 (65.6%)	118 (64.5%)	181 (64.9%)	
	Missing	2 (2.1%)	1 (0.5%)	3 (1.1%)	
Lymphovascular invasion	Absent	76 (79.2%)	123 (67.2%)	199 (71.3%)	
	Present	13 (13.5%)	49 (26.8%)	62 (22.2%)	
	Missing	7 (7.3%)	11 (6.0%)	18 (6.5%)	
Vascular invasion	Absent	5 (5.2%)	10 (5.5%)	15 (5.4%)	
	Present	2 (2.1%)	6 (3.3%)	8 (2.9%)	
	Missing	89 (92.7%)	167 (91.3%)	256 (91.8%)	
Surgical procedure	Bilobectomy	2 (2.1%)	1 (0.5%)	3 (1.1%)	
	Lobectomy	72 (75.0%)	138 (75.4%)	210 (75.3%)	
	Lobectomy, Wedge	2 (2.1%)	3 (1.6%)	5 (1.8%)	
	Pneumonectomy	0	1 (0.5%)	1 (0.4%)	
	Segmentectomy	6 (6.3%)	8 (4.4%)	14 (5.0%)	
	Segmentectomy, Wedge	2 (2.1%)	0	2 (0.7%)	
	Wedge	10 (10.4%)	28 (15.3%)	38 (13.6%)	
	Missing	2 (2.1%)	4 (2.2%)	6 (2.2%)	
	Tumor location	LLL	9 (9.4%)	23 (12.6%)	32 (11.5%)
LLL, LUL		1 (1.0%)	0	1 (0.4%)	
LUL		24 (25.0%)	36 (19.7%)	60 (21.5%)	
RLL		15 (15.6%)	33 (18.0%)	48 (17.2%)	
RLL, RML		1 (1.0%)	2 (1.1%)	3 (1.1%)	
RLL, RUL		0	2 (1.1%)	2 (0.7%)	
RML		8 (8.3%)	11 (6.0%)	19 (6.8%)	
RML, RUL		2 (2.1%)	5 (2.7%)	7 (2.5%)	
RUL		36 (37.5%)	70 (38.3%)	106 (38.0%)	
Missing		0	1 (0.5%)	1 (0.4%)	
Tumor grade		Well differentiated	32 (33.3%)	17 (9.3%)	49 (17.6%)
		Moderately differentiated	56 (58.3%)	98 (53.6%)	154 (55.2%)
	Poorly differentiated	7 (7.3%)	62 (33.9%)	69 (24.7%)	
	Undifferentiated	1 (1.0%)	3 (1.6%)	4 (1.4%)	
	Missing	0	3 (1.6%)	3 (1.1%)	
Lymph node evaluation	No	3 (3.1%)	6 (3.3%)	9 (3.2%)	
	Yes	92 (95.8%)	177 (96.7%)	269 (96.4%)	
	Missing	1 (1.0%)	0	1 (0.4%)	

Figure 4. Visual Representation of Key Characteristics in Table 1.



## Conclusions

- This study demonstrates that a validated measure of recurrence in patients with stage IB adenocarcinoma can identify high risk patients that would have been otherwise designated as low risk according to pathological features.
- In the stage IB population, prognostic score provides quantitative risk information above that captured by current NCCN high risk features.
- The prognostic score increases the number of high risk patients with resected stage IB lung adenocarcinoma that may be candidates for adjuvant therapy to reduce cancer related mortality relative to the NCCN high risk factors.

## References

1. NCCN Guidelines Version 7.2015 Non-Small Cell Lung Cancer.
2. Bueno R, et al. *J Thorac Oncol.* 2015; 10(1): 67-73.
3. Eguchi T, et al. *J Clin Oncol.* 2015; 33 (suppl: abstr 7522).
4. Rakha E, et al. Presented at General Thoracic Surgical Club. 2015.