Prediction of Survival in Resected Non–Small Cell Lung Cancer Using a Protein Expression–Based Risk Model: Implications for Personalized Chemoprevention and Therapy

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Abstract

Purpose: Patients with resected non–small cell lung cancer (NSCLC) are at risk for recurrence of disease, but we do not have tools to predict which patients are at highest risk. We set out to create a risk model incorporating both clinical data and biomarkers.

Experimental Design: We assembled a comprehensive database with archival tissues and clinical follow-up from patients with NSCLC resected between 2002 and 2005. Twenty-one proteins identified from our preclinical studies as related to lung carcinogenesis were investigated, including pathways related to metabolism, DNA repair, inflammation, and growth factors. Expression of proteins was quantified using immunohistochemistry. Immunohistochemistry was chosen because it is widely available and can be performed on formalin-fixed paraffin-embedded specimens. Cox models were fitted to estimate effects of clinical factors and biomarkers on recurrence-free survival (RFS) and overall survival (OS).

Results: A total of 370 patients are included in our analysis. With median follow-up of 5.3 years, median OS is 6.4 years. A total of 209 cases with recurrence or death were observed. Multicovariate risk models for RFS and OS were developed including relevant biomarkers, age, and stage. Increased expression of phospho-adenosine monophosphate-activated protein kinase (pAMPK), phospho-mTOR (pmTOR), epithelial cell adhesion molecule (EpCAM), and calcium/calmodulin-dependent serine protein kinase were significant (P < 0.05) predictors for favorable RFS; insulin receptor, chemokine (C-X-C motif) receptor 2 (CXCR2), and insulin-like growth factor-1 receptor predicted for unfavorable RFS. Significant (P < 0.05) predictors for favorable OS include pAMPK, pmTOR, and EpCAM; CXCR2 and flap structure–specific endonuclease-1 predicted unfavorable OS.

Conclusion: We have developed a comprehensive risk model predictive for recurrence in our large retrospective database, which is one of the largest reported series of resected NSCLC. Clin Cancer Res; 20(7); 1946–54. ©2013 AACR.

Introduction

Lung cancer is the leading cause of cancer-related death for both men and women in the United States. Only a minority of patients are diagnosed with disease amenable to surgical resection. The standard of care following surgical resection for patients with stage II or III tumors is adjuvant chemotherapy with a cisplatin-based doublet, but recurrence is common and there are no clinically useful biomarkers to predict the risk of recurrence. As computed tomography–based screening gains wider acceptance, more patients will be diagnosed with early-stage disease, and effective risk stratification models could be very useful.

Numerous risk models for the development of lung cancer have been developed, incorporating clinical factors with or without serum biomarker assays (1–4). Individual biomarkers have been studied, including ERCC1, which predicts for a good prognosis and a lack of benefit to
Translational Relevance

Many patients with surgically resected non–small lung cancer will eventually develop tumor recurrence or metastasis. We are not yet able to predict who is at highest risk for recurrent disease. In this study, we evaluated a number of biomarkers identified in our laboratories as particularly important in carcinogenesis and correlated their expression to prognosis of patients with surgically resected tumors to create a risk model for tumor recurrence and survival. With an improved understanding of the mechanisms of early stage disease, our goals are to create a program of personalized chemoprevention and therapy for all patients at risk for lung cancer. For example, studies such as this could help us to improve the adjuvant treatment of patients with cancer, by sparing toxicities of chemotherapy for those with a good prognosis and identifying patients with poor prognosis who may benefit from clinical trials utilizing novel therapeutics.

Adjuvant chemotherapy (5), and RRM1, which predicts an improved overall survival (OS) when expressed at high levels (6). No risk prediction models are widely used in clinical practice, however, and a risk model incorporating tissue biomarkers as well as clinical factors could inform clinical decision making.

Our goal with this project was to develop a risk model for the development of recurrence and metastases in patients following lung cancer resection, and to assess the relationships between biomarkers, clinical patient characteristics, and outcome. Immunohistochemistry (IHC) was chosen because it is a readily available assay in diagnostic pathology labs and can be applied to routine formalin-fixed paraffin-embedded (FFPE) tissues. We selected biomarkers belonging to a series of important molecular pathways involved in lung carcinogenesis, including many pathways associated with the hallmarks of cancer (7). These markers have been investigated using in vitro and in vivo early carcinogenesis models, and were found to be key to the pathogenesis of NSCLC, both adenocarcinoma and squamous cell carcinoma. The markers chosen relate to cell adhesion and extracellular matrix interactions [calcium/calmodulin-dependent serine protein kinase (CASK), CD51 (also known as integrin-αV; ref. 8), epithelial cell adhesion molecule (EpCAM; ref. 9), secreted phosphoprotein-1 (SPP1; ref. 10)], inflammation [chemokine (C-X-C motif) receptor 2 (CXCR2; ref. 11)], growth factors and effector pathways [insulin-like growth factor-1 receptor (IGF-1R; ref. 12), insulin-like growth factor binding protein-3 (IGFBP3; ref. 13), insulin receptor (14), pIGF-1R, phospho-epidermal growth factor receptor (pEGFR; refs. 15 and 16)], growth and metabolism [pAkt (17, 18), pSrc (19), pmTOR (18), phospho-adenosine monophosphate-activated protein kinase (pAMPK; ref. 20), pS6 (17), stratifin (SFN; ref. 21), ubiquitin-conjugating enzyme E2C (UBE2C)], and DNA replication and repair [flap structure–specific endonuclease-1 (FEN1), minichromosome maintenance complexes 2 and 6 (MCM2 and MCM6), targeting protein for Xklp2 (TPX2) (21, 22)]. We then aimed to investigate these biomarkers in early-stage lung cancer and to gain a better understanding of the cellular and molecular processes that drive lung carcinogenesis.

Materials and Methods

Selection of biomarkers

Twenty-one biomarkers were selected by a team of investigators based on our preclinical work in cell lines as particularly important to lung carcinogenesis. The selected markers were: CASK, CD51 (also known as integrin-αV), CXCR2, EpCAM, FEN1, IGF-1R, IGFBP3, insulin receptor, MCM2 and MCM6, phospho-Akt, pAMPK, pEGFR, pIGF-1R, pmTOR, pS6, pSrc, SFN, SPP1, TPX2, UBE2C.

Identification of patients and gathering of clinical data

Patients with early stage (stages I, II, and IIIA) non–small cell lung cancer (NSCLC) who underwent surgical resection at MD Anderson Cancer Center between 2002 and 2005 were eligible for enrollment (Supplementary Fig. S1). Patients with stage IIIB or IV disease, surgery less extensive than a lobectomy, or a prior history of malignancy (other than non-melanoma skin cancer) were excluded from this analysis. A total of 370 patients were included in the analysis. Detailed clinical data were obtained from the electronic medical record and follow-up visits and direct contact with patients and/or their families, either by certified letter or telephone. OS was defined as time from tumor resection to death from any cause; recurrence-free survival (RFS) was defined as time from tumor resection to lung cancer recurrence or death.

Lung tumor specimens

NSCLC specimens from surgical cases were fixed using standard clinic protocols. Fixation in formalin occurred within 30 minutes of resection and the tissue stayed in formalin for 24 to 48 hours. Archival and de-identified FFPE specimens were analyzed. The use of tissues was approved by the Institutional Review Board at MD Anderson Cancer Center. After histologic examination of the NSCLC specimens by our dedicated pathologist, the tumor tissue microarrays (TMA) were constructed by obtaining three 1-mm-diameter cores from each tumor at 3 different sites (periphery, intermediate, and central). The TMAs were prepared using a manual tissue arrayer (Advanced Tissue Arrayer ATA100; Chemicon International).

Analysis of biomarkers

Biomarkers examined were: IGF-1R, IGFBP3, insulin receptor, phosphorylated-(p)AKT, phosphorylated-(p)IGF-1R, phosphorylated-(p)SRC, phosphorylated-(p)pmTOR, phosphorylated-(p)AMPK, phosphorylated-(p)EGFR, pS6, FEN1, MCM2, MCM6, SFN, TPX2, UBE2C, CASK, CD51, CXCR2, EpCAM, and SPP1. Antibodies were chosen because
they were shown to be specific by Western blot analysis using NSCLC cell lines and other cell line models, such as human bronchial epithelial cells. The same NSCLC cell lines tested by Western blot analysis were utilized for IHC optimization using cell line pellets fixed in formalin and embedded in paraffin. Those cell lines were used as controls when the TMAs were assayed by IHC.

IHC (Fig. 1) was performed on histology sections of FFPE tissue samples. See Supplementary Table S1 for details of antibodies used. The sections were deparaffinized, hydrated, subjected to antigen retrieval by heating in a steamer for 20 minutes with 10 mmol/L sodium citrate (pH 6.0), and then incubated in peroxidase-blocking reagent (DAKO). Sections were then washed with Tris-containing buffer and incubated overnight at 4°C with the primary antibodies. Subsequently, the sections were washed and incubated with secondary antibodies using the EVision Plus Labeled Polymer Kit (DAKO) for 30 minutes followed by incubation with avidin–biotin–peroxidase complex (DAKO) and development with diaminobenzidine chromogen for 5 minutes. Finally, the sections were rinsed in distilled water, counterstained with hematoxylin (DAKO), and mounted on glass slides before evaluation under the microscope. FFPE samples processed similarly, except for the omission of the primary antibody, were used as negative controls.

Experienced lung cancer pathologists blinded to the clinical data examined the immunostainings jointly at the same time using light microscopy to generate one set of readings (P. Yuan and I.I. Wistuba). The antigens studied exhibited different patterns of expression, including mainly nuclear (UBE2C, FEN1, MCM2, MCM6, SFN, SPP1, and TPX2), cytoplasmic (p-AMPK, IGF-1R, IGFBP3, insulin receptor, p-Akt, p-S6) and membrane (p-IGF-1R, p-Src, p-mTor, EpCAM) expression. The immunostainings were quantified using a 4-value intensity score (0, 1+, 2+, and 3+) and the percentage (0–100%) of tumor cells with reactivity in each core. The final score was then obtained by multiplying the intensity and reactivity extension values (range, 0–300) as previously reported (23–25). The same 2 pathologists also scored the samples for necrosis (measured in percentage of cells) and inflammation (graded as mild, moderate, or severe).

Statistical analysis

Summary statistics, including frequency tabulation, means, SDs, median, and range, were given to describe subject characteristics and biomarkers. The continuous markers were dichotomized by either 0 versus positive or median when appropriate after examining the martingale residuals. The Kaplan–Meier method was used to construct OS and RFS curves and log-rank test was used to test the
difference in survival by covariates. Univariate and multivariate Cox models were fitted to estimate the effect of prognostic factors, including age, gender, histology, stage, markers (continuous or dichotomized levels when appropriate) on time to event endpoints, including OS and RFS. All statistical tests were 2-sided, and \( P \) values of less than 0.05 were considered to be statistically significant.

The predictive accuracy of Cox regression models was quantified by C-index, which provides the area under the receiver operating characteristics curve for censored data (26, 27). A C-index of 0.5 indicates that outcomes are completely random, whereas a C-index of 1 indicates that the model is a perfect predictor. To protect against overfitting during stepwise regression, we used the bootstrap method for internal validation, which allows for computation of an unbiased estimate of predictive accuracy, C-index. We chose bootstrap method because it has been considered as the most efficient among the internal validation methods, data splitting, cross validation, and Bootstrap (28, 29). Calibration curves, which plot the average Kaplan–Meier estimate against the corresponding 1-, 3-, and 5-year predicted probability of OS or RFS rate (by equally dividing patients into 3 groups according to the predicted probability of surviving), were provided to evaluate the performance of the Cox models. We used 200 bootstrap samples in both bootstrap validation and calibration. All computations were carried out in SAS 9.2 and S-plus 8.0 or R 2.12.2.

Results

Patient demographics for the 370 participants with an average age of 65.7 years [SD 10.7, median 66.3, range (32.2, 90)] are shown in Table 1. Our population was evenly split between male and female, and the majority of patients were Caucasian (330 patients, 89%). Over 63% of patients had stage I disease, and most had adenocarcinoma (227, 61%). Most patients were treated only with surgery, although 128 patients (36%) received adjuvant treatment, either with chemotherapy or radiation, and 54 patients (15%) received preoperative therapy. With median follow-up time of 5.3 years, 160 deaths have been observed. A total of 209 cases with recurrence or death have been recorded to date. The median RFS time is 4.1 years [95%
clinical variables, remained significant predictors of outcome. Controlling for age and stage, the multivariate Cox model (Table 3) indicates that adjusting for age (HR = 1.024 per year increase, P = 0.001) and stage [HR = 1.765 (II) and 2.676 (III)] compared with stage I, P = 0.002 and <0.001, respectively], positive membrane insulin receptor (HR = 1.442, P = 0.012), cytoplasmic CXCR2 above the median (HR = 1.360, P = 0.038), and elevated IGF-1R (HR = 1.517 per 100 increase, P = 0.040) were found to be significant predictors for shorter RFS, whereas positive cytoplasmic pAMPK (HR = 0.648, P = 0.004), positive cytoplasmic pmTOR (HR = 0.696, P = 0.029), positive cytoplasmic EpCAM (HR = 0.708, P = 0.024), and higher membrane CASK (HR = 0.680 per 100 increase, P = 0.049) were associated with longer RFS.

Multivariate Cox model for OS

The multivariate Cox model for OS (Table 4) includes age, stage, and 5 biomarkers: age (HR = 1.028 per year increase, P = 0.001), stage [HR = 1.425 (II) and 2.620 (III) compared with stage I, P = 0.087 and <0.001, respectively], positive cytoplasmic pAMPK [HR = 0.669, P = 0.018], positive cytoplasmic pmTOR [HR = 0.662, P = 0.026], and positive cytoplasmic EpCAM [HR = 0.648, P = 0.012] were significant predictors for longer OS, whereas higher cytoplasmic CXCR2 [HR = 1.568, P = 0.007], and higher nuclear FEN1 [HR = 1.424, P = 0.035] were significant predictors for shorter OS.

Predictive accuracy of models

Predictive accuracy of the models from internal validation demonstrates good accuracy for predicting RFS and OS, with bootstrap-corrected C-index of 0.66 and 0.67 for RFS and OS, respectively. Calibration curves for 1-, 3-, and 5-year OS and RFS estimates revealed acceptable model calibration, with good correlation between the OS and RFS.

Table 2. Two- and 5-year RFS rates and OS rates by stage and biomarker groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>RFS (95% CI)</th>
<th>OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-year</td>
<td>5-year</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>74% (69–80%)</td>
<td>54% (48–61%)</td>
</tr>
<tr>
<td>II</td>
<td>57% (47–70%)</td>
<td>35% (25–48%)</td>
</tr>
<tr>
<td>III</td>
<td>41% (30–55%)</td>
<td>24% (15–38%)</td>
</tr>
<tr>
<td>m-Insulin receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>70% (64–76%)</td>
<td>48% (42–55%)</td>
</tr>
<tr>
<td>c-pAMPK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>58% (50–66%)</td>
<td>40% (33–49%)</td>
</tr>
<tr>
<td>0</td>
<td>55% (47–65%)</td>
<td>33% (25–44%)</td>
</tr>
<tr>
<td>c-pmTOR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>69% (64–75%)</td>
<td>50% (44–57%)</td>
</tr>
<tr>
<td>0</td>
<td>53% (44–65%)</td>
<td>34% (25–45%)</td>
</tr>
<tr>
<td>c-CXCR2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>69% (64–74%)</td>
<td>49% (43–55%)</td>
</tr>
<tr>
<td>&lt;Median</td>
<td>70% (63–77%)</td>
<td>49% (42–57%)</td>
</tr>
<tr>
<td>≥Median</td>
<td>61% (54–68%)</td>
<td>41% (35–49%)</td>
</tr>
<tr>
<td>c-EPCAM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>69% (63–75%)</td>
<td>49% (43–56%)</td>
</tr>
<tr>
<td>0</td>
<td>58% (50–67%)</td>
<td>39% (31–48%)</td>
</tr>
<tr>
<td>n-FEN1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>69% (63–75%)</td>
<td>49% (43–56%)</td>
</tr>
<tr>
<td>&lt;Median</td>
<td>69% (63–77%)</td>
<td>50% (43–58%)</td>
</tr>
<tr>
<td>≥Median</td>
<td>61% (54–68%)</td>
<td>41% (34–49%)</td>
</tr>
</tbody>
</table>
estimates from the multivariable Cox model and those derived from Kaplan–Meier estimates (Supplementary Fig. S2).

Stage I patients

We further evaluated the prognostic effect of these markers in stage I patients by Kaplan–Meier curves (Supplementary Fig. S3) and fitting the same multivariable models for RFS and OS, excluding stage variable (Supplementary Tables S2 and S3). Adjusted for age, cytoplasmic CXCR2, cytoplasmic pAMPK, and cytoplasmic pmTOR remained significant factors in RFS, and cytoplasmic pAMPK, cytoplasmic CXCR2, and nuclear FEN1 remained significant factors in OS. Positive cytoplasmic CXCR2 above the median (HR = 1.673, P = 0.01) was a significant predictor for shorter RFS, whereas positive cytoplasmic pAMPK (HR = 0.581, P = 0.009) and positive cytoplasmic pmTOR (HR = 0.511, P = 0.003) were significantly

### Table 3. Multivariable Cox model for RFS

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.024 (1.009–1.039)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stage (II vs. I)</td>
<td>1.765 (1.239–2.516)</td>
<td>0.002</td>
</tr>
<tr>
<td>(III vs. I)</td>
<td>2.676 (1.873–3.824)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>c-IGF-1R (per 100 increase)</td>
<td>1.517 (1.018–2.259)</td>
<td>0.040</td>
</tr>
<tr>
<td>m-Insulin receptor (Pos vs. 0)</td>
<td>1.442 (1.085–1.915)</td>
<td>0.012</td>
</tr>
<tr>
<td>c-pAMPK (Pos vs. 0)</td>
<td>0.648 (0.483–0.870)</td>
<td>0.004</td>
</tr>
<tr>
<td>c-pmTOR (Pos vs. 0)</td>
<td>0.696 (0.502–0.963)</td>
<td>0.029</td>
</tr>
<tr>
<td>c-CXCR2 (above vs. below median)</td>
<td>1.360 (1.017–1.820)</td>
<td>0.038</td>
</tr>
<tr>
<td>c-EPCAM (Pos vs. 0)</td>
<td>0.708 (0.524–0.956)</td>
<td>0.024</td>
</tr>
<tr>
<td>m-CASK (per 100 increase)</td>
<td>0.680 (0.470–0.998)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Abbreviations: c, cytoplasmic; m, membrane.

### Table 4. Multivariable Cox model for OS

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.028 (1.011–1.046)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stage (II vs. I)</td>
<td>1.425 (1.050–2.140)</td>
<td>0.087</td>
</tr>
<tr>
<td>(III vs. I)</td>
<td>2.820 (1.737–3.951)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>c-pAMPK (Pos vs. 0)</td>
<td>0.669 (0.480–0.932)</td>
<td>0.018</td>
</tr>
<tr>
<td>c-pmTOR (Pos vs. 0)</td>
<td>0.662 (0.460–0.952)</td>
<td>0.026</td>
</tr>
<tr>
<td>c-CXCR2 (above vs. below median)</td>
<td>1.568 (1.132–2.173)</td>
<td>0.007</td>
</tr>
<tr>
<td>c-EPCAM (Pos vs. 0)</td>
<td>0.648 (0.461–0.910)</td>
<td>0.012</td>
</tr>
<tr>
<td>n-FEN1 (above vs. below median)</td>
<td>1.424 (1.024–1.980)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Abbreviations: c, cytoplasmic; n, nuclear.
associated with longer RFS. Positive cytoplasmic pAMPK (HR = 0.505, $P = 0.003$) was a significant factor for longer OS, whereas higher cytoplasmic CXCR2 above median (HR = 1.954, $P = 0.004$), and higher nuclear FEN1 above median (HR = 2.116, $P = 0.001$) were significant predictors for shorter OS.

**Discussion**

We sought to investigate the impact of specific biomarkers and their relationship to outcome in early-stage patients with lung cancer. Based on our results, we have identified some important biomarker associations and begun early development of a risk model. Risk modeling is an evolving field in cancer biology. Studies incorporating clinical variables have evolved over the years (1, 2), and molecular epidemiology studies have identified germ line markers that predict for risk or benefit with certain interventions, including retinoids (30), statins (31), and celecoxib (32). The Director’s Challenge Consortium, which created a large microarray database of resected adenocarcinoma samples, found that models incorporating both clinical data and gene expression data had an improved predictive accuracy compared with models using either alone. Models with only clinical variables were comparable to models with gene expression data alone and no clinical data (33), suggesting the importance of combining the 2 approaches. Our risk model incorporates both biomarkers and clinical factors and includes all histologic subtypes of NSCLC.

We utilized immunohistochemistry because it is a widely available and clinically applicable technique, which can be applied to FFPE tissues. We studied a number of phosho-proteins, which are known to be labile, however, we collected these samples using routine clinical standards (fixation in paraffin in about 30 minutes after tissue was sliced and placement in formalin for less than 24 hours). As these markers were prognostic under these conditions, we believe that they could be useful in routine clinical practice as well.

Several of our markers have previously been described as prognostic. In our study, expression of EpCAM predicted for improved OS and RFS. The literature on this topic is mixed, with studies in some malignancies suggesting worse outcomes with higher expression of EpCAM and in other malignancies finding an association with improved prognosis in cancers of the thyroid, kidney, and oral cavity (34, 35). FEN1 was found to be predictive of shorter OS in our study. This protein is involved in the replication and repair of DNA and has been associated with high-grade tumors and poor prognosis (36). Another series from our institution confirmed our results by demonstrating that higher expression of FEN1 is a marker of poor prognosis in resected stage 1 lung cancer (22). IGF-1R predicted for shorter RFS in our group; this has previously been reported (37).

Our findings about pAMPK and pmTOR were intriguing; positivity for either marker was associated with improved RFS and OS. The mTOR signaling pathway is a complex pathway involved in energy sensing and control of cell growth (38). It has been implicated in carcinogenesis, and mTOR inhibitors are in clinical use for renal cell carcinoma and neuroendocrine tumors (39, 40). mTOR has been found to be a poor prognostic marker in other malignancies (41, 42), although other groups have reported that it is a marker of good prognosis in resected NSCLC (43, 44). Among its other roles, mTOR negatively regulates autophagy (45), which could explain why we found it to be a marker of good prognosis. Also, activity of mTOR is partially controlled by posttranslational mechanisms; therefore, mTOR expression may not correlate with mTOR activity (46). AMPK is a negative regulator of mTOR activity, so it is somewhat surprising that both are found to be markers of good prognosis; however, mTOR is also regulated by many other mechanisms (38). pAMPK has been reported as a marker of good prognosis elsewhere (20).

Our results suggest that individual protein IHC is unlikely to be clinically useful, as observed differences in outcome between favorable and unfavorable groups are small. Our study is somewhat limited because of a heterogeneous patient population, with multiple different histologies and with some patients who received adjuvant therapy and others who did not. We are not able to create a predictive model for the benefit of adjuvant chemotherapy based on our data. Although there have been numerous efforts by our group and others to create predictive and prognostic risk models, currently these models are not useful to select patients for therapy after surgical resection of NSCLC.

Lung cancer is a deadly malignancy, and cancer prevention and early detection are important goals. By gaining a better understanding of the biology of lung carcinogenesis, we hope to use this knowledge to accurately assess risk and personalize chemoprevention strategies following lung cancer resection.

**Disclosure of Potential Conflicts of Interest**

D.C. Rice is a consultant/advisory board member for Olympus America. No potential conflicts of interest were disclosed by the other authors.

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**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** K.A. Gold, E.S. Kim, P. Yuan, C. Behrens, L.M. Solis, D.C. Rice, I.I. Wistuba, W.K. Hong

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** K.A. Gold, E.S. Kim, D.D. Lai, P. Yuan, H. Kadara, I.I. Wistuba, J.J. Lee, W.K. Hong

**Writing, review, and/or revision of the manuscript:** K.A. Gold, E.S. Kim, P. Yuan, L.M. Solis, H. Kadara, D.C. Rice, I.I. Wistuba, W.L. Hofstetter, J.J. Lee, W.K. Hong

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** K.A. Gold, E.S. Kim, H. Kadara, W.K. Hong

**Study supervision:** K.A. Gold, E.S. Kim, W.K. Hong

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