**Is There Clinical Value to Prognostic Signatures in Early-Stage NSCLC?**

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pAMPK and pmTOR favorably predicted outcome in early non–small cell lung cancer (NSCLC). The differences were small. Phosphoprotein lability makes routine clinical use and validation difficult. Protein immunohistochemistry is unlikely to be clinically useful, and numerous efforts to create predictive models to select resected patients for therapy have been unsuccessful. *Clin Cancer Res*; 20(7); 1727–9. ©2014 AACR.

In this issue of *Clinical Cancer Research*, Gold and colleagues report on their study in which they attempted to define prognostic signatures to predict outcomes in patients with early-stage lung cancer who undergo surgical resection but are at risk for recurrence following the surgery (1). This study not only took on this difficult challenge but also attempted to develop a signature based on analysis of protein and/or activated protein expression by immunohistochemistry, targeting proteins identified through gene array data. The authors report that they were able to find several proteins that were significantly associated with either progression-free or overall survival, some of which were associated with improvement in both endpoints. However, the magnitude of the differences was small and there are many technical difficulties to the routine assessment of activated (phosphorylated) proteins highlighting the difficulties in creating predictive and prognostic risk models. Among these were pmTOR and pAMPK. These findings will add to evidence of their role in non–small cell lung cancer (NSCLC) and could lead to an explanation of why high mTOR expression was associated with a favorable outcome. However, the magnitude of the differences in progression-free and overall survival was small. As acknowledged by the authors, there are many technical difficulties to the routine assessment of activated (phosphorylated) proteins by immunohistochemistry. Furthermore, the study was complicated by a heterogeneous patient population, which could theoretically result in the impact of this approach being understated. Thus, the authors appropriately concluded that their findings were unlikely to be adopted clinically. Their findings also highlight the importance of the distinction between prognostic and predictive factors and the difficulty of validating proposed signatures for either prognosis or prediction of optimal therapy. The proposed commercial development of gene signatures highlights the importance of the issues.

Since the reports from Duke University that gene signatures could predict outcomes in surgically resected patients with NSCLC, there have been numerous reports that failed to validate their findings and numerous other reports that reported prognostic signatures with a different panel of genes (2–12). Still other studies have reported that DNA methylation profiles and microRNA signatures may also have prognostic relevance (13, 4). So why do we not have a clinically useful prognostic signature in lung cancer such as the mammprint or Oncotype DX signatures used in breast cancer? The lack of annotated tissues for validation and the lack of prospective studies in early-stage NSCLC are part of the reason. Interestingly, there is little overlap in the genes and proteins that best predicted outcomes, and the results of validation studies invariably showed lesser degrees of prognostic distinction (2–12). The studies illustrate many of the difficulties encountered in attempting such studies, including inadequate cases with tissue available for study, variations in assay methodology, variations in histology and clinical features, and the use of differing adjuvant therapies. Despite these difficulties, several prognostic signatures have been validated not only in the original series but also in some follow-up series demonstrating relatively large differences in the outcomes based on the signatures. In addition, the Squamous Lung Cancer Consortium supported by the National Cancer Institute’s (NCI) Specialized Program for Evaluation of Cancer Signatures is reevaluating many published gene signatures under standardized circumstances in terms of tissue processing, RNA extraction, histology, and clinical features both in a large prospective test set and a defined validation set.

The major question is what is the clinical relevance of these differences. Are any of these prognostic signatures predictive of benefit from adjuvant chemotherapy? Would the knowledge that a resected patient has a high or a low risk of relapse be associated with benefit (or lack thereof) from chemotherapy and thus affect the subsequent management? If this knowledge would affect
subsequent follow-up or therapy, then the utility of such an approach is clear. Figure 1 illustrates the differences between a signature that is prognostic only and one that is prognostic and predictive. Proof that one of the prognostic signatures is predictive would require a prospective randomized trial with randomization to adjuvant or no adjuvant chemotherapy.

Current therapeutic guidelines recommend that patients with completely resected stage I NSCLC receive no adjuvant therapy and that patients with stage II and IIIA NSCLC receive adjuvant chemotherapy (14, 15). Unfortunately, there is no convincing evidence that current gene signatures that predict a poor outcome in stage I would also indicate that such patients would have their poor outcome reversed by adjuvant chemotherapy. And there is no convincing evidence that stage II or III patients with a good signature would fail to benefit from adjuvant chemotherapy. Moreover, none of the signatures developed to date were designed to predict the best therapy that might be given in the adjuvant setting. Thus, there is a need for separating prognostic and predictive signatures, even if overlap may occur.

The design issues of these trials can be overcome, but it is unclear whether such trials are feasible with our current clinical trial infrastructure and accrual rates. The NCI-supported alliance attempted such a trial but it was closed for lack of accrual. We must hope that we can develop therapeutic choices that are less toxic and biomarker/signatures that better predict outcomes from these therapies and are also associated with prognosis. Currently, there are no prospective trials that are likely to identify signatures that are prognostic or predictive, although it is possible that the ALCHEMIST trials evaluating specific molecular changes with specific molecular therapies could serve some of this functionality. Obstacles include the potential need to evaluate multiple prognostic approaches from one source of tissue, controlling for adjuvant therapy selected with appropriate planned subgroup analysis, controlling for the prognostic information inherently seen in well-defined driver alterations and the need to evaluate single-analyte approaches as well as complex “signatures.”

The difficulties seen in this and other studies highlight the need for additional worldwide early-stage lung cancer clinical trials.

Disclosure of Potential Conflicts of Interest
P.A. Bunn Jr is a consultant/advisory board member for Myriad Genetics and Life Technologies. F.R. Hirsch is a consultant/advisory board member for Myriad Genetics. D.L. Aisner reports receiving speaker’s bureau honoraria from Illumina, Inc. and Abbott Molecular and is as a consultant/advisory board member for Boehringer Ingelheim.

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References


