Editorial

Indolence versus aggression in non-small cell lung cancer: defining heterogeneity to impact clinical outcomes

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While important new findings in the treatment of advanced non-small cell lung cancer (NSCLC) have led to significant progress, it has been incremental. In the past 30 years, the five-year survival rate for lung cancer has increased by only 5% (1). Despite the major survival advantage conferred to patients with localized disease, only 17% of NSCLC diagnoses were made at stage I–II as of 2014 (2). For this reason, considerable efforts have historically focused on improving early detection through development of screening programs. Following the publication of the NCI-funded National Lung Screening Trial (NLST), the Centers for Medicare and Medicaid Services (CMS) added annual low-dose computed tomography (LDCT) as a preventive service benefit in 2015. This has led to a rapid expansion of lung cancer screening programs. The NLST demonstrated a 20% relative reduction in cancer-specific mortality with annual LDCT screening in high-risk patients and resulted in a much improved probability of early stage disease at diagnosis (3). Specifically, amongst patients with screen-detected lung cancers, approximately 70% were stage I–II at diagnosis and over 50% were stage IA (3). The observation that screen-detected lung cancer is more likely to be at an early, localized stage is consistent with the findings of other large-scale prospective screening studies. Thus, the implementation of lung cancer screening programs is expected to lead to a stepwise increase in early stage diagnoses.

As our ability to detect lung cancer at an earlier stage improves, the focus must now shift to our therapeutic approach. The primary therapeutic option for localized disease is surgical resection. Despite considerable advances in surgical techniques and intraoperative pathologic evaluation, as many as 30% of patients have a recurrence during the 5 years following surgical resection (2). While adjuvant platinum-based chemotherapy is considered standard for the care of patients with stage II NSCLC following surgical resection, adjuvant chemotherapy for stage I disease remains controversial and is not overtly endorsed by major society guidelines. Several studies have suggested that some patients with stage IB disease may benefit from adjuvant chemotherapy, in particular those with larger tumor sizes (4,5). For this reason, NCCN guidelines currently recommend that adjuvant chemotherapy be considered for patients with stage I NSCLC with high-risk features, such as poor differentiation, vascular invasion, tumors >4 cm, visceral pleural involvement and/or incomplete lymph node sampling (6). This reflects the inability of the TNM staging system alone to identify which patients will benefit from a more aggressive therapeutic approach. A large meta-analysis performed by the Lung

Adjuvant Cisplatin Evaluation (LACE) collaborative group confirmed a survival benefit for patients receiving post-operative cisplatin-based chemotherapy except for those with stage IA disease, where an increase in mortality was observed (7). Recently, however, a study by Liu *et al*. suggested that patients with poorly-differentiated stage IA NSCLC who received post-operative chemotherapy had a survival benefit compared to those who only underwent resection (8). It should be noted, however, that this finding was shown by subgroup analysis and thus needs more rigorous evaluation in the future. While studies have not shown a clear benefit for multimodal treatment in patients with stage IA NSCLC thus far, it is reasonable to assume that this group is comprised of a heterogeneous population of cancers with a range of biological behaviors, and a proportion may benefit from a multimodal approach.

Improvement of the current decision criteria for selection of the patients with resected stage I NSCLC that would benefit from adjuvant chemotherapy is an unmet medical need. In order to address this need and improve upon our stage-based therapeutic approach, the development of predictive molecular assays has become a focus of research efforts. Early microarray studies demonstrated an association between gene expression profiles and survival in patients with NSCLC (9). As our technology has improved, it has led to further exploration of prognostic signatures, including gene expression-based and other "omic" approaches.

While a substantial number of studies have reported gene expression-based prognostic signatures for early stage NSCLC, none to date have successfully translated to improvements upon the current clinical approach. Early studies were plagued by a small sample size, single-institutional datasets and the lack of independent, external validation of the prognostic signature. In 2010, a critical review of 16 existing publications by Subramanian *et al*. underscored the need for a consistent approach to the development and validation of a prognostic signature for early stage NSCLC (9). The authors found that a minority of the studies reviewed reported a clear protocol for procurement of tissues and gene expression assays. Furthermore, the majority of studies did not clearly specify criteria for patient selection nor report data regarding known risk factors, thus raising serious concerns of sampling bias within the training data set. Finally, details of the analysis method and the actual prognostic model itself were often not provided. Instead, authors often only reported the genes included in the model and left out details such as weights and cut points. Poor transparency in documentation of patient selection, molecular and statistical methodologies, and models have had limited critical review and independent validation of published gene expression-based prognostic signatures.

Another barrier to the development of prognostic biomarkers is the lack of a widely accepted predictive model for early stage NSCLC that incorporates known clinicopathological risk factors, such as age, tumor size, and gender. As mentioned previously, current guidelines recommend consideration of these factors in therapeutic decision-making but provide no rule-based nor model-based guidance (6). As a result, there exists no gold standard for the comparison of gene expression profile performance characteristics. Shedden *et al*. were the first to evaluate gene expression classifiers with and without inclusion of clinical covariates in a large multi-institutional, blinded collaborative study (10). In this study, the researchers developed classifiers using several different computational methods to analyze the same high-quality gene expression data gathered across four sites using a standardized protocol. Validation for each classifier was conducted in two separate, independent datasets. While the study was not sufficiently powered to compare performance between each classifier method, the authors concluded that each gene expression classifier performed better when clinical covariates were included in the model.

In 2007, Bianchi *et al*. reported a 10-gene signature, detectable by real-time PCR (RT-qPCR), predictive of prognosis and overall survival in patients with stage I lung adenocarcinoma (11). Of note, the authors utilized a unique approach that integrated models derived from both biased and unbiased screenings to develop the final signature. This approach was aimed at reducing the high individual genetic noise that comes with the traditional, unbiased approach. As a result, the final model contained 5 genes derived from the biased *in vitro* E1A signature, 4 genes from the unbiased meta-analysis of existing microarray data and 1 gene from the literature. While the signature was robust and compared favorably to several other existing models, the clinical relevance was limited by the small size of the validation dataset.

In their recent publication in *Clinical Cancer Research*, Dama *et al*. further validated their 10-gene prognostic signature in a large, independent cohort of 507 patients with lung adenocarcinoma (12). The authors moved their signature towards clinical application by optimizing its use in formalin-fixed paraffin-embedded (FFPE) specimens.

Within the pooled cohort of 351 patients with stage I adenocarcinoma, the 10-gene signature identified high-risk patients with a significantly increased risk of death at 3 years [stage IA: HR =4.04 (1.11–14.66), P=0.03; stage IB: HR =3.83 (1.29–11.39), P=0.02]. Utilizing the Cancer Genome Atlas (TCGA) lung cancer database, the authors were able to further characterize the high-risk group identified by the classifier by examining mutational profile, copy number variation, DNA methylation and protein expression. This multi-omics approach showed consistently that patients categorized as high-risk using the 10-gene signature had stage I tumors with characteristics similar to more advanced tumors. Furthermore, they explored potential mechanisms underlying the aggressive behavior of the high-risk subgroup and noted alterations to the redox-sensitive transcription factor, nuclear factor (erythroid-derived 2)-like 2 (NFE2L2), which is known to be involved in chemotherapy resistance in lung cancer.

While Dama *et al*. have clearly moved their 10-gene signature closer toward clinical utility with this recent study, it should be noted that several other groups have recently reported their own gene expression-based prognostic signatures with validation in cohorts of similar size (13,14). Bueno *et al*. validated their own molecular expression signature, based on cell cycle progression (CCP score), in a cohort of over 600 patients with early stage lung adenocarcinoma (14). They were able to show a further improvement in the predictive ability of the CCP score when additional clinical factors were included in the model. The extent of the analysis performed by Dama *et al*. using the TCGA database represents an important strength of their work. Existing studies of prognostic biomarkers do not address the mechanisms underlying their gene expression profiles, which may limit their potential to define heterogeneity and apply precision therapies, thus leading to a meaningful clinical impact.

An additional area of concern related to application of therapy in this setting is that the paradigm that underlies most clinical trials is currently focused on drugs that promote growth inhibition rather than reduce metastatic behavior. Because tumor growth and metastases appear to encompass two distinct molecular pathways, it has been suggested that drug development targeting the biophysical properties of metastatic cells may be required (15). Finally, trial design for metastasis prevention in the clinical setting following surgery can be challenging due to both the large number of patients required and prolonged study duration (15).

As screening programs improve our ability to detect NSCLC at an early stage, it is increasingly important that we identify the subset of patients who are at high risk for recurrence following surgical resection. This most recent publication represents meaningful progress towards a useful prognostic biomarker in early stage NSCLC that notably attempts to understand the biology of the high-risk subgroup that it identifies. The challenge ahead for Dama *et al*. and the few other research groups who have reached large-scale validation is to translate their predictive models into the clinical setting. This will require large-scale prospective, randomized studies to show that the high-risk group identified by a prognostic signature will benefit from adjuvant chemotherapy or targeted therapies.

How can the accuracy of prediction be enhanced? Cellular and molecular elements related to the tumor microenvironment (16) as well as imaging characteristics (17) of the tumor and lung parenchyma are additional areas of rich datasets that can be integrated with gene expression and other "omic" data to reveal outcomes. Importantly, the knowledge gained from a systems approach can enable precision medicine with therapies linked to individual characteristics as well as disease aggressiveness.

To address the problem of distinguishing aggressive versus indolent disease in early stage cancer, the National Cancer Institute recently funded the Molecular Characterization Laboratories: a consortium focused on molecular characterization of screen-detected lesions comprised of seven centers throughout the US (18). Two of these centers focus on lung cancer. For example, the UCLA-Boston University Integrated Molecular, Cellular and Imaging Characterization Center takes advantage of a multi-disciplinary team to undertake a comprehensive molecular characterization of tumor cell (including whole exome and RNA sequencing), microenvironment components and imaging features of screen-detected early cancers and non-screen-detected lung cancers. It should be noted that the majority of genomic profiling studies to date, including Dama *et al*., have focused on incidental tumors. For this reason, the UCLA-Boston University Integrated Molecular, Cellular and Imaging Characterization Center will provide novel insight into the differential characteristics of screen-detected lung cancers.

Understanding the factors underlying tumor indolence or aggression that result in heterogeneous clinical outcomes may facilitate clinical decision-making in the context of lung cancer screening and thereby greatly increase its effectiveness. The pathways underlying heterogeneity in screen-detected lung cancers may be revealed by

an integrated systems analysis of molecular, cellular, microenvironment and imaging characteristics of screen-detected lesions.

The detailed molecular and imaging-based characterization of screen-detected tumors will ultimately impact clinical management of those cancers. Beyond determining the aggressiveness of treatment for early stage disease, insight into the molecular heterogeneity that underlies screen-detected lung cancer will help usher in the era of personalized targeted therapy to the screening setting. Molecular characterization of the tumor microenvironment will enable development and application of new forms of immunotherapy for screen-detected tumors, a promising avenue of treatment for lung cancer. Integration of these cellular and molecular findings with imaging-based features of disease will enable development of less invasive markers of disease outcome that can be routinely applied in the clinical setting.

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Footnote

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References

1. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271-89.
2. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD. Available online: http://seer.cancer.gov/csr/1975_2012/
3. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
4. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589-97.
5. Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-51.
6. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. Non-small cell lung cancer (Version 3.2015). Available online: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp
7. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.
8. Liu CH, Peng YJ, Wang HH, et al. Heterogeneous prognosis and adjuvant chemotherapy in pathological stage I non-small cell lung cancer patients. Thorac Cancer 2015;6:620-8.
9. Subramanian J, Simon R. Gene expression-based prognostic signatures in lung cancer: ready for clinical use? J Natl Cancer Inst 2010;102:464-74.
10. Director's Challenge Consortium for the Molecular Classification of Lung Adenocarcinoma, Shedden K, Taylor JM, et al. Gene expression-based survival prediction in lung adenocarcinoma: a multi-site, blinded validation

study. Nat Med 2008;14:822-7.
11. Bianchi F, Nuciforo P, Vecchi M, et al. Survival prediction of stage I lung adenocarcinomas by expression of 10 genes. J Clin Invest 2007;117:3436-44.
12. Dama E, Melocchi V, Dezi F, et al. An Aggressive Subtype of Stage I Lung Adenocarcinoma with Molecular and Prognostic Characteristics Typical of Advanced Lung Cancers. Clin Cancer Res 2017;23:62-72.
13. Kratz JR, He J, Van Den Eeden SK, et al. A practical molecular assay to predict survival in resected non-squamous, non-small-cell lung cancer: development and international validation studies. Lancet 2012;379:823-32.
14. Bueno R, Hughes E, Wagner S, et al. Validation of a molecular and pathological model for five-year mortality risk in patients with early stage lung adenocarcinoma. J Thorac Oncol 2015;10:67-73.
15. Fontebasso Y, Dubinett SM. Drug Development for Metastasis Prevention. Crit Rev Oncog 2015;20:449-73.
16. Donnem T, Kilvaer TK, Andersen S, et al. Strategies for clinical implementation of TNM-Immunoscore in resected nonsmall-cell lung cancer. Ann Oncol 2016;27:225-32.
17. Liu Y, Balagurunathan Y, Atwater T, et al. Radiological Image traits Predictive of Cancer Status in Pulmonary Nodules. Clin Cancer Res 2016. [Epub ahead of print].
18. Consortium for Molecular Characterization of Screen-Detected Lesions. Available online: https://prevention.cancer.gov/news-and-events/news/consortium-molecular

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