added to the work of Martini and Melamed with similar effect, but in a different manner through adding foundational elements that shape a new paradigm in which SPLCs and IPMs can be evaluated. As their work establishes the preliminary findings for others to stand on, Zheng and colleagues most assuredly will demonstrate that they have broad shoulders as well.

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Commentary: How to "spot" a leopard: It's in the genes

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CENTRAL MESSAGE

Next-generation sequencing should be performed on all multifocal lung cancer, but how to apply this information requires further thought and investigation.

One of the truly important, yet confounding, questions in thoracic oncology is how to approach multifocal non–small cell lung cancer (NSCLC). It remains an elemental question in regard to our approach to preoperative staging—a critical time for both the patient and the clinicians. A moment when our treatment decisions have the longest reach of effect. The Tumor Board's task of deciphering the multifocal decision tree is an immensely tangled puzzle with no right answer glaring back at us no matter how hard we study it. Confounding matters further are the treatment pathway biases of each individual institution, tainting any ability to approach this problem from a uniform methodology.

The hope of next-generation sequencing (NGS) is to dispel the mystery of multifocal NSCLC. As long as we have tissue, we can hope to identify a synchronous primary lung cancer (SPLC) or intrapulmonary metastasis (IPM) simply by looking its genetic code.

Underlying this hope are a lot of assumptions, assumptions that require good science to parcel them out. In my mind, there are 2 elemental questions in regard to applying NGS to multifocal NSCLC: (1) when to test and (2) which is the best test.

Zheng and colleagues[1] has taken on the question of multifocal NSCLC by examining their own database using a custom NGS panel. According to the authors, this is the first paper to examine what happens when NGS is not employed on multifocal NSCLC.

From the 18 tumor pairs examined via NGS, 8 were downstaged from IPM to SPLC. This is a staggering 44% reduction in stage with obvious treatment implications, albeit in hindsight. Importantly, this study showed what we would hope to see from any applied technology: an improvement in accurately making a diagnosis. In this case, 22% of IPMs were rediagnosed as SPLC that histopathology assessment alone failed to correctly identify. In developing their own NGS, the authors took cost, specimen volume, and time to analyze into account to produce a test, according to the authors, that is cheap, reliable, quick, and comparatively requires very little tissue.

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Despite its favorable results, the significant limitations of this paper underlie the problem of multifocal NSCLC. Specifically, this study is a small, single-center retrospective study with 18 total pairs of which 90.2% are adenocarcinoma. Also, 16% of the pairs do not have an identifiable driver mutation despite the homogeneity of the dataset. These issues demonstrate the complexity of defining and treating multifocal NSCLC. NGS is not a silver bullet, forcing clinicians to find additional and overlapping tests to differentiate SPLC and IMP.

The central benefit of this study is not to answer how we should approach multifocal NSCLC once and for all. Instead we need to ask "Does the test add value? Does it change treatment?" By accepting the results of Zheng and colleagues in this light, the simple answer is yes; the crucial caveat is that we still have a long way to go.

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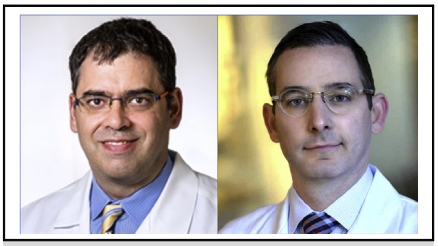
Commentary: The A, C, G, and Ts of differentiating stage I and stage IV lung cancer

Ory Wiesel, MD,[a] and Bryan M. Burt, MD[b]



Ory Wiesel, MD, and Bryan M. Burt, MD

CENTRAL MESSAGE

Molecular profiling will resolve the long-standing staging uncertainty around multiple non–small cell lung cancers.

Discriminating 2 non–small cell lung cancers (NSCLCs) in the same individual as separate primary lung cancers or intrapulmonary metastatic disease remains a formidable challenge. Whether found at the same or different times, these patients contend with a gnawing uncertainty about whether they have 2 early-stage cancers curable with surgery or stage IV metastatic disease and its unnerving survival. Moreover, physicians caring for these patients are faced with difficult treatment decisions surrounding the utility of systemic therapy that stymie their tumor boards.

It has been almost half a century since Martini and Melamed introduced a system for distinguishing synchronous primary NSCLCs from intrapulmonary metastases. Aside from the separation of NSCLCs by broad histologic categories, this time-honored system is based on empiric criteria including tumor location in the same anatomic segment or lobe, disease in shared lymphatics, extrapulmonary metastases, and a relatively arbitrary time interval between tumors. Although these criteria have retained their state-of-the-art position for decades, they are imprecise and far from definitive.

In our current era of precision medicine, we prescribe drugs that target the secondary mutations that develop as resistance mechanisms to initial targeted molecular therapy for subtypes of subtypes of lung cancer. It is in some ways shocking that genetically discriminating multiple primary lung cancers from metastatic disease is currently not a standard, even reflex practice. It has been only 16 years, however, since the human genome was sequenced, and the practical use of genomics is being rapidly adopted in medicine.

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