Commentary: How to “spot” a leopard: It’s in the genes

John F. Lazar, MD

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 colleagues1 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.

References
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.

Reference