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

1. Zheng R, Shen Q, Mardekian S, Solomides C, Wang Z-X, Evans NR. Molecular profiling of key driver genes improves staging accuracy in multifocal non–small cell lung cancer. *J Thorac Cardiovasc Surg*. 2020;160:e71-9.

See Article page e71.

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

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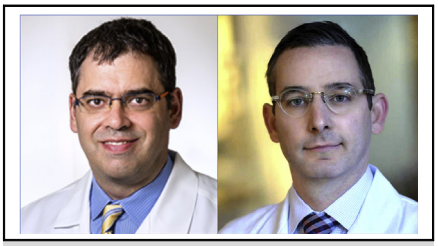

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CENTRAL MESSAGE

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.

Zheng and colleagues[1] applied a 4-gene mutation panel of 4 oncogenes common in NSCLC (KRAS, EGFR, BRAF, and NRAS) to a cohort of 18 patients treated surgically for multifocal NSCLC. The authors combine this

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molecular assay with histologic evaluation that maximizes our contemporary understanding of lung adenocarcinoma subclass histology, using the International Association for the Study of Lung classification system. The authors demonstrate that this combined platform improved staging accuracy for multiple NSCLC lesions. In their modest sample of 18 patients, 22% of tumor pairs were identified as multiple primary lung cancers after conventional histologic assessment could not, showcasing how the addition of basic genomic information can resolve critical staging gridlocks.

We can expect a series of articles corroborating these and other published molecular staging data in NSCLC and that expand the reach of these platforms. Seventeen percent of tumor pairs in the current study did not express any of the 4 driver mutations included in the panel, suggesting that the inclusion of additional mutations and/or expanded sequencing (whole genome in select cases, for example) may be required improve test characteristics and enable widespread applicability. Perhaps the most important element of the study by Zheng and colleagues was exploratory but demonstrated that a substantial fraction of molecularly downstaged patients were overtreated with cytotoxic chemotherapy. These findings highlight the magnitude of importance of initial best staging on assignment of survival-altering therapy and refresh our rationale for molecular staging.

Reference

1. Zheng R, Shen Q, Mardekian S, Solomides C, Wang Z-X, Evans NR. Molecular profiling of key driver genes improves staging accuracy in multifocal non–small cell lung cancer. *J Thorac Cardiovasc Surg*. 2020;160:e71-9.