Editorial Commentary

Challenges in diagnosis and management of patients with synchronous multiple primary lung cancers

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Lung cancer stands as the primary contributor to cancer-related fatalities globally, causing an estimated 1.8 million deaths in 2020 alone (1). Of lung cancer patients referred for surgical resection, 15% or more present with more than one lung nodule (2). If two or more lung nodules are in fact cancer, this represents one of two clinical scenarios. The first is intrapulmonary metastasis (IPM) and the second possibility is synchronous multiple primary lung cancer (SMPLC)—defined as multiple unrelated primary lung cancers at the same time (3). Clinical differentiation of these two distinct scenarios is difficult, often misunderstood, and can frequently result in inaccurate staging, leading to inappropriate treatment of these patients.

It is challenging to manage patients presenting with two or more distinct and suspicious lung nodules. As a result of misperceptions, these lung nodules are frequently considered IPM. Radiographic reports often focus on the larger high-index lesion and fail to comment on secondary lung nodule(s). Alternatively, there is a tendency to interpret multiple lung nodules as "metastatic disease". Biopsies are not helpful either, as tumors with the same histology within the same lobe might be incorrectly categorized as metastatic disease. However, the same histology does not prove IPM. In fact, nearly 80% of patients with SMPLC have similar or the same histology (4). Next-generation sequencing technology holds significant promise and has demonstrated the ability to accurately differentiate SMPLC from metastasis in over 90% of cases (5,6). Nevertheless, this approach is still in its infancy (7).

The modified Martini-Melamed criteria offer a different perspective (4). According to these criteria, *in situ* diseases or tumors of the same histological subtype lacking positive intervening lymph nodes are classified as SMPLC. Modifications of these criteria have been accepted to include histologic sub-typing (4).

SMPLC are frequently misunderstood by clinicians caring for lung cancer patients, which may lead to severe repercussions. In the worst-case scenario, the patient with two small bilateral stage I non-small cell lung cancer is mislabeled as stage IV. Since the treatment for stage IV disease is not curative, this patient will unnecessarily succumb to the disease despite it being potentially curable. These are critical implications in approximately 1 in 5 lung cancer patients, yet there seems to be an insufficient emphasis on addressing this issue.

The large variability in the reported incidence of SMPLC reflects the wide range of understanding by clinicians. The incidence of SMPLC ranges from 2.6% in 2018 to over 20% by our group in 2023 (8,9). Both the World Health Organization (WHO) and the International Association for the Study of Lung Cancer (IASLC) recognize the challenges faced by patients with multiple lung cancers and have made several recommendations (10,11). In 2015, the WHO recommended the use of a multidisciplinary tumor board to improve the accurate diagnosis of these patients—a recommendation we firmly endorse. The IASLC has presented guidelines to enhance the management of these patients, but often combines issues related to IPM and

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SMPLC, leaving a void, and at times, inconsistency.

The nomenclature may add to the confusion. It is our impression that multiple primary lung cancers (MPLC), SMPLC, metachronous MPLC (MMPLC), and IPM are frequently misused in the literature, national presentations, and while discussing patients amongst colleagues. For clarity, MPLCs refer to unrelated tumors occurring at the same time (synchronous) or at separate times (metachronous). IPM are advanced cancers that have spread to a secondary site in the lung and represent T3 (ipsilateral same lobe), T4 (ipsilateral different lobe), or M1a (contralateral lung) disease. In the absence of metastasis to the intervening lymph node(s) and/or extrapulmonary sites, IPM is a surprisingly uncommon event. There is no evidence that lung cancer has any proclivity to spread to the lung. In fact, there is mounting evidence based on surgical survival data that this scenario almost never happens.

From a clinical perspective, we recommend that patients with multiple suspicious pulmonary nodules to be evaluated with imaging, including chest computed tomography scan, positron emission tomography scan, and magnetitic resonance imaging, as well as invasive mediastinal staging to determine nodal status. We also advise against biopsies targeted at multiple nodules. Boldly stated, same histology does not mean metastatic disease or IPM. Following a thorough preoperative work-up, these patients should be presented at a multidisciplinary tumor board led by thoracic surgeons (12).

The future implications of the recent advances in radiographic imaging in patients with multiple primary nodules are encouraging. Detecting lung nodules, distinguishing between benign and malignant nodules, and characterizing histology may be enhanced with the advent of artificial intelligence (13,14). However, future studies must delineate their clinical significance and role in detecting SMPLC.

Typically, surgical resection remains the cornerstone of treatment. Sub-lobar resection has been proven to be non-inferior to lobar resection and may be favored due to its ability to preserve lung function. For bilateral lesions, there appears to be no substantial difference in outcomes between one- and two-stage video-assisted thoracoscopic surgery, although the latter might offer advantages, especially in elderly patients (15). In high-risk patients, particularly those with residual lesion(s) following initial surgery, a combination of surgical intervention and another treatment modality, such as ablation, stereotactic body radiation therapy, or immunotherapy, may be employed (16).

Finally, we suggest modifying the nomenclature, replacing synchronous to simultaneous (SMPLC) and metachronous with non-simultaneous (NSMPLC) when discussing patients with MPLCs.

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