Peer Review File
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Review Comments

Reviewer A

The subject of the paper is interesting and topical. The paper is well written, clear in explanations. The content and structure are appropriate for an Editorial Commentary, considering the length of the paper and the topics covered in a non-overly specific manner. I find the paper useful because it emphasizes the importance of thinking about SMPLCs in patients with molteplici lung lesions suspected for neoplasia.

Reply: Thank you for your kind remarks. We are glad you enjoyed our manuscript.

Reviewer B

Recently, the treatment methods for lung cancer have changed significantly with the advent of molecular target drugs and immunotherapy that can now be used as a therapeutic agent in clinical practice. However, before treatment, it is important to have an accurate diagnosis. Diagnosis involves pathological diagnosis as clear evidence of cancer, genetic and immunological diagnosis, which has become essential for selecting therapeutic drugs, and stage diagnosis, which is the theme of this research. In general clinical practice, pathological diagnosis is performed by tissue biopsy starting from the tumor that is thought to be the largest primary tumor, and smaller lesions are considered to be metastatic lesions. In actual clinical practice, tissue collection from different lung lobe lesions is rarely performed. If we can obtain more evidence to suspect SMPLC through image diagnosis, which is the theme of this research, we will be able to take a step forward and provide treatments that are even more beneficial to patients. Recently, after treatment with molecular-targeted drugs, re-biopsy is being performed when resistance is detected and recurrence occurs. For patients, if there is clear evidence, biopsies from different lung lobes should be performed at the initial diagnosis to diagnose the disease stage. Clear evidence will be needed for this in the future, so I think this paper makes very important recommendations.

Reply: Thank you for your thorough review and kind remarks. We agree with you in that there is a dire need for ongoing research to evaluate the role of biopsies in the treatment of these patients, as well as continued assessment of preoperative radiographic images to help distinguish between SMPLC and IPM.

Finally, as a supplement, I felt that the comments would be more clinically relevant if there was a discussion not only about MDT but also about the future, which is the basis for image diagnosis.

Reply: We agree and have included a brief discussion on future implications:

Changes in text: “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.” Please see page 4.

Reviewer C

The article presents crucial information regarding the differentiation between metastatic lung cancer and multiple primary lung cancer in patients with multiple pulmonary nodules. Despite its relevance, there are areas that could be significantly improved:

Reply: Thank you for your thorough review.

Firstly, the references cited in the article are notably outdated. Ensuring the robustness of the claims, it is essential to rely on up-to-date data and evidence. The statistics provided in the article, such as the incidence of SMPLC, should be supported by recent and reliable data.

Reply: We have updated our reference on the incidence of SMPLC to include our most recent article that is currently in-press.

Changes in text: “The incidence of SMPLC ranges from 2.6% in 2018 to over 20% by our group in 2023 (7, 11)” on Page 3; “Next-generation sequencing technology holds significant promise and has demonstrated the ability to accurately differentiate SMPLC from metastasis in over 90% of cases (7, 8)” on Page 2.

Additionally, an error has been detected in the bibliographic references: citation number "9" is missing. Addressing these issues, the article titled "Challenges in Diagnosis and Management of Patients with Synchronous Multiple Primary Tumors" could meet the necessary standards for publication.

Reply: We apologize for the confusion. We suspect that the formatting may have changed upon submission. In our copy, citation 9 (now citation 10) (Detterbeck et al. J Thorac Oncol, 2016;11(5):639-50) is mentioned in the discussion: “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).”

Reviewer D

The criteria used to determine SMPLC were initially based on tumor locations and histological findings. It was difficult to validate the clinicopathological assessment and to distinguish primary lung cancer from metastasis. We agree with the points in the article that new accurate nomenclature, replacing SMPLC, need to be proposed. Obviously, Solid nodules are significantly different from ground glass opacity (GGO) nodules, and GGO nodules are primary tumors rather than metastases. With the recent advance of molecular biology, researchers have assessed molecular genetic characteristics using various markers, it may be useful to help define SMPLC.

Reply: Thank you for your kind remarks.