Editorial

Separate or intrapulmonary metastasis?

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Multiple primary lung cancers (MPLCs) appear to be increasing in global frequency. This may be a result of improvements in the resolution of cross-sectional imaging technology, as well as increased rates of low-dose chest computed-tomography screening programs. The incidence of MPLCs among patients with non-small cell lung cancer varies from 0.2% to 20% (1). Diagnosis and management of MPLCs remains controversial, as criteria for identifying MPLCs have been proposed and standardized for years (2,3), we still lack reliable and robust means of clearly discriminating patients with MPLCs from those with intrapulmonary foci of metastatic disease.

Surgical results for MPLCs have been reported as acceptable and compatible for patients with solitary primary lung cancer (4-6). Additional studies have documented the dominant tumor (DT) in MPLCs possesses a crucial prognostic role. Chen *et al.* (7), in *The Journal of Thoracic and Cardiovascular Surgery*, describe the experience of 96 patients over a 7-year period who underwent surgical excision of two or more malignant pulmonary lesions (according to the clinical-pathological criteria for MPLCs). Patients were categorized according to the tumors' characteristics (preoperative radiological appearances). In addition to the DT, the relationship among the secondary nodule (SN) in MPLCs was also investigated. Group A included patients with ground glass opacity (GGO)-dominant lesions, group B included patients who had primary solid nodules with additional secondary GGOs, and group C included patients whose primary and secondary lesions were all solid in nature and evaluate surgical outcomes (8). A significant difference was observed among the 3 groups and an overall favorable prognosis was identified in patients with MPLCs. These results support a role for different strategies that could be applied when treating patients with metastatic disease.

Available resected specimens were also examined for genetic mutations (82 samples originating from 39 patients) and distinct metastatic versus synchronous diseases, such as somatic mutations in *EGFR*, *TP53*, *PIK3CA*, and *BRAF* genes, as well as EML4-ALK, ROS1, and RET fusions. The results revealed a high rate of different mutations across tumor types (94% discordance rate when mutations were identified) and a significant difference in the recurrence rate between patients who had discordant driver mutations and consistent driver mutations (5.7% *vs.* 100%).

Important issues have been raised by the contributions of Chen *et al.* First, multiple foci GGOs have excellent surgical outcomes. The 5-year overall and recurrence-free survival were both recorded as 100% in multiple GGOs group (group A). Interestingly, a high discrepancy between genetic abnormalities was observed when comparing resected GGOs in group A, suggesting multiple foci GGOs developed as separate primary tumors rather than as intrapulmonary metastases. Importantly, most of the residual GGOs in this group (10 out of 11) had no change at follow-up. Consistent with previous studies (9), observation of the patients without further adjuvant (or target) therapy for residual GGOs should be advocated, even the driver mutations were detected. On the other hand, excellent

surgical outcomes in multiple foci GGOs raises other possible strategies to manage this group of patients—do we need to resect all the foci of GGOs (included SN) even if losing lung parenchyma during a concurrent operation may occur? Should we perform sequential excision for the contralateral GGOs considering resection of the ipsilateral DT showed only minimally invasive adenocarcinoma or adenocarcinoma *in situ*? There is still a lack of evidence that compares surgery with other treatment modalities for this group. In the near future, surgical resection will be challenged by other local treatment modalities, such as local ablation therapy, stereotactic radiation, and observation-only for this group of patients.

Secondly, categorizing patients by MPLC subgroup may offer a link to survival. Gu *et al.* (4) have reported on a series of patients with dominant adenocarcinoma with multifocal GGOs that does not behave as advanced disease. This confirms Chen and colleagues' finding that a surgical approach improved survival in this group of MPLCs (group B in Chen's study). Shimada *et al.* (9) also demonstrated that survival of patients with MPLCs is strongly affected by radiological findings of the DT. Therefore, rigorous determination and surgical control for DT is an important surgical approach for MPLCs. Chen *et al.* also inspires thoracic surgeons to ruminate over the question of how extension of parenchyma resection should be planned in order to manage patients with MPLCs. For example, in group A, MPLCs (multiple GGOs groups), parenchyma preservation is reasonable due to the observed excellent surgical outcomes. Also, left the central location GGOs foci observation looks properly. On the contrary, in groups B and C, aggressive anatomic resection (segmentectomy or lobectomy) with radical lymph node dissection should be considered based on the location of the DT, whereas limited resection is considered suitable for the SN. Determination of DT could be based on the solid components on HRCT and FDG uptake by PET as Chen and colleagues suggested (7).

Third, high discrepancy of genetic features among patients with MPLCs is linked to disease recurrence. Ideally, it is possible that the genetic assays are included into the clinical and pathological criteria used to separate MPLCs from intrapulmonary metastases. Unfortunately, in clinical practice, obtaining multiple biopsies pre-operatively for different individual tumors in MPLCs in a single patient is not clinical practically. Moreover, the small specimens obtained from multiple core biopsies are not able to represent all genetic features of each tumor in MPLCs. Biological examinations could be performed assuming that independent tumor clones harbor distinct mutations, but not vice versa. Not surprisingly, as reported by Chen and colleagues, 2 patients in group C (solid-solid MPLCs) had concordant driver mutations between the 2 lesions, which strongly suggests they were more likely to have intrapulmonary metastases, and both of them had tumor recurrence. Although this genetic criterion could be applied to the indication for further aggressive adjuvant treatments in MPLCs, such as treatment of advanced stage lung cancers, additional evidence combined with clinical, pathological, and genetic criteria acumination is mandatory. In brief, the data regarding molecular genetic features of MPLCs should be taken into account but should not be regarded as definitive unto themselves (3). An optimal strategy to manage MPLCs has been suggested by Martini and Melamed's (2) criteria and ACCP guidelines (10), which may already be accurate enough to clarify such a distinction.

Although there are various limitations of this study and they have been adequately presented by Chen and colleagues, the value of this study remains significant. This study provides compelling evidence that an aggressive surgical approach should be considered as a treatment modality and reinforces the opportunity to discriminate MPLCs from the intrapulmonary metastases of currently clinical and pathological criteria. Finally, the treatment strategy for MPLCs should be carefully evaluated with discussion of an experienced multidisciplinary team that recognizes a favorable prognosis in select surgical patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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