Lung nodule in patients with extrathoracic primary cancer—not always what it seems

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Comment on: Karjula T, Niskakangas A, Mustonen O, *et al.* Results of intention-to-treat pulmonary metastasectomies in northern Finland revealing significant number of new lung primary carcinomas: time to move on from wedge resections? J Thorac Dis 2023;15:3319-29.

In the current study by Karjula *et al.*, the colleagues examined patients who underwent surgery for pulmonary metastasectomy at their hospital between 2000 and 2020. In total, they were able to include 127 patients with different primary tumors. The colleagues found primary lung cancer in 9.7% of patients, benign findings in 13.0%, and lymphoma in 0.6%. The remaining cases were metastases from their extrathoracic primary (76.7%) (1). For many extrathoracic carcinomas, initial staging as well as follow-up includes computed tomography of the chest. It is not uncommon that unclear pulmonary lesions are diagnosed. Like in the present study, in addition to benign findings, metastases or secondary carcinomas in the sense of a lung cancer may be the histology of the lesions. It is known from the literature that in patients with breast carcinoma and a singular pulmonary nodule, approximately 60% are lung carcinomas, about 30% are metastases and about 10% are benign findings (2). In our clinic, we once analyzed 139 patients with the differential diagnosis of pulmonary metastases of a urothelium carcinoma. Of these patients, 86% had a malignant lesion and 14% had a benign lesion. The most common diagnosis of the malignant lesions was lung cancer (53%), followed by metastases of urothelial carcinoma 38% and other malignancies (9%) (3). These results, as well as the current results of the Finnish colleagues, show that metastases cannot always be assumed in the presence of a pulmonary nodule and preexisting extrathoracic primary cancer.

In addition to these results, Karjula *et al.* investigated predictors regarding lung cancers in their patients. Only a disease-free interval longer than 24 months showed a significant result (1).

Looking at the literature, different studies have also investigated predictors of lung cancer in solitary lung lesions after extrathoracic primary cancer. Nakadate *et al.* found that radiologic parameters, such as spiculation, non-homogeneous density or pleural indentation, as well as smoking history and the type of primary cancer, were predictive against metastases and predictive for lung cancer (4). Other studies have investigated whether differentiation by positron emission tomography computed tomography (PET-CT) and CT radiomics features is possible. Studies have come to different conclusions in this regard (5,6). Li *et al.* investigated whether artificial intelligence may distinguish between a metastasis, a lung cancer, and a benign lesion. Good accuracy was achieved for lung cancer, but the accuracy for benign findings and metastases was low at 40.8% and 50.9%, respectively (7).

Even though progress is being made in imaging diagnostics including artificial intelligence, ultimately only the pathologist can make a clear statement. However, even

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for pathologists, accurate differentiation is sometimes not possible with certainty. For example, it is precisely in the frozen section examination that a distinction can be made between adenocarcinoma and squamous cell carcinoma. However, if the patient has squamous cell carcinoma as extrathoracic primary and the lung finding in the frozen section diagnosis is also squamous cell cancer, it is not possible to make a distinction without additional immunohistochemical examinations. The WHO itself requires an immunohistochemical examination for the determination of whether it is lung cancer or not (8). Thus, without it, the pathologist can only make a probability but not a definite judgment in the frozen section examination. Another option is gaining a preoperative histology via CT-guided or transbronchial biobsy. However, this is not always possible due to the size and location of the foci. If the lesions are peripheral, a thoracoscopic workup with wedge resection is also possible; followed by an anatomic resection including lymph node dissection when the pathologist finds a different histology in the frozen section or the final pathology has been a lung cancer.

However, based on their results, the colleagues of the present study postulate that in patients with a long disease-free interval as well as a smoking history, a primary segmentecomy could be considered as the primary extent of resection (1).

Because the extent of resection of metastasis differs from that of lung cancers, preoperative nondifferentiation may present the thoracic surgeon with a dilemma. This is the reason why Karjula *et al.* might recommend primary segmentectomy in some cases. Welter *et al.* were able to show that in case of lung metastases a different safety margin is required for metastasectomy depending on the extrathoracic primaries (9). Similarly, Renaud *et al.* were able to show that this may even differ depending on the mutational status within a tumor entity (10). However, it is important to note that metastasis usually does not necessarily require anatomic resection, so primary segmentectomy may lead to overtherapy. Approximately 40% of patients may suffer recurrent metastases and may benefit from reoperation (11). Previous anatomic resection leads to more adhesions to hilar structures and may complicate reoperation. However, even if the latest studies are showing that sublobar resections are acceptable for lung cancers smaller than 2 cm, most of them are segmentectomies (12,13). Whether wedge resection is adequate for lung cancers smaller than 2 cm may become apparent in the future. Nevertheless, lymph nodes were dissected in these studies (12,13). For this reason, in the case of unclear pulmonary lesions, the question arises firstly about the type of resection and secondly about the lymph node dissection to do justice to the patient.

Overall, the study by Karjula *et al.* confirms the literature and highlights that in the case of unclear pulmonary lesion and extrathoracic primary cancer, one cannot necessarily assume metastasis. This is an important aspect to be considered in interdisciplinary tumor conferences. The decision whether a preoperative histologic workup should be performed depends on several predictors including postinterventional risk, location, and size of the pulmonary lesion. Overall, there are certainly cases in which primary segmentectomy is reasonable, but in this case lymph node dissection should be considered. Nevertheless, each patient should be presented in an interdisciplinary tumor conference to offer the patient a tailored concept.

Acknowledgments

Footnote

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