

Exploring the Need and Strategy for Intraoperative Freezing to Identify Metastatic Adenocarcinoma of the Lungs

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Abstract: *Objective:* To explore the necessity and strategy of intraoperative freezing to identify primary and metastatic adenocarcinoma of the lung. *Methods:* This study retrospectively analyzes the impact of failing to make a definitive diagnosis of metastatic adenocarcinoma of the lung on the clinical surgical approach in four cases of intraoperative freezing. It also examines the reasons for this failure and reviews the relevant literature. *Results:* All 4 cases of intraoperative freezing were diagnosed as invasive adenocarcinoma, and none of them made a definitive diagnosis of metastatic adenocarcinoma. *Conclusion:* It is difficult to confirm the diagnosis of metastatic adenocarcinoma of the lung by intraoperative frozen section, and the combination of patient history, rapid immunohistochemistry, and histological morphology of intraoperative frozen section for its identification can guide the surgeon to adjust the surgical approach in time and provide evidence for the establishment of surgical protocols for reference.

Keywords: Lung tumor; Metastatic adenocarcinoma; Intraoperative freezing

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1. Introduction

The lung is a common target organ for malignant tumor metastasis, and there is a significant difference in the choice of surgical approach between metastatic lung cancer and primary lung cancer. Some patients can only be clearly diagnosed with the help of surgical resection. Currently, domestic reports on intraoperative frozen diagnosis of lung tumors mainly focus on distinguishing between benign and malignant lesions and determining the infiltration degree of lung adenocarcinoma. However, reports on intraoperative frozen diagnosis of metastatic lung adenocarcinoma are extremely rare. This article analyzes four cases of metastatic adenocarcinoma in the lungs and reviews relevant literature to explore the necessity and strategy of intraoperative freezing for differentiating primary adenocarcinoma from metastatic adenocarcinoma in the lungs. This study aims to provide more accurate guidance for the clinical determination of surgical plans.

2. Materials and methods

2.1. General information

Four cases of lung metastatic adenocarcinoma specimens that underwent intraoperative freezing were collected from January 2021 to December 2022 from the Affiliated Hospital of Hebei University. All pathological sections were reviewed by two senior pathologists.

2.2. Methods

Frozen pathological specimens were taken from surgically resected fresh tissues, submerged in an OCT embedding agent, and placed in a B freezer for freezing. Sections were cut to a thickness of 4–5 μm , fixed in amniotic fluid (AF), stained with hematoxylin and eosin (HE) stain, and observed under a microscope. Conventional pathological specimens were fixed in 10% neutral formalin, routinely dehydrated, paraffin-embedded, cut into 4- μm thick sections, stained with HE stain, and observed under a microscope.

3. Results

3.1. Case 1: lung metastatic breast cancer

Patient, female, 73 years old, intraoperative delivery of a piece of lung tissue, size of $6 \times 2.5 \times 2$ cm, the largest diameter of about 1.0 cm nodule was seen on the section, greyish-white, hard, adjacent to the dirty layer of the pleura; clinical history of the patient's breast cancer was provided, and in combination with histological morphology, the diagnosis was made by intraoperative freezing: invasive adenocarcinoma was seen in the lung tissue, and the primary and metastasis needed to be determined by paraffin wax and immunohistochemistry (**Figure 1**); no additional surgery was performed.

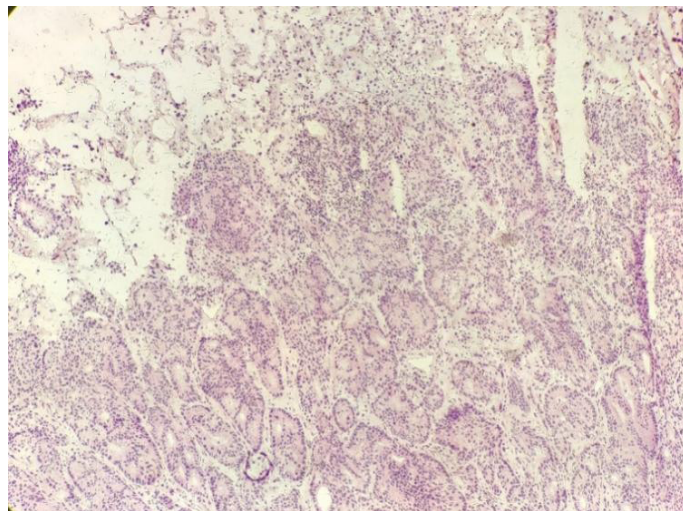


Figure 1. Pulmonary metastatic breast cancer (frozen)

3.2. Case 2: lung metastatic rectal cancer

Patient, male, 59 years old, intraoperative delivery of a piece of lung tissue, the size of $12 \times 8 \times 3.5$ cm, cut surface to see a diameter of about 4 cm mass, greyish-white, hard; clinical provision of the patient's history of rectal cancer, combined with the morphology of the tissue, intraoperative frozen diagnosis: infiltrative adenocarcinoma in the lung tissue, the morphology of the lung tissue does not exclude the metastatic rectal cancer, need to wait for the paraffin wax and immunohistochemistry to determine (**Figure 2**); no additional surgery was performed.

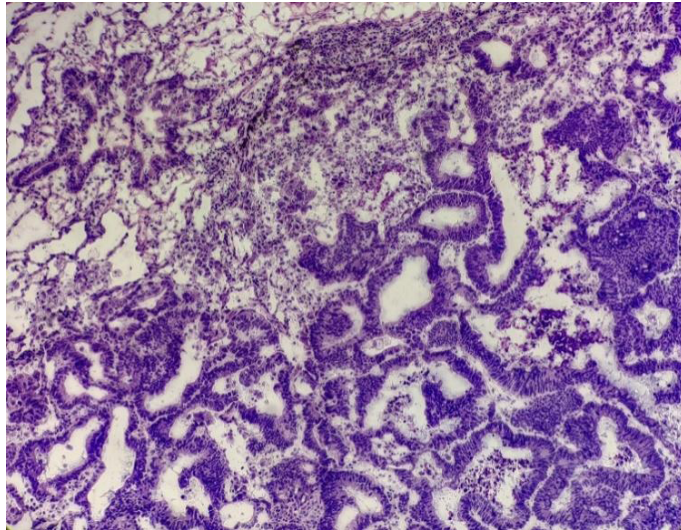


Figure 2. Pulmonary metastatic rectal cancer (frozen)

3.3. Case 3: lung metastatic papillary thyroid carcinoma

Patient, female, 53 years old, intraoperative exploration of the lower lobe of the left lung near the left lower lobe vein could be palpable about 2cm in diameter, because the lesion was close to the left lower lobe vein, it was impossible to perform wedge resection, so it was directly performed lobectomy; intraoperative examination of the lower lobe of the left lung: a lobe of the lung, the size of 14×9×3.5cm, 1.5cm from the end of the bronchial tube, 0.5cm from the visceral layer of pleura can be seen a 2.2×2.0×1.7cm mass. 1.7 cm mass, greyish white and hard; no clinical history was provided; intraoperative frozen diagnosis: infiltrative adenocarcinoma (**Figure 3**); lymph nodes were cleared as the primary lung tumor was considered in both clinical and imaging.

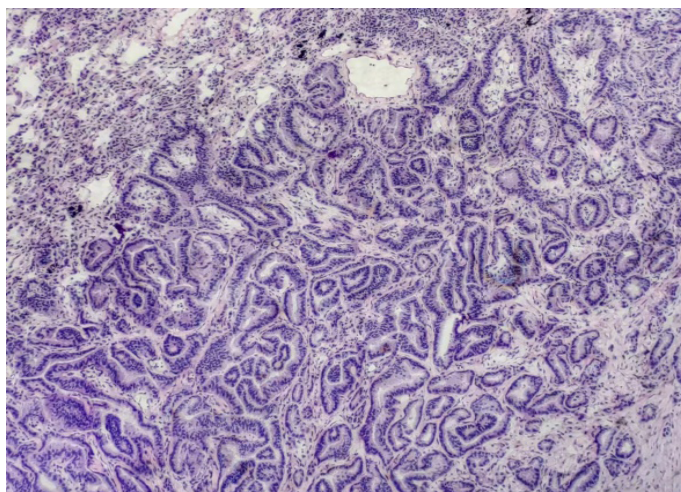


Figure 3. Pulmonary metastatic papillary thyroid carcinoma (frozen)

3.4. Case 4: lung metastatic cervical adenocarcinoma

Patient, female, 49 years old, intraoperative delivery of a piece of lung tissue, the size of 7.6 × 5.5 × 1.5 cm, cut surface see 1.5 cm in diameter mass, light brown, tough, some areas of papillary, the texture of the bad brittle; the clinical did not provide a history of the disease, intraoperative freezing diagnosis of invasive adenocarcinoma (**Figure 4**), because of the clinical and imaging considerations of the primary tumor, and therefore underwent the lower lobe resection of the right lung and the lymph nodes of the removal of the lymph nodes.

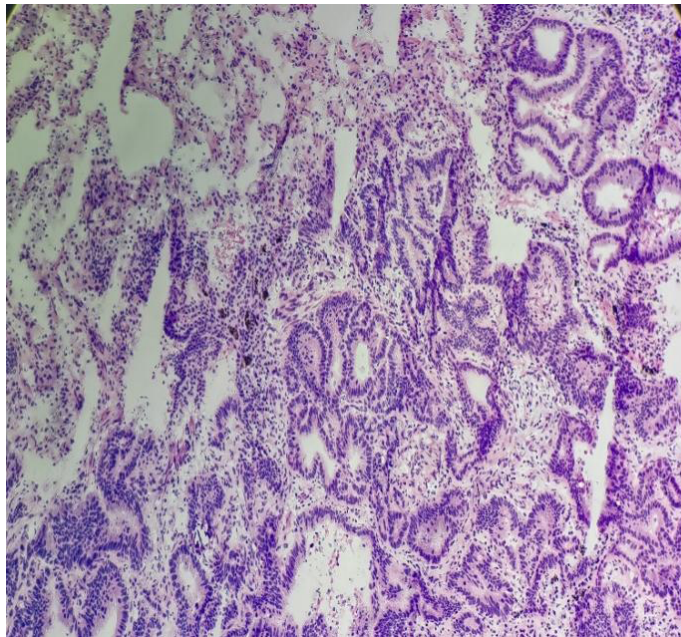


Figure 4. Lung metastatic cervical adenocarcinoma (frozen)

4. Discussion

Systemic treatment of cancer has made great progress in recent years, but the incidence of various types of cancer metastases continues to rise ^[1]. The lung is the most common site of tumor metastasis besides the liver ^[2], and approximately 20%–54% of patients with primary malignant tumors develop pulmonary metastases during disease progression ^[3].

Puncture of an intrapulmonary nodule leads to a definitive diagnosis in approximately one-third of patients ^[4]. However, due to tissue volume limitations, it is often not possible to differentiate between primary and metastatic tumors. Additionally, because of the limitations regarding the location and size of intrapulmonary nodules, most patients can only be clearly diagnosed with the help of surgical resection. In the four cases of lung tumors discussed in this paper, surgical resection of the tumor was chosen due to the difficulty and risk of puncture at the tumor's location suggested by imaging.

There are significant differences in the choice of operative modality for metastatic versus primary lung cancer. Lobectomy combined with systematic lymph node dissection is the standard treatment for primary non-small cell carcinoma of the lung ^[5,6]. Sublobar resection is recommended for metastatic cancers, as lobectomy may result in poorer spirometry and is not recommended for metastatic nodules. In this paper, diagnosing invasive adenocarcinoma via intraoperative freezing of the four tumors presented no difficulty. However, none were definitively diagnosed as metastatic carcinoma, which was confirmed by paraffin and immunohistochemistry. Previous studies have demonstrated that metastatic adenocarcinoma of the lungs is difficult to differentiate from invasive adenocarcinoma of the lung primarily in frozen sections if a history of the primary tumor is not provided by the clinic ^[7].

Han *et al.* ^[8] retrospectively analyzed 767 cases of intraoperative frozen sections of lung nodules. The results showed that the accuracy rate of intraoperative frozen pathological examination for the differential diagnosis of benign and malignant lung nodules was 99.2%, and the accuracy rate of typing lung malignant tumors was 85.3%. Specifically, the diagnostic accuracy rate for lung adenocarcinoma was 87.1% (440/505); however, 4 cases of metastatic carcinoma did not have a clear diagnostic typing, making accurate diagnosis

more difficult. The accuracy of the diagnosis of metastatic cancer was 85.3%.

Therefore, current intraoperative freezing is more difficult and less accurate in confirming whether a lung tumor is primary or metastatic. When precise differentiation between primary and metastatic tumors cannot be achieved with frozen sections, clinicians generally use a combination of disease-free intervals, age, and imaging findings to determine the next surgical option^[9]. Although the CT imaging features of primary lung cancer and metastatic lung tumors usually differ, the use of radiological examinations for differential diagnosis may be misleading because some lung metastases have an irregular morphology similar to that of primary cancers^[10].

Frozen sections have become one of the main tools to guide the surgical strategy for lung nodules as an effective method for rapid intraoperative assessment of the benignity and malignancy of lung nodules and their histological type^[11].

Through the analysis of the four cases of intraoperative freezing of the lung discussed, we explored the reasons why metastatic cancer could not be clearly defined. The first and second patients were informed intraoperatively that they had a history of breast cancer and rectal cancer, respectively, and the morphology was consistent with the characteristics of breast and bowel cancers. However, studies have shown that the prevalence of primary lung cancer in patients with breast cancer was 56.2% (86/153), and the prevalence of lung metastases was 30.7% (47/153)^[12]. The most common pathological type of lung metastatic cancer in patients with breast cancer is adenocarcinoma^[13]. Intraoperative cryopathological diagnosis was challenging because both breast and lung adenocarcinomas showed similar histological manifestations. In case 2, due to the similar histological pattern of pulmonary intestinal-type adenocarcinoma and pulmonary metastatic colorectal adenocarcinoma, no definitive diagnosis of metastatic carcinoma was made intraoperatively, and only a cryopathological report that metastatic carcinoma could not be excluded was given. In cases 3 and 4, without knowing the patient's history of cervical cancer and thyroid cancer, the possibility of metastatic cancer was not considered because the morphology resembled the primary alveolar adenocarcinoma of the lung.

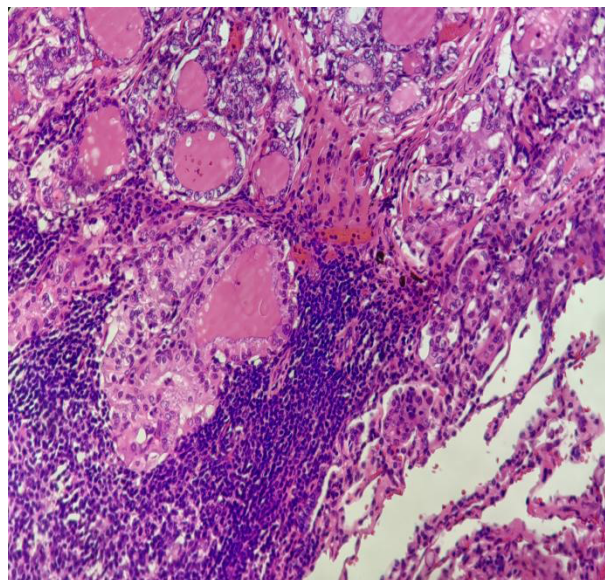


Figure 5. Pulmonary metastatic papillary thyroid carcinoma (paraffin)

With an understanding of the patient's medical history, sufficient material can be taken intraoperatively to look for evidence of metastases. Typical thyroid follicular components were observed in the paraffin section of the 3rd case (**Figure 5**). Increasing the number of frozen section blocks can aid in diagnosis. Recent advancements in pathological technology suggest that the application of rapid immunohistochemistry can be

beneficial. Approximately 75%–85% of primary lung adenocarcinomas express TTF-1. Yun *et al.* found that intraoperative rapid immunohistochemistry staining was more effective for detecting TTF-1, showing higher specificity for the intraoperative diagnosis of lung adenocarcinoma ^[14]. In this paper's four cases of metastatic adenocarcinoma of the lungs, immunohistochemical sections, except for thyroid adenocarcinoma, were negative for TTF-1. Gao *et al.* demonstrated that establishing a rapid manual immunohistochemical detection system for intraoperative auxiliary diagnosis of difficult cases achieved good results ^[15].

Therefore, when imaging reveals an isolated lung tumor and it is difficult to distinguish between primary and metastatic origins, several steps can greatly aid in determining if the tumor is metastatic. These steps include understanding each patient's history who needs a frozen section preoperatively, comparing primary tumor sections, taking sufficient material intraoperatively, and applying rapid immunohistochemistry. In most cases, intraoperative freezing can clarify the diagnosis.

The development of intraoperative freezing of lung nodules can be divided into three phases ^[16]:

- (1) Era 1.0: The thoracic surgeon's need for rapid intraoperative freezing diagnosis was primarily to differentiate between benign and malignant nodules, avoiding indiscriminate lobectomy for all lesions.
- (2) Era 2.0: The focus shifted to diagnosing the extent of lung adenocarcinoma infiltration intraoperatively, allowing for less damaging sublobar lobectomy while ensuring radical tumor resection.
- (3) Era 3.0: Intraoperative freezing aimed to identify adenocarcinoma histological subtypes, pleural invasion, airspace dissemination, lymphovascular infiltration, and other pathological high-risk factors for sublobar resection, to select a relatively safe group for this procedure.

When lung tumor resection is used as a diagnostic measure and the clinic is unsure whether it is therapeutic, intraoperative freezing that accurately indicates whether the tumor is metastatic can avoid unnecessary lobectomies and lymph node dissections. This plays a crucial role in the next steps of patient treatment. We may be moving towards a 4.0 era of freezing: accurately distinguishing whether an isolated invasive adenocarcinoma in the lung is primary and even determining the origin of metastatic cancer. Intraoperative freezing will thus fully establish itself as the gold standard of pathology.

Disclosure statement

The authors declare no conflict of interest.

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