

# Evaluation of Safety and Diagnostic Accuracy of Video-Assisted Thoracoscopic Biopsy in Patients with Suspected Pulmonary Metastases

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## Abstract

**Background:** The incidence of thoracic metastatic disease is increasing. This study aimed to evaluate the diagnostic effectiveness and complication rate of thoracoscopic pulmonary biopsy and evaluate the impact of the biopsy results on subsequent treatment decisions. **Methods:** Our prospective single-cohort diagnostic accuracy study included patients who had thoracic metastatic disease and underwent uniport thoracoscopic pulmonary biopsy at our centers between January 2022 and June 2024. Demographic data, preoperative clinical evaluation, positron emission tomography/computed tomography (PET/CT) findings, operative, pathological and postoperative data were collected and analyzed. Patient epidemiological and clinical features were expressed as range, mean  $\pm$  standard deviation, median value and percentage. Continuous variables were expressed as mean  $\pm$  SD or median (IQR), and categorical variables as percentages. P value was considered significant if  $\leq 0.05$ . **Results:** This study included 680 (48.5%) males and 720 (51.5%) females, median age of 64 years (interquartile range: 55 - 71 years). The mean preoperative disease-free interval was  $23 \pm 4.5$  months. The distribution of primary cancer origins among patients with pulmonary metastases was highly statistically significant ( $P < 0.001$ ). The most common indication for uniport thoracoscopic biopsy was the need for molecular profiling to guide targeted therapy (386 patients, 27.6%) and immunotherapy. Wedge resection or local excisional biopsy was performed. Mediastinal lymph node sampling was performed in 171 (12.2%). Postoperative complications occurred in 92 (6.6%) cases. Frozen section was

performed in 128 (9.1%) of selected cases. The median length of hospital stay was 6 days (IQR, 4 - 8 days). No patient required conversion to thoracotomy or reoperation. Thoracoscopic biopsy demonstrated a diagnostic sensitivity, specificity and accuracy of 100%. **Conclusions:** Uniport thoracoscopic lung biopsy is a safe, minimally invasive, and highly accurate procedure guided by PET/CT findings and frozen section in selected cases. This provides adequate tissue for definitive histopathological and immunophenotypic evaluation, guiding proper multidisciplinary oncological treatment.

## Keywords

Thoracoscopic Pulmonary Biopsy, Immunophenotyping, Immunotherapy in Metastatic Lung Disease, Postoperative Complications of Thoracoscopic Pulmonary Biopsy

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## 1. Introduction

The incidence of thoracic metastatic disease is increasing, largely owing to improved survival among patients with malignant diseases [1]. Pulmonary metastases are common and have been identified in approximately 20% - 54% of autopsies performed in patients who die from non-pulmonary malignant tumors. The lungs are among the most frequent sites of metastatic cancer spread, ranking second overall [2]. Malignancies that commonly metastasize to the lungs include breast, colorectal, head and neck, renal, testicular, and uterine (endometrial) cancers, as well as lymphoma. Other primary malignancies may also give rise to pulmonary metastases, although less commonly [2].

Several methods are available for obtaining tissue for histopathological diagnosis, including fine-needle aspiration, core-needle biopsy, thoracoscopic biopsy, and open surgical biopsy [3]. Thoracoscopic biopsy of clinically suspicious pulmonary metastatic lesions can provide definitive histopathological confirmation, identify discrepancies in receptor status between primary and metastatic lesions, and exclude or confirm the presence of a new primary pulmonary malignancy [4]. These findings may significantly influence subsequent therapeutic strategies.

Receptor-status discordance refers to a difference in the receptor profile between a primary tumor and its metastatic lesion and may indicate the need for a different therapeutic approach than that initially used for the primary malignancy [4]. Because therapy-predictive biomarkers may change during tumor progression, histopathological and molecular assessment of metastatic lesions can provide additional clinically relevant information that may facilitate more personalized management of patients with advanced malignancy [5]. Furthermore, the development of targeted therapies increasingly relies on obtaining adequate metastatic tissue to facilitate comprehensive molecular profiling and identify actionable genetic alterations that may guide personalized treatment [6].

Despite these potential benefits, the diagnostic success rate, accuracy, and safety

of thoracoscopic biopsy of suspected pulmonary metastases require further evaluation. Therefore, the primary objective of this single-cohort diagnostic accuracy study was to assess the diagnostic accuracy and safety of uniport thoracoscopic lung biopsy in patients with suspected pulmonary metastases. The secondary objectives were to determine the rate and nature of procedure-related complications, characterize the pathological diagnoses obtained, and evaluate the impact of biopsy results on subsequent treatment decisions.

## 2. Patients and Methods

### 2.1. Study Design and Patient Population

Patients were referred to our centers between January 2022 and June 2024 with pulmonary metastases. Patients underwent PET/CT before surgery. Standardized uptake value (SUV) cutoff of 2.5 was used for nodules  $> 8$  mm [6].

There is no absolute cutoff, but a commonly used guide. Borderline uptake means the FDG uptake is neither clearly benign nor clearly malignant. It usually refers to lesions with SUVs around 2.5 - 4, although the exact range varies by institution [6]. Each patient had uniportal thoracoscopic biopsy.

### 2.2. Inclusion Criteria

Patients were eligible for inclusion if they fulfilled the following criteria:

- 1) Adults aged  $>18$  years.
- 2) Patients with a history of a primary malignant tumor and suspected pulmonary metastases.
- 3) Patients with single or multiple pulmonary lesions suspicious for metastatic disease.
- 4) Patients with preserved pulmonary function and considered potentially operable.
- 5) Patients with pulmonary lesions that were potentially resectable or unresectable, with or without associated pleural deposits.
- 6) Patients with radiological findings suspicious for pulmonary metastases, including multiple peripheral pulmonary nodules, particularly those with irregular margins.
- 7) Patients with serial chest CT findings suggestive of disease progression, such as an increase in the size or number of pulmonary lesions, pleural involvement, or development of malignant pleural effusion.
- 8) Patients in whom further tissue diagnosis was clinically indicated based on clinical, radiological, and/or PET/CT findings.
- 9) Patients who underwent uniportal video-assisted thoracoscopic pulmonary biopsy for pathological diagnosis.

### 2.3. Exclusion Criteria

- Patients who refused to be included.
- Patients with severely impaired pulmonary or cardiac functions:

(Inability to tolerate general anesthesia, Severe respiratory failure prevents single-lung ventilation).

- Uncorrectable coagulopathy, Hemodynamic instability. Extensive pleural adhesions, Severe pulmonary hypertension, or Advanced cardiac dysfunction.
- Diffuse bilateral diseases where biopsy will not alter management.
- Poor performance status.
- Patients who cannot complete the study.

The uniportal VATS technique for lung biopsy: through a single port incision, a video thoracoscope, a lung grasper, and an Endo stapler are introduced into the pleural cavity. Uniport VATS lung wedge resections have been introduced into clinical practice.

**Sample Size:** By comparing incidence of pulmonary metastases with diagnostic failure,

We used  $P_1 = 40.6\%$  and  $P_2 = 14.7\%$ .

$$n = \frac{\left[ Z_{\alpha/2} \sqrt{2\bar{P}(1-\bar{P})} + Z_{\beta} \sqrt{P_1(1-P_1) + P_2(1-P_2)} \right]^2}{(P_1 - P_2)^2}$$

$P_1 = 0.406$ ,  $P_2 = 0.147$ ,  $Z_{\alpha/2} = 1.96$ ,  $Z_{\beta} = 0.84(80\%)$ .

This was a prospective, single-cohort diagnostic accuracy study conducted from January 2022 to June 2024. The study included consecutive adult patients with suspected pulmonary metastases who underwent uniportal video-assisted thoracoscopic pulmonary biopsy. Clinical, radiological, operative, pathological, and postoperative data were prospectively collected and analyzed to evaluate the diagnostic accuracy and safety of the procedure.

The sample size was calculated based on previously published review data. Two proportions were considered: an estimated incidence of pulmonary metastases of 40.6% ( $P_1$ ) and an anticipated diagnostic failure rate of 14.7% ( $P_2$ ). Assuming a two-sided significance level of  $\alpha = 0.05$  and a statistical power of 80%, the minimum required sample size was calculated to be approximately 1,366 patients. To account for potential exclusions and incomplete data, the sample size was rounded to 1,400 patients. A total of 1,400 consecutive patients were ultimately included in the study.

Univariate and multivariate analysis determined risk factors.

## 2.4. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 26.0. Continuous variables were assessed for distribution and are presented as mean  $\pm$  standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for non-normally distributed data. Categorical variables are presented as frequencies and percentages. Comparisons of categorical variables were performed using the Pearson chi-square test or Fisher's exact test, as appropriate, while continuous variables were compared using the independent-samples Student's t-test or Mann-Whitney U test, as appropriate.

For diagnostic accuracy analysis, sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy were calculated with corresponding 95% confidence intervals. The diagnostic odds ratio was calculated where estimable. The reference standard used for determination of the final diagnosis was defined independently of the index VATS biopsy result.

Univariable analyses were initially performed to identify variables potentially associated with postoperative mortality. Variables meeting the predefined criterion for inclusion were considered for multivariable analysis. Effect estimates were reported with 95% confidence intervals. A two-sided P value <0.05 was considered statistically significant.

**Ethical Considerations:** Patients were included in the study after obtaining written informed consent from surviving participants. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, as established by the World Medical Association. All patient data were anonymized to ensure confidentiality, and no personally identifiable information was retained in the analytical dataset.

**Registration and ethical approval of the study:** We obtained registration of Research Ethics Committee of Suez Canal University, Faculty of Medicine No.853C/Jan, 2021 & Egyptian Medical Care Authority. Department in Abo-Khalifa Hospital for Emergency and Fine Surgeries (one of the centers of The Egyptian Health Care Authority & Research Ethics Committee of Suez Canal University, Faculty of Medicine).

### 3. Results

Present Cohort study included 1400 consecutive patients, male/female: 680/720; median age: 64 years, interquartile range 55 - 71 years. Surgical approach consisted of Uniport-VATS in all patients. Thoracoscopic biopsy was indicated when there was one main primary indication per patient:

- 1) Pulmonary nodules were suspected to be metastatic, but diagnosis was uncertain in (13.3%).
- 2) Percutaneous CT-guided biopsy was non-diagnostic or technically difficult (8.9%).
- 3) Molecular profiling was needed for targeted therapy in (27.6%).
- 4) Patient had history of malignancy and developed new lung lesions in (23.3%).
- 5) Isolated pulmonary nodule(s) in (18.7%).
- 6) Pleural lesions associated with suspected metastases required biopsy in (8.2%).

Thus, the most common indication for thoracoscopic biopsy in our group of patients was pleural lesions associated with suspected metastases followed by molecular profiling needed for targeted therapy.

Thoracoscopic biopsy was managed by wedge or local excision in 61% ( $n = 55$ ) of cases (**Table 1**). Lymph node assessment and sampling were done in 171 (12.2%).

Indications of metastatic biopsy as in (Table 2) and results of the biopsy (Table 3). Overall rate of minor complications: 92 patients (6.6%) (Table 4).

**Table 1.** General features of the patients.

| Variable                             | Value (n = 1400) |
|--------------------------------------|------------------|
| Sex                                  |                  |
| Male                                 | 680 (48.6%)      |
| Female                               | 720 (51.4%)      |
| Age at surgery (years)               |                  |
| 18 - 59                              | 685 (48.9%)      |
| 60 - 64                              | 483 (34.5%)      |
| 65 - 70                              | 186 (13.3%)      |
| >70                                  | 46 (3.3%)        |
| Surgical approach: Uniport           |                  |
| Video-assisted thoracoscopic surgery | 100%             |
| Type of pulmonary resection          | 1400(100%)       |
| Wedge resection (local excision)     |                  |
| Mediastinal lymph node Sampling      | 171 (12.2%)      |
| Frozen section                       | 128 (9.12%)      |
| Median stay in hospital:             | 6 days           |
| Range:                               | 4 - 8 days       |

**Table 2.** Indications of thoracoscopic pulmonary biopsy.

| Indications for VATS biopsy                           | Value (n = 1400) |
|-------------------------------------------------------|------------------|
| CT-guided biopsy was non-diagnostic                   | 186 (13.3%)      |
| CT-guided biopsy was technically difficult            | 125 (8.9%)       |
| Molecular profiling was needed for targeted therapy   | 386 (27.6%)      |
| Developed new lung lesions                            | 326 (23.3%)      |
| Isolated pulmonary nodule(s)                          | 262 (18.7%)      |
| Pleural deposits associated with suspected metastases | 115 (8.2%)       |

**Table 3.** Pathological diagnosis: origin of Metastases.

| Primary origin | Site of pulmonary metastases | N = 1400    | P value                            |
|----------------|------------------------------|-------------|------------------------------------|
| Breast         | Lung, pleura, L.N.           | 454 (32.4%) | $\chi^2 = 633.15$ ,<br>P < 0.001). |
| Colorectal,    | Lung,                        | 293 (20.9%) |                                    |
| Head and neck  | lung                         | 251 (17.9%) |                                    |
| Testicular     | Lung. Pleura, lymph nodes    | 155 (11.1%) |                                    |
| Renal          | Lung, pleura                 | 126 (9.1%)  |                                    |

**Continued**

|                     |                |           |
|---------------------|----------------|-----------|
| Endometrial cancers | lung           | 63 (4.5%) |
| Lymphoma            | Lymph nodes    | 48 (3.4%) |
| Non metastatic      | Benign nodules | 10 (0.7%) |

We used The Pearson chi-square test. Pearson chi-square goodness-of-fit test; expected frequencies were assumed to be equal across the seven primary tumor categories. **Index test:** uniportal VATS biopsy. L.N. = Mediastinal and/or hilar lymph nodes.

**Table 4.** Complications of thoracoscopic biopsy and later oncotherapy.

| Item                                         | Number of patients                                                                                                            | Free of this event | Percentage | P value   |
|----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|--------------------|------------|-----------|
| Prolonged air leak (>5 - 7 days).            | 15                                                                                                                            | 1385               | 1.1%       | P = 0.027 |
| Wound infection.                             | 31                                                                                                                            | 1369               | 2.2%       |           |
| Atelectasis.                                 | 14                                                                                                                            | 1386               | 1.0%       |           |
| Pneumonia.                                   | 16                                                                                                                            | 1384               | 1.1%       |           |
| Empyema.                                     | 16                                                                                                                            | 1384               | 1.1%       |           |
| Total rate of complications                  | 92                                                                                                                            | 1308               | 6.5%       |           |
|                                              | 7                                                                                                                             |                    |            |           |
| 1 <sup>st</sup> month Mortality Risk Factors | Diabetes, hypertension, Receptor discordance pleural effusion, disease, L N. Mets, preop. Disease-free intervals < 12 months. |                    | 0.5%       |           |

Pearson  $\chi^2$  test was used. L. N. Mets = lymph node metastases.

Median hospital stay was 6 days (interquartile range 4 - 8).

Mean disease-free preoperative interval was  $23 \pm 4.5$  months (ranged between 8 and 36 months).

One-month postoperative mortality of 7 patients (0.8%). Univariate and multivariable analyses identified the following independent predictors of poor survival: preoperative disease-free survival <12 months ( $P < 0.001$ ), age > 65 years ( $P = 0.0003$ ), and positive mediastinal lymph node involvement ( $P < 0.05$ ).

In present study, we reviewed the PET/CT test (according to **Table 5**) for each patient to exclude biopsy of benign lesions and to choose the lesion that will provide the highest diagnostic yield.

Common complications included; bleeding, pain, infection and unintended organ injury. Organ-specific complications are commonly associated with biopsy of that specific organ, such as pneumothorax, pneumonia or empyema after a lung biopsy (**Table 4**). Results proved the following points:

VATS was feasible in all patients without reported conversion to thoracotomy.

Thoracoscopic biopsy provided diagnostic tissue and supported subsequent oncological treatment. The distribution of primary cancer origins among patients with pulmonary metastases was highly statistically significant ( $P < 0.001$ ) (**Table 3**).

A disease-free interval <12 months was associated with early mortality, highlighting its prognostic significance.

Thoracoscopic biopsy is a safe approach for diagnosing unexplained lung nodules, pleural nodules, and masses. It boasts a diagnostic success rate (yield) 100%. We achieved a diagnostic sensitivity of 100 % and specificity of 100%.

The length of time between first presenting with cancer symptoms and receiving a diagnosis (Diagnostic interval). ranged between 10 and 20 days. There were a group of 10 patients who were ultimately proven to have benign disease as we expected. Oncologists were in need to exclude malignancy. They proved to be truly negative (**Table 3**).

**Table 5.** (from Reference number [6]) Interpretation of Standardized uptake value (SUV).

| SUV       | Interpretation                                                                                                                                         |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| <2.5      | Usually low suspicion for malignancy (many benign lesions fall here). However, some cancers can also have SUV <2.5.                                    |
| 2.5 - 4   | Borderline or indeterminate uptake. Could represent benign inflammation or low-grade malignancy. Correlation with CT appearance and clinical findings. |
| 4.5 - 9.5 | Increasing suspicion for malignancy, although infection, inflammation, granulomatous disease, and healing tissue can also produce these values.        |
| >10       | Often highly suspicious for aggressive malignancy, but severe infection or inflammation may also reach these values [6].                               |

#### Diagnostic effectiveness (accuracy):

Diagnostic performance: a diagnostic success rate (Diagnostic yield) 100%

- Sensitivity =  $TP/(TP + FN) = 1390/1390 = 100\%$
- Specificity =  $TN/(TN + FP) = 10/10 = 100\%$
- Positive Predictive Value (PPV) =  $TP/(TP + FP) = 1390/1390 = 100\%$
- Negative Predictive Value (NPV) =  $TN/(TN + FN) = 10/10 = 100\%$
- Accuracy =  $(TP + TN)/Total = (1390 + 10)/1400 = 100\%$
- Youden's Index = Sensitivity + Specificity - 1 = 1.00
- Diagnostic Odds Ratio (DOR) =  $(TP \times TN)/(FP \times FN) = (1390 \times 10)/(0 \times 0) = \infty$  (infinite)

Among the 1390 patients with pathologically confirmed metastatic disease, breast cancer was the most common primary tumor, accounting for 454 cases (32.4%), followed by colorectal cancer in 298 cases (21.3%) and head and neck malignancies (18.3%) (**Table 3**). Also, receptor status, tumor marker levels and antigen presentation on tumor cells are laboratory significant factors that can af-

fect prognosis of the disease. For example, discordance means tumor evolution, genetic heterogeneity resistant tumor cell clones. Thus, comparison between pre-operative histopathological diagnosis and postoperative histopathological diagnosis biopsy material in lung metastases is essential.

There was a statistically significant difference in the distribution of complication types ( $P = 0.024$ ), with wound infection being the most frequent complication.

#### 4. Discussion

Video-assisted thoracoscopic surgery (VATS) has become an established minimally invasive approach for the diagnosis and management of pulmonary metastatic disease [7]. In the present study, all patients underwent uniportal thoracoscopic procedures without conversion to thoracotomy, demonstrating the technical feasibility of VATS in carefully selected patients with suspected pulmonary or pleural metastatic disease in agreement with other previous studies [7] [8].

Wedge or local excision was the most frequently performed surgical technique in this study. This approach reflects the principle of preserving functional pulmonary parenchyma whenever complete removal of the lesion can be achieved with adequate margins, while anatomical resection can be reserved for centrally located lesions or situations in which an adequate oncological margin cannot be obtained by wedge resection. Similar parenchyma-sparing surgical strategies have been reported [9] [10].

Previous investigators comparing VATS with open thoracotomy reported significantly fewer anatomical resections with VATS (24% vs. 49%;  $P < 0.001$ ), less frequent lymph node assessment (36% versus 70%), lower morbidity (9% vs. 18%), and shorter median hospital stay (4 versus 7 days) [10]. These findings support the potential advantages of minimally invasive surgery in appropriately selected patients with pulmonary metastatic disease. More than two-thirds of pulmonary metastases originating from extra thoracic malignancies have been reported to occur in peripheral or subpleural regions, whereas approximately one-third are located centrally or deep within the lung [11] [12].

Diagnostic Modalities for suspicious Pulmonary Lesions:

Percutaneous transthoracic needle biopsy (PTNB) remains a widely used minimally invasive diagnostic technique, particularly for peripheral pulmonary lesions [11] [12]. Previous studies have reported diagnostic failure rates of approximately 5% - 10%. Pneumothorax is the most common complication, occurring in approximately 15% - 25% of patients, although only 4% - 7% require chest tube drainage. Minor pulmonary hemorrhage or hemoptysis has been reported in approximately 4% - 27% of cases, whereas major bleeding is uncommon [11] [12]. In our study, the overall rate of minor complications was 6.6%.

Transbronchial biopsy (TBB) performed through bronchoscopy is particularly useful for centrally located pulmonary lesions [11] [12]. Reported diagnostic failure rates range from approximately 10% to 15%, with lower diagnostic accuracy

in lesions smaller than 2 cm or those surrounded by dense fibrotic lung tissue. Pneumothorax occurs in approximately 1% - 6% of procedures, substantially less frequently than following PTNB because the pleural surface is not traversed. Bleeding is generally mild and occurs in approximately 1% to 4% of cases [11] [12].

Surgical lung biopsy (SLB), particularly when performed by VATS, provides a relatively large tissue specimen and is commonly used when less invasive diagnostic techniques are inconclusive or inadequate. Its high diagnostic accuracy is accompanied by the risks inherent to an operative procedure. Reported overall complication rates range from approximately 5% to 15%, including prolonged air leak, postoperative bleeding, and cardiopulmonary complications, while operative mortality is generally low [12] [13].

Several factors influence the diagnostic yield of pulmonary biopsy procedures. Lesions smaller than 2 cm have been associated with lower diagnostic accuracy than larger lesions [12]. Deeply located pulmonary nodules or lesions distant from the pleural surface are technically more challenging to access and may therefore be associated with lower diagnostic success rates. In addition, patients with severe emphysema have an increased risk of pneumothorax following PTNB [13].

Although tumor implantation along the biopsy tract has been reported, it is an exceptionally rare complication. With meticulous technique and adherence to current procedural standards, the risk of tumor seeding is considered extremely low [14].

In our cohort, no patient required reoperation or conversion to thoracotomy. Thoracoscopic biopsy demonstrated 100% diagnostic sensitivity and specificity when compared with the final histopathological diagnosis, which served as the reference standard in the present study. This excellent diagnostic performance may be attributable, at least in part, to meticulous preoperative review of PET/CT imaging, careful selection of the most diagnostically informative lesion, and the use of intraoperative frozen-section examination in selected cases. These findings support VATS as a definitive minimally invasive tissue-diagnostic approach for pulmonary lesions, providing adequate tissue for histopathological diagnosis and, when required, further molecular profiling.

The predominance of peripheral lesions may therefore contribute to the feasibility of minimally invasive resection and biopsy.

Mediastinal lymph node assessment and sampling were performed in 171 patients (12.2%). Positive mediastinal lymph node involvement was associated with a poorer prognosis in our cohort ( $P < 0.05$ ). This finding emphasizes the potential prognostic importance of mediastinal nodal status in patients undergoing thoracoscopic evaluation for metastatic disease. It supports selective mediastinal lymph node assessment when clinically indicated, particularly when PET/CT demonstrates suspicious pulmonary nodules or metabolically active lymph node stations.

The distribution of primary cancer origins among patients with pulmonary metastases differed significantly across the various primary tumor sites ( $P < 0.001$ ).

Breast cancer was the most common primary malignancy in the present cohort, which is consistent with the predominance of female patients in the study population. It has been reported that approximately 20% - 30% of patients diagnosed with early-stage breast cancer will eventually develop metastatic recurrence. The bone and lungs are among the most common sites of metastatic spread in breast cancer.

Nevertheless, diagnostic interpretation may occasionally be limited by necrotic, crushed or otherwise inadequate tissue, which can potentially result in misleading or inconclusive pathological findings [15] [16]. This risk was technically preventable, and thoracoscopic biopsy achieved a diagnostic yield of 100%. The overall postoperative complication rate in our cohort was 6.6% (92 patients). In our series, most complications were minor and manageable. They included bleeding, postoperative pain, wound infection, atelectasis, pneumonia, and empyema. These findings suggest that thoracoscopic biopsy can be performed with an acceptable morbidity profile in appropriately selected patients with suspected metastatic disease. Seven patients died within one month after surgery, corresponding to an early postoperative mortality rate of 0.5% (7/1,400). Although early mortality was low, the presence of postoperative mortality highlights the complexity and comorbidity burden of patients undergoing surgical intervention for metastatic malignancy.

The mean preoperative disease-free interval was  $23 \pm 4.5$  months, with a range of 8 - 36 months. Notably, all patients who died during follow-up had a preoperative disease-free interval of less than 12 months. Furthermore, a disease-free interval of less than 12 months was independently associated with poorer survival in multivariable analysis ( $P < 0.001$ ). These findings suggest that the interval between treatment of the primary malignancy and the development of thoracic metastatic disease may represent an important prognostic factor and should be considered when selecting patients for surgical intervention.

The median postoperative hospital stay was 6 days (IQR, 4 - 8 days). This relatively short hospital stay may reflect the advantages of the minimally invasive thoracoscopic approach, including reduced surgical trauma, faster postoperative recovery, and the potential for earlier initiation or continuation of systemic oncological treatment.

Overall, our findings support the role of thoracoscopic surgery as a safe and effective approach for selected patients with suspected pulmonary and pleural metastatic disease. In addition to providing adequate tissue for definitive histopathological and immunophenotypic evaluation, thoracoscopy allows complete resection of selected lesions while preserving pulmonary parenchyma whenever feasible. The combination of preoperative PET/CT assessment, careful lesion selection, and intraoperative pathological evaluation may contribute to the high diagnostic yield observed in our prospective cohort. Furthermore, the minimally invasive nature of VATS, together with its ability to provide both diagnostic tissue and therapeutic resection in selected patients, makes it a valuable component of

the multidisciplinary management of metastatic thoracic disease.

## 5. Limitations

The present study has several limitations, the study was conducted at a limited number of centers, which may restrict the generalizability of the findings. Deep or occult pulmonary metastatic lesions may have been missed because an intraoperative ultrasound probe was not available. Finally, the very high diagnostic performance observed in our cohort should be interpreted in the context of the selected patient population and the pathological reference standard used for diagnostic assessment.

## 6. Future Directions

Future multicenter prospective studies involving larger and more diverse patient populations are warranted to validate these findings. Further research should also evaluate the role of intraoperative ultrasound in identifying deep or non-palpable pulmonary lesions and should assess the long-term oncological outcomes of thoracoscopic biopsy and metastasectomy in relation to tumor biology, disease-free interval, mediastinal lymph node status, and molecular characteristics.

## 7. Conclusion

Thoracoscopic lung biopsy is a safe and cost-effective procedure that provides an adequate tissue sample for histopathological evaluation and immunophenotyping, thereby facilitating targeted therapy and immunotherapy.

## Author Contributions

All authors equally contributed to the study conception and design, material preparation, data collection and analysis. The first draft of the manuscript was written by A. H. Elayouty. All authors read and approved the final report. All authors have read and agreed to the content and are accountable for all aspects of the content.

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## Declarations

### Statement of Competing Interests

- The authors have no relevant financial or non-financial interests to disclose.
- All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.
- The authors report no conflict of interest. Conflict of interest: none declared.

### Human Ethics and Consent:

All procedures performed were in accordance with the ethical standards of the

institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Identifying details (names, dates of birth, identity numbers, biometrical characteristics, other distinguishing characteristics and other information of the participants that were studied) should not be published in written descriptions or photographs. Complete anonymity was achieved in all cases. All patient data were anonymized to protect confidentiality, and no identifying information was retained in the analytical dataset. The aspect of confidentiality as well as any wishes from the participants were respected.

Consent from individuals to publish their data prior to submitting the paper to a journal.

Informed consent was obtained from all individual participants included in the study.

## Ethics Approval and Registration

We obtained registration of Research Ethics Committee of Suez Canal University, Faculty of Medicine No.853C/Jan, 2021 & Egyptian Medical Care Authority. & Egyptian Medical Care Authority. Department in Abo-Khalifa Hospital for Emergency and Fine Surgeries (one of the centers of The Egyptian Health Care Authority & Research Ethics Committee of Suez Canal University, Faculty of Medicine).

## Statement of Data Availability

Data Available on Request:

The data underlying this article will be shared at a reasonable request to the corresponding author.:

[https://docs.google.com/document/d/1GiAjRIB1IWGOEpr1RRog-dqH6O3SSH -  
s/edit?usp=drivesdk&ouid=112024197390049416959&rtpof=true&sd=true](https://docs.google.com/document/d/1GiAjRIB1IWGOEpr1RRog-dqH6O3SSH-/s/edit?usp=drivesdk&ouid=112024197390049416959&rtpof=true&sd=true)

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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