# Microcoil-Guided Video-Assisted Thoracoscopic Excision of Nodules Suspicious for Metastasis in Patients With Extra-Thoracic Malignancies

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The purpose of this study is to determine the utility of preoperative CT-guided microcoil localization followed by fluoroscopy guided video-assisted thoracoscopic resection in the diagnosis and management of small peripheral pulmonary nodules in patients with extra-thoracic malignancies. This study is a retrospective analysis of prospectively collected data between August 2003 and September 2013. Fifty patients with extra-thoracic malignancies underwent preoperative localization of small indeterminate pulmonary nodules using CT-guided microcoil localization. Nodules were then resected by video-assisted thoracoscopic resection wedge excision and intraoperative fluoroscopy guidance. Univariate and multivariate logistic regression analysis were conducted. Fifty patients with a history of 14 different extra-thoracic cancers (57% female, mean age 62 years) had 55 nodules resected (mean size = 12 mm, depth from visceral pleura = 22 mm). Histology of resected nodules showed metastasis (25 of 50 patients), benign (10 of 50), and (15 of 50) early stage primary lung cancer. Smokers were found 6 times more likely to present with primary lung cancer than metastasis ($P < 0.009$). CT-guided microcoil localization procedure was successful in all patients with a mean time of 31(10) minutes and allowed successful wedge resection in all cases with no major complications. The mean operative time and fluoroscopy time were 27(12) minutes and 3(5) minutes, respectively. Microcoil-guided thoracoscopic wedge resection was effective in achieving early definitive diagnosis and changed management in 50% of patients with presumed metastasis with minimal morbidity.

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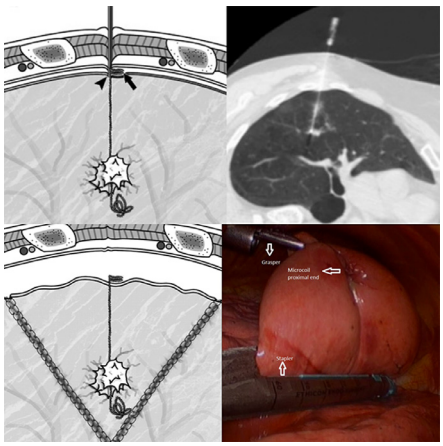
**Keywords:** VATS, Lung cancer, Micro-coil localization, Malignancy, Lung nodules



CT-guided microcoil localization and VATS resection of small suspicious lung nodule.

**Central Message**

Indeterminate small pulmonary nodules in patients with extra-thoracic malignancies have a 50% chance of being non-metastasis, which mandate definitive tissue diagnosis for accurate management.

**Perspective Statement**

Lack of universally accepted approach for management of indeterminate small pulmonary nodules in patients with extra-thoracic cancer is due to diagnostic challenges. Microcoil-guided wedge resection provided definitive diagnosis with minimal morbidity.

## INTRODUCTION

Although lung nodules are frequently encountered in patients with extra-thoracic malignancies, they represent a diagnostic dilemma with no consensus on their management. Data

*Abbreviations:* CT, computed tomography; CTML, computed tomography microcoil localization; SPPN, small peripheral pulmonary nodules; SPSS, statistical package for the social sciences; VATS, video-assisted thoracoscopic resection

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regarding optimal approach of pulmonary nodules in this subset of patients are scarce.[1] Advances in radiological techniques have facilitated early detection of suspicious lung nodules, but this has been complicated by an increasing number of small indeterminate pulmonary nodules which lack benign and/or malignant characteristics in initial images.[2,3] Because lungs are the second most common site for metastasis in patients with extra-thoracic malignancies with up to 54% of patients developing lung metastasis during the course of disease,[4] usually lung lesions found in the course of a neoplastic disease or during initial staging are considered to be metastasis of the primary cancer. This assumption directly affects the treatment and prognosis of patients. In some malignancies like colorectal cancer and osteosarcoma, with good control of primary site, surgical resection of pulmonary metastasis is considered to optimize survival. While with other types of cancer, patients thought to have pulmonary metastasis are deemed incurable and assigned to palliative treatment.[1] Other pathologies have also been reported in retrospective data in populations of patients with cancer showing a high frequency of primary lung cancers (up to 50%), and benign lesions (up to 58%), which has a significant clinical impact on patients' treatment and prognosis.[1] Knowing that survival rates are enhanced with early detection and management of new primary lung cancer, local control of disease in metastatic tumors, and avoidance of unnecessary interventions or serial radiation exposure in benign lesions[5] increased the demand for definitive tissue diagnosis. Unfortunately, percutaneous computed tomography (CT)-guided biopsy has been shown to have several limitations with small nodules including difficult accessibility, sampling error, and inadequate tissue sample.[6]

Nodules' small size and deep location have also complicated their video-assisted thoracoscopic resection (VATS) resection.[2,7] CT-guided microcoil localization (CTML) technique has proven its safety and efficacy in a previous randomized clinical trial, facilitating successful VATS resection of small peripheral pulmonary nodules (SPPN).

The purpose of our study is to determine the utility and clinical significance of preoperative CTML followed by fluoroscopy guided VATS wedge resection in the management of SPPN in patients diagnosed with extra-thoracic malignancies. We also seek to evaluate variables associated with higher odds of finding metastatic disease vs primary lung cancer vs benign lesions in this group of patients.

## MATERIALS AND METHODS

Adult patients referred to thoracic surgery service at Vancouver General Hospital between August 1, 2003 and September 30, 2013, for thoracic surgical evaluation of small growing peripheral lung nodules that manifested during initial staging or follow-up after treatment of an extra-thoracic malignancy. Patients with nodules showing growth or thickening over 3 consecutive months on CT scan required diagnostic intervention. Patients with small nodules (2 cm or less) were found difficult to be biopsied and therefore assigned for diagnostic VATS using the CTML technique. Patients who did not meet the inclusion criteria and those with primary malignant tumors of the lung or within the thorax, or with nodules larger than 2 cm were excluded. Inclusion criteria included: adult patients 18 years of age and above, patients physically fit for surgery, previous history of extra-thoracic malignancy, and growing or thickening nodules measuring 2 cm or less in largest diameter, and subpleural nodules that are at least 2 cm away from main pulmonary arteries and veins. Exclusion criteria included patients under 18 years of age, history of thoracic malignancy, patients with no cancer diagnosis, lung nodules that are larger than 2 cm in diameter, nodules within 2 cm from major vessels, and those physically unfit for surgery.

Informed consents were obtained from patients if they met the inclusion criteria and agreed to participate in the study. The study was approved by the institutional review boards of the University of British Columbia (CREB H02-70,562) and Vancouver General Hospital (C02-0562).

As previously described[8] preoperative localization of the lung nodule was carried out in the department of radiology on the day of surgery using local anesthesia. Through a 22-gauge needle, a percutaneous placement of platinum microcoils (VortX-18; Diamond Shape; Boston Scientific, Cork, Ireland) was conducted under CT-guidance (Fig. 1). After successful completion of localization with the distal end of the microcoil deep to the nodule and the superficial end coiled on the visceral pleural surface, the patient was transferred to the operating room for VATS procedure. Patients usually have their microcoil placed in the department of radiology early in the morning and booked as the second case in the operating room (OR) so there was no delay in the OR. Under general anesthesia using thoracoscopy, the superficial coiled end was visualized (Fig. 2) guiding to the deep coil end attached to the nodule. Using endostapler (Endo GIA II, United States Surgical, Norwalk, Conn; Echelon Endostapler, Ethicon Endo-Surgery, Cincinnati, Ohio) and facilitated by fluoroscopy (Fig. 3), the nodule was then removed by wedge excision. Patient are positioned in lateral decubitus throughout the procedure and a sterile C-arm fluoroscope was rotated around them for all OR interventions. Fluoroscopy imaging done to ensure wedge resection below the level of the deep end of the microcoil (Fig. 4), enabling complete resection of nodule with adequate resection margins. Resected specimens are x-rayed to confirm full inclusion of the microcoil.

### Pathologic Analysis

Specimens were sent as frozen sections and examined by a pulmonary pathologist for histology (malignant vs benign), and adequacy of the resection margins (Fig. 5). VATS was found sufficient if the lesion was benign, a metastasis from an extrathoracic malignancy (lymph nodes were not routinely sampled), or the diagnosis was indeterminate. However, If the frozen section of the excised nodule showed a NSCLC the patient had staging of regional N1 and N2 lymph nodes and went on to an anatomical

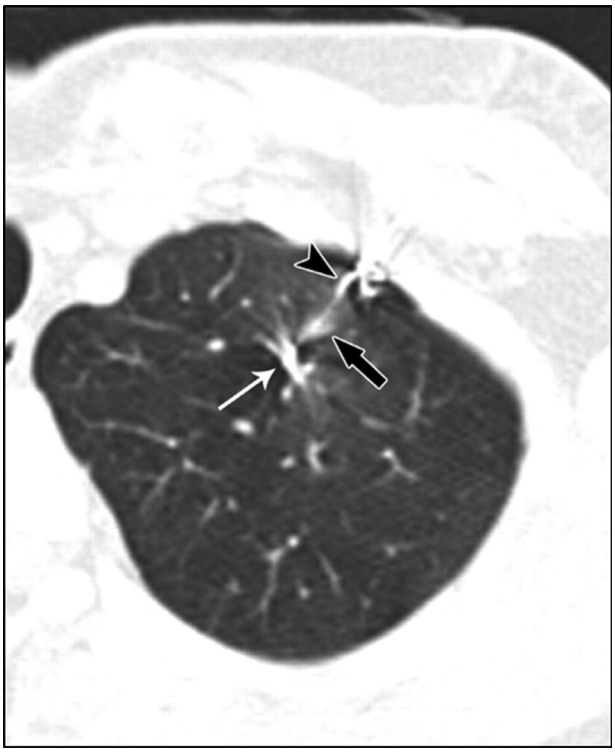


**Figure 1.** Nonenhanced transverse chest CT scan shows complete ejection of the microcoil from the Chiba needle and successful localization of a nodule at the left lung apex (black arrow). The deep end of the microcoil is coiled into a ball adjacent to the nodule (white arrow) and the superficial end is coiled on the visceral pleural surface. No hemorrhage is noted in the normal lung tissue adjacent to the wire (arrow head). CT, computed tomography.

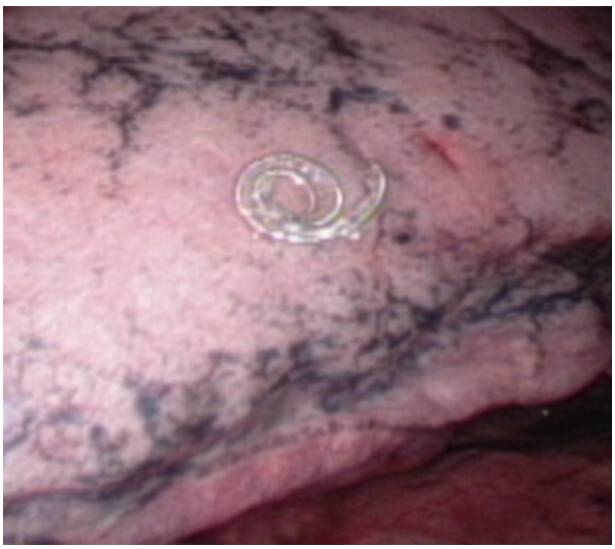


**Figure 2.** Intraoperative thoracoscopic view showing superficial end of the microcoil on the visceral pleura of the lung.

resection during the same operation unless the patient had inadequate pulmonary function to tolerate a lobectomy, or the pathology showed noninvasive cancer.

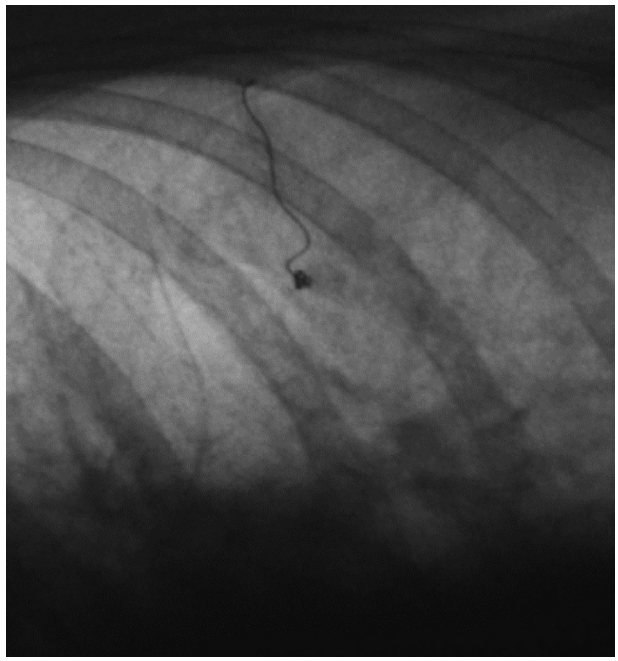


**Figure 3.** Intraoperative fluoroscopic view showing both the superficial end of the microcoil on the lung surface and the deep end of the microcoil (attached to the nodule) in the lung parenchyma.

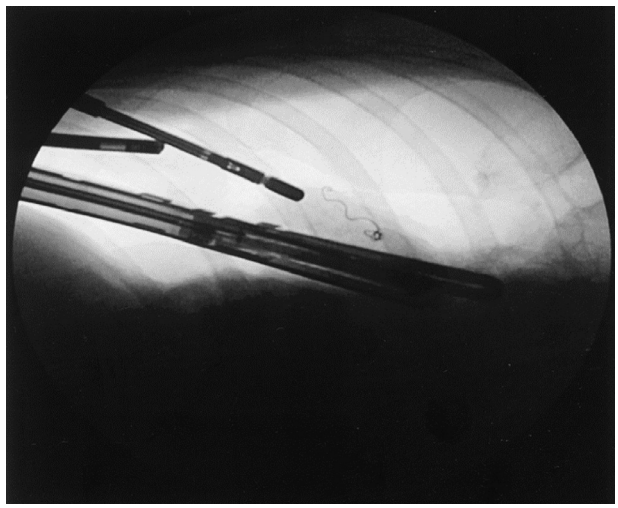


**Figure 4.** Intraoperative fluoroscopy image showing the deep end of the microcoil within the lung parenchyma and a GIA stapler bellow it. A grasper was applied to the lung adjacent to the superficial end of the microcoil on the visceral pleura.

### Follow-Up and Local Recurrence

Follow-up was done with serial CT scans at 3, 6, 12, and 24-month intervals for 5 years, and reviewed by 2 chest radiologists.

### Statistical Analysis

Univariate and multivariate logistic regression analysis were performed with the SPSS ver. 22.0 software package (SPSS Inc.

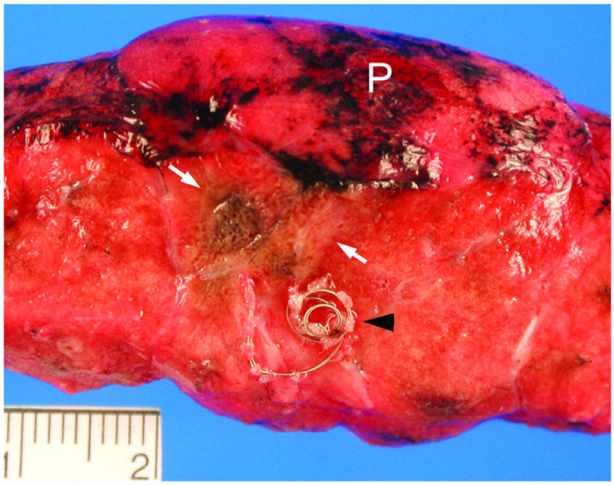



**Figure 5.** Resected wedge specimen shows the microcoil (arrow head) coiled on the pleural surface.

Chicago, Illinois). *P* value of <0.05 was considered statistically significant, with a 95% confidence interval. The 3 outcome results, metastatic lesions, primary lung cancer and pulmonary benign lesions, were compared for prevalence using Z-tests. Preoperative factors with assumed associations with malignant nodules were further investigated by regression analysis. These factors included age, gender, history of smoking, nodules' location, nodules' number, and time between diagnosis of primary extra-thoracic cancer to lung nodules development. Except for history of tobacco smoking, the regression analysis added little to this study.

## RESULTS

Between August 2003 and September 2013, 50 patients with extra-thoracic malignancy underwent fluoroscopy guided VATS resection for pulmonary nodules after "CTML." The majority of the patients were women (57%), with an average age of 62 years for all patients. A total of 14 different extra-thoracic cancers were identified in the 50 patients, with 3 patients having more than 1 extra-thoracic cancer. The median time interval between the diagnosis of the primary tumor and the finding of pulmonary nodule(s) on CT scans was 36 months (range 4—588). Colorectal adenocarcinoma was the most prevalent primary extra-thoracic cancer. The previously treated extra-thoracic malignancies were colorectal (16), breast (8), urogenital (7), sarcoma (5), melanoma (3), lymphoma (3), thyroid (3), gastro-esophageal (2), and others (3). Fifty-five nodules were resected with a mean size of 12 (4) mm, and a mean depth from visceral pleura of 22 (10) mm. The resected nodules locations were Right Upper Lobe (RUL) ($n = 17$), Right Lower Lobe (RLL) ($n = 20$), Left Lower Lobe (LLL) ($n = 7$), Right Middle Lobe (RML) ($n = 5$), Left Upper Lobe (LUL) ($n = 5$), and Lingula ($n = 1$). The mean time for CT-guided microcoil placement procedure was 31 (10) minutes. Nodules were successfully resected in all patients, with a mean operative time of 27 (12) minutes (excluding lobectomy time), and fluoroscopy time of 3 (5) minutes. Frozen section usually took approximately 30 minutes.

All resected specimens included the microcoils which were confirmed with fluoroscopy during surgery and on x-rays post-resection. Video-assisted thoracoscopic surgery wedge resection after CTML was successfully diagnostic in 98% of the patients. Open wedge resection was required for 1 patient with extensive pleural adhesions from a previous thoracic surgery.

No complications were developed during and/or following the coiling procedure or the surgical resection of the lung nodules such as pneumothorax, pleural hemorrhage, prolonged air leak, or coil dislodgement. There were no deaths or clinically relevant wound infections, pneumonia, empyema, or myocardial infarctions in the postoperative period. Mean time of hospital stay was 2(1) days for VATS wedge resection and 4(1) days for lobectomy. Of 50 patients studied, 40 (80%) had malignant lung nodules (50% metastasis, 30% primary lung cancer) and 10 (20%) had benign lesions.

In relation to the histology of primary extra-thoracic tumors, metastasis was noted more frequently in patients with urogenital carcinoma (85%), sarcoma (80%), melanoma (66%), and colorectal carcinoma (62%). On the other hand, primary lung cancer was more commonly in patients with lymphoma (100%) and breast cancer (62%) (Table 1). History of tobacco smoking was found in 73%, 36%, and 20%, in patients with primary lung cancer, metastatic lesions, and benign lesions, respectively.

**Table 1.** Histology of Previous Extra-Thoracic Primary Cancer and Its Relation to Pathology of Resected Nodules

| Primary Cancer Histology | Number of Patients | Metastasis | Primary Lung Cancer | Benign |
|---|---|---|---|---|
| Colorectal | 16 | 10 (62.5%) | 3 (18.75%) | 3 (18.75%) |
| Breast | 8 | 0 (0%) | 5 (62.5%) | 3 (37.5%) |
| Melanoma | 3 | 2 (66.66%) | 1 (33.33%) | 0 (0%) |
| Sarcoma | 5 | 4 (80%) | 0 (0%) | 1 (20%) |
| Lymphoma | 3 | 0 (0%) | 3 (100%) | 0 (0%) |
| Urogenital (renal, prostate, cervical, and bladder) | 7 | 6 (85.71%) | 1 (14.28%) | 0 (0%) |
| Gastroesophageal carcinoma | 2 | 1 (50%) | 1 (50%) | 0 (0%) |
| Thyroid | 3 | 1 (33.33%) | 1 (33.33%) | 1 (33.33%) |
| Chordoma | 1 | 1 (100%) | 0 (0%) | 0 (0%) |
| Leukemia | 1 | 0 (0%) | 0 (0%) | 1 (100%) |
| Tongue invasive squamous cell carcinoma | 1 | 0 (0%) | 0 (0%) | 1 (100%) |

The mean follow-up was overall short (35 months) for those who underwent curative resection of metastatic lesions and new primary lung cancer (VATS wedge and/or lobectomy), with no signs of local recurrence.

## DISCUSSION

In contrast to the general assumption of metastasis in patients with previous history of extra-thoracic cancer, pulmonary nodules in 50% of our patients were unrelated to primary tumor, including 30% of new primary lung cancer and 20% of benign lesions. Our study showed that pulmonary nodules in patients with extra-thoracic malignancies have an equal chance of being nonmetastasis vs metastasis, which lowers the threshold for diagnostic and therapeutic measures. The proposed surgical technique for removal of small pulmonary nodules provided 100% success rate and resulted in a radical change in the final diagnosis and therapeutic plan among 50% of patients with nonmetastatic lesions. Benign lesions were observed, and new primary lung cancers were staged and treated accordingly. If all pulmonary nodules were assumed to be metastasis, half of the patients would have received inappropriate treatment. The accurate tissue diagnosis achieved through CTML and VATS allowed for optimal therapeutic approach without delay in management.

Hanamiya et al reported high rate of detection of the noncalcified pulmonary nodules to be 75% in patients with extra-pulmonary malignant tumors, and surgeons are often challenged to balance the benefits of obtaining an early diagnosis with the potential risks of unnecessary intervention.[9] Furthermore and similar to our results, high frequency of newly diagnosed lung cancer (26–36%), and benign lesions (9–35%) in patients with history of malignant tumors were reported in previous studies.[1,10,11] Therefore, the approach of VATS wedge resection was found essential to clarify the nature of these nodules.[10,11]

If detected early, the chance of cure is high, especially in the case of an early stage lung cancer.[9] Primary lung cancer is the leading cause of cancer related deaths worldwide with poor 5-year survival rates of less than 14% on late diagnosis, which could be significantly improved to as high as 92% upon early detection and management.[12,13] In the case of benign lesions, reliable histopathological clarification by VATS provides peace of mind and prevention of unnecessary management, with minimal morbidity.[10]

The clinical impact of this approach has also been demonstrated in those diagnosed with metastasis. In 1991, an International Registry of Lung Metastases was established to assess the long-term results of pulmonary metastasectomy in patients with cancer. The registry accrued 5206 patients from 18 departments of thoracic surgery in United States, Canada, and Europe, and proved that lung metastasectomy is a potentially curative procedure in selected cases.[14] The impact of pulmonary metastasectomy on overall survival was further established by several clinical trials showing 30–50% 5-year survival rates after VATS wedge resection with curative intent.[15] Further, several meta-analyses confirmed no difference in survival between VATS and conventional thoracotomy for treatment of pulmonary metastases, making VATS a safe and feasible option.[16]

Unfortunately, the initial management options of lung nodules in patients diagnosed with cancer are usually limited by lesion size. Small nodules cannot be reliably classified as benign or malignant using CT criteria or PET/CT scan analysis.[7] Failure to characterize these nodules by imaging and difficult accessibility by percutaneous or CT-guided biopsy with substantially low accuracy have resulted in the utilization of serial imaging as a commonly employed alternative technique in the evaluation of small nonspecific pulmonary nodules.[6] In patients with extra-thoracic cancer, the possibility of delayed cancer diagnosis and treatment, with consequently uncertain effects on prognosis is the main disadvantage of the serial imaging approach.[17]

Although demand for surgical excisional biopsy by VATS is increasing to clarify the histologic substrate of indeterminate lung nodules in high risk patients, loss of tactile perception often made it difficult to resect small lung nodules. CTML and fluoroscopy-guided VATS has proved to be safe and effective in providing pathologic diagnosis with complete excision of the target nodule without conversion to open thoracotomy.[2] This was successfully accomplished in our study with clear resection margins of all target nodules. The minimally invasive procedure provided patients with short hospital stay, minimal postoperative pain, and early mobilization. Prior to instituting this technique, patients with small and deep nodules were more likely to be observed with serial imaging, or with open thoracotomy and excision if the lesion was growing.

In terms of factors found predictive of malignant nodules, our analysis showed 6-fold increase in the likelihood of primary lung cancer in smokers (univariate $P < 0.009$, multivariate $P < 0.03$) which was also confirmed in previous literature.[7,18] Hence, lung nodules identified in former or current smokers are more suspicious of early stage lung cancer rather than metastasis.

Histology of the primary extra-thoracic cancer has been the focus of several recent studies and found to influence the final pathology of lung nodules. Lung nodules in patients with breast cancer were more frequently reported to represent primary lung cancer (48–67%) than metastasis (23–37%) and benign lesions (5–7%).[19,20,21] Our data were similar showing higher incidence of primary lung cancer (62%) in comparison to metastasis (0%), and benign lesions (37%) in breast cancer patients (Table 1). On the other hand, higher rates of lung metastasis were reported in patients diagnosed with colorectal cancer reaching 75%,[22] matching our data of 62% metastasis, in this group of patients (Table 1). Like colorectal cancer, melanoma, sarcoma, and renal cell carcinoma are neoplasms known to frequently metastasize to lungs.[23–25] Our sample size was small, but it showed similar rates of high metastases in those patients.

Understanding the histologic nature of the primary cancer and its association with the final pathologic outcome of lung nodules is important but tissue sampling is fundamental for accurately diagnosing and treating patients with extra-thoracic cancer.

There are several limitations of our study including the retrospective design, small sample size, and being conducted by single-institution. Also, the overall follow-up observation period was short. Therefore, a relatively long follow-up observation period should be considered for long-term results.

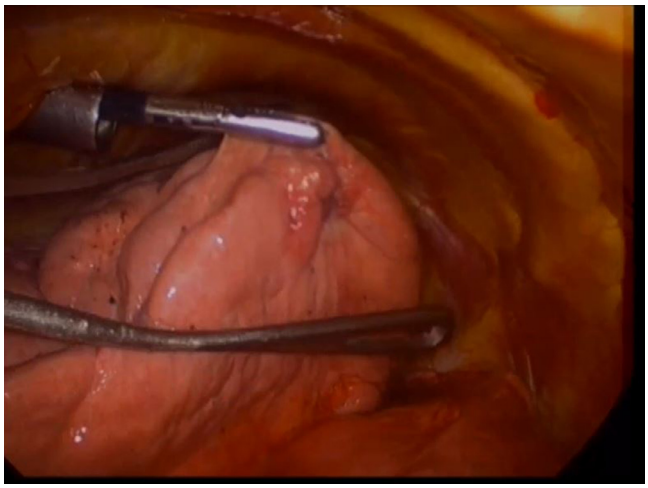
## CONCLUSION

Fluoroscopy guided VATS after CTML changed the management in half of our patients with presumed metastasis.

Primary lung cancer and benign lesions constitute major etiologies of lung nodules in patients with extra-thoracic malignancies. Given the difficulty to accurately estimate the origin of a pulmonary nodule based solely on imaging studies, and the relative safety of VATS following microcoil localization, we recognize this surgical approach as an important tool for therapeutics guidance of SPPN that are difficult to biopsy and challenging to locate. This approach allowed timely diagnosis and proper management of suspicious nodules, avoiding delays with observational serial imaging, sampling errors with biopsies, and invasiveness with open thoracotomy.

## SUPPLEMENTARY MATERIAL

The following is the supplementary data to this article:



**Video 1.** CT-guided microcoil localization technique followed by video-assisted thoracoscopic surgery of a small peripheral pulmonary nodule.

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