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Warranting Investigation of Primary Lung Adenocarcinoma in Patients With an Extrapulmonary Malignancy and Lung Nodules Due to High Frequency

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Abstract

Objectives—To distinguish primary lung adenocarcinoma (PLA) from metastatic adenocarcinoma/malignancy to optimize therapy.

Methods—We investigated the utility of thyroid transcription factor 1 (TTF-1) and napsin A in distinguishing PLA from metastatic adenocarcinoma/malignancy and assessed the frequency of PLA in patients with extrapulmonary malignancy/adenocarcinoma (PLA-EPM/EPA).

Results—TTF-1 and napsin A identified PLA in PLA-EPM/EPA with a sensitivity of 89.4% and 93.3% and a specificity of 93.9% and 94.7%, respectively. PLA was confirmed in 47.4% of PLA-EPM and 40.2% of PLA-EPA. Overall, 38.5% of patients with PLA had EPM. The common organs for PLA-EPA were breast (35.8%), colon (13.2%), and others, whereas the common organs resulting in pulmonary metastasis were the colon (32.8%), breast (28.1%), and others. A patient with a smoking history and without EPM had a higher chance of having PLA. Multiple nodules are not a reliable indication of metastatic adenocarcinoma.

Conclusions—Our results firmly support the role of TTF-1 and napsin A in identifying PLA-EPM/EPA. We reason that all new lung nodules in patients with a history of EPM should be screened using these techniques due to the high frequency of PLA-EPM, which will affect treatment and prognosis of patients with EPM/EPA.

Keywords

Frequency; Primary lung adenocarcinoma; Metastatic malignancy; Extrapulmonary malignancy; Immunohistochemistry

In the United States, there was an estimated 228,000 new cases of lung cancer and 159,500 deaths in 2012.¹ In males, lung cancer is the most common cancer worldwide and the leading cause of death, whereas in females, lung cancer is the fourth leading cause of cancer and the second leading cause of cancer deaths.² Adenocarcinoma is the most common histologic type of lung cancer, accounting for nearly 40% of all lung cancers. The lung is

also the organ that is most frequently involved by metastatic malignancies, with an incidence of 20% to 54% of nonpulmonary solid malignancies.³ When patients have an extrapulmonary malignancy (EPM) and lung nodules, a question is raised as to the origin of the tumor (eg, metastatic vs primary). In patients with adenocarcinoma, distinction of a second primary lung adenocarcinoma (PLA) from metastatic adenocarcinoma (MA) in a patient with a history of extrapulmonary adenocarcinoma (EPA) is critical for several reasons. First, it affects tumor staging (M1 for MA vs T1–T3 for PLA). Second, a correct diagnosis affects the choice of treatment (possible resection for PLA vs chemotherapy and/or radiation for MA). Finally, an accurate diagnosis has prognostic significance. It is critical to establish a correct diagnosis of PLA vs MA before initiating therapy. However, it can be challenging to make this distinction based on cytomorphology of a fine-needle aspiration (FNA) and/or histomorphology of a needle core biopsy (NCB). Thus, more sensitive and specific biomarkers would advance our management of EPM presenting with a solitary pulmonary nodule.

Thyroid transcription factor 1 (TTF-1) is considered a reliable marker for PLA, with high sensitivity (75%–82%) and specificity (89%–91%).^{4,5} Because approximately 20% of PLAs are immunonegative for TTF-1, there is a need for additional markers for PLA. Napsin A, an aspartic proteinase involved in the maturation of the surfactant protein B, has high specificity (88%–100%) and similar sensitivity (58%–80%) in detecting PLA as TTF-1.^{4,5} Combining TTF-1 and napsin A stains has been proposed to achieve higher sensitivity and specificity (95%) for diagnosing PLA with a greater diagnostic accuracy.^{4,5} The double staining of TTF-1 (nuclear) and napsin A (cytoplasmic) achieves excellent accuracy in small specimens while conserving the tissue for potential predictive marker testing, which is now an essential consideration in advanced lung cancer specimens.⁶ However, it is unclear whether this TTF-1/napsin A staining strategy is beneficial in establishing a diagnosis of PLA in patients with EPM who have a pulmonary nodule.

In this study, we evaluated the clinical utility of TTF-1 and napsin A immunohistochemical (IHC) staining in distinguishing primary from metastatic lung adenocarcinoma among 116 patients with EPM and 88 patients with PLA without EPM (PLA-WOEPM). We also investigated the frequency of PLA in patients with a history of EPA who have a new lung nodule.

Materials and Methods

Cases

The study was approved by the institutional review board of Northwestern University. The criterion for selecting the cases was that patients with or without a history of EPM were diagnosed as having adenocarcinoma with FNA and/or NCB. In total, 225 FNA and/or NCB cases were retrieved from January 2008 through July 2011 from the cytology records of the Northwestern Memorial Hospital. IHC results, clinical information (sex, age, smoking, and number of lung nodules detected by computed tomography [CT] scan), surgical follow-up (56 cases), and clinical follow-up were recorded.

First, the patients were divided into two major groups, with or without a history of EPA/nonadenocarcinoma malignancy based on their medical history in the patients' chart. The cytomorphology and histology of the lung nodules were compared with their previous EPM, whether same or different. IHC results, including TTF-1 and napsin A performed on FNA cell blocks/NCB or follow-up surgical resections, were recorded. If IHC for TTF-1 and napsin A had not been performed, it was conducted on residue cell blocks or NCBs. If the patients had follow-up surgical resection of lung nodules, the histology and IHC results were also reviewed. Clinical information, such as time from the previous diagnosis of EPM, stage, histologic type, lung nodule number and size, and one side of the lung or bilateral lung, was also considered. Based on cytomorphology and histology of cell blocks and/or NCB, IHC profile, and follow-up of surgical resection and clinical information, the patients were divided into five groups: (1) primary lung adenocarcinoma with a history of extrapulmonary adenocarcinoma (PLA-EPA), (2) primary lung adenocarcinoma with a history of extrapulmonary nonadenocarcinoma malignancy (PLA-EPNAM), (3) metastatic adenocarcinoma (MA), (4) primary lung adenocarcinoma without a history of extrapulmonary malignancy (PLA-WOEPM), and (5) metachronous lung adenocarcinoma with a history of previous lung adenocarcinoma. Twenty-one metachronous lung adenocarcinoma cases were excluded because they did not fit the purpose of the study. Twelve patients had a history of two EPMs and two patients had a history of three EPMs.

FNA and NCB

FNAs and NCBs were performed under image guidance (CT scan or ultrasonography). The FNA smears and touch prep slides of NCB were stained with Diff-Quik and Papanicolaou stains. On-site evaluation for adequacy and preliminary diagnosis was performed by cytology-certified cytopathologists. FNA aspirates were used to prepare cell blocks.

Histology and IHC

The cell blocks and needle cores were formalin fixed, paraffin embedded, sectioned, and stained with H&E. The H&E-stained cell block or core sections together with cytomorphology were examined for cytology diagnosis and compared with corresponding surgical pathology reports.

IHC stains for TTF-1 (cat 343M-98, Cell Marque, Rocklin, CA) and napsin A (cat CM388CK, Biocare Medical, Concord, CA) were performed on the sections of paraffin-embedded cell blocks or NCBs with appropriate positive and negative controls. Paraffin-embedded blocks were sectioned, deparaffinized, rehydrated, and blocked with methanolic 3% hydrogen peroxide. Antigen retrieval was performed in citrate buffer. The cutoff for positive staining is at least 5% of cells with moderate or strong intensity staining for IHC markers.

Statistical Analysis

Sensitivity is defined as number of patients with PLA with positive IHC results divided by all patients with PLA with or without EPM. Specificity is defined as the number of patients without PLA with negative IHC results divided by all patients without PLA. Positive predictive value is defined as the number of patients with PLA with positive results divided

by all patients with positive results. Negative predictive value is defined as the number of patients without PLA with negative results divided by all patients with negative results. The χ^2 tests were applied to test the correlation of PLA with smoking and multiple nodules. Bayesian probabilities were applied to show the prior and posterior probabilities for new lung adenocarcinoma as a function of smoking, multiple nodules, and known history of EPM. Prior probability is defined as the number of patients with PLA with or without positive results divided by all patients with PLA. Posterior probability is calculated as follows: incidence in the population $\times$ prior probability / [incidence in the population $\times$ prior probability + (1 – incidence in the population) $\times$ (1 – prior probability)].

Results

FNA and NCB Cytomorphology and Histomorphology

Diff-Quik–stained FNA and touch prep NCB slides showed pleomorphic cuboidal, columnar, or polygonal cells arranged in acinar, tubular, papillary, or three-dimensional architectures, with a delicate or vacuolated cytoplasm Image 1A and Image 1B. Histomorphology of cell blocks and NCB showed invasive adenocarcinoma Image 1C and Image 1D. Based on the cytomorphology and histomorphology, a diagnosis of adenocarcinoma was rendered.

Immunohistochemistry

IHC for TTF-1, napsin A, and some other suitable biomarkers for metastatic malignancies was performed on 168 cases. Among 61 metastatic carcinomas, two were focally positive for TTF-1 (one metastatic colonic and one metastatic pancreatic adenocarcinoma). The sensitivity, specificity, positive predictive value, and negative predictive value of TTF-1 were 89.4%, 93.9%, 98.1%, and 72.1%, respectively Image 1E and Image 1F.

Our study showed that one metastatic breast carcinoma case was focally positive for napsin A. The sensitivity, specificity, positive predictive value, and negative predictive value of napsin A were 93.3%, 94.7%, 93.3%, and 94.7%, respectively Image 1G and Image 1H.

High Frequency of Second PLA-EPM/EPA in Patients With Lung Nodules

Our study showed that in patients with a history of EPM, 47.4% of new lung nodules were PLA Table 1. In patients with a history of EPA, 40.2% of new lung nodules were PLA (Table 1).

In patients with a diagnosis of PLA, 38.5% had a history of EPM, including 28.7% with EPA Table 2. Patients' ages ranged from 41 to 91 years, with a mean of 69.1 years. PLA predominantly involved women (71.3%).

Primary Organs for EPM

The primary organs for EPM are listed in Table 3. The most common organs for patients with PLA-EPA were the breast (35.8%), followed by the colon (13.2%), prostate (11.3%), endometrium (5.7%), and ovary (5.7%) (Table 3). The most common organs for patients

with MA were the colon (32.8%), followed by the breast (28.1%), pancreas (7.8%), prostate (7.8%), endometrium (6.3%), and ovary (6.3%) (Table 3).

Correlation of Smoking History, Pulmonary Nodules, and History of EPM With PLA

In this study, 37 (67.3%) of 55 patients with PLA-EPM, 71 (80.7%) of 88 patients with PLA-WOEPM, and 24 (39.3%) of 61 patients with MA had a history of smoking Table 4. The incidence of smoking history was significantly higher in patients with PLA (EPM or WOEPM) than in those with MA ($P < .005$ and $P < .005$, respectively). The incidence of smoking history in patients with PLA-EPM was less than that in patients with PLA-WOEPM, although this was not statistically significant (P was just slightly larger than .05).

The CT scan results were collected to determine the number of pulmonary nodules and whether they were single vs multiple nodules (≥ 2 nodules). Thirty (54.5%) of 55 patients with PLA-EPM, 48 (54.5%) of 88 patients with PLA-WOEPM, and 52 (85.2%) of 61 patients with MA had multiple nodules (Table 4). The incidence of pulmonary multiple nodules was significantly higher in patients with MA than in patients with PLA-EPM or PLA-WOEPM (Table 4) ($P < .005$ and $P < .005$, respectively), whereas there was no significant difference in incidence between PLA-EPM and PLA-WOEPM.

The correlation of PLA with smoking history, multiple nodules, and a history of EPM was determined by Bayesian prior and posterior probabilities Table 5. In this study cohort, 143 patients were diagnosed with PLA. A patient with a smoking history had a posterior probability of 87.8% of having PLA, while a patient with no smoking history had a posterior probability of 43.2%. A patient with multiple nodules had a posterior probability of 73.7% of having PLA, while a patient with a single nodule had a posterior probability of 66.2%. A patient with a history of EPM had a posterior probability of 59.5% of having PLA, while a patient with no history or EPM had a posterior probability of 78.9%. Therefore, a patient with a smoking history, multiple nodules, and WOEPM had a higher chance of having PLA.

Discussion

The major finding of this study is the high frequency of PLA identified in the lung nodules of patients with a known EPM (47.4%) or a known EPA (40.2%), which has not been stressed before, to our knowledge. In our patient cohort, the Bayesian posterior probabilities for patients with PLA with EPM and WOEPM were 59.5% and 78.9%, respectively. Previous studies showed that the lungs are quite often involved, with tumor spread from extrapulmonary solid malignancies in 20% to 54% of cases.³ Based on our single-center study, it will be of interest determining the prevalence of PLA in a prospective study using dual immunostaining with TTF-1 and napsin A of all lung nodules in patients with a history of EPM and how management based on these results alters outcome. Surgical resection is safe, effective, and warranted in patients with a second PLA if they satisfy the usual criteria of operability after full assessment.⁷

In our study series, we also found that 38.5% of patients who were diagnosed with PLA based on TTF-1 and napsin A staining as well as follow-up surgical resection had a history of EPM, which is much higher than the rate reported in the literature (3%–7%).³ One

possibility to account for the discrepancy in the prevalence of PLA in patients with EPM is that some patients with widespread metastasis may not undergo lung biopsy but rather have a biopsy of an alternative site (eg, liver, lymph nodes, bone, or other organs). This substantially increases the frequency of detecting MA/metastatic malignancy and decreases the frequency of detecting PLA in patients with a history of EPM with a lung nodule. Another possibility to account for the disparity is the differences between the study cohorts.

Our results showed that the incidence of patients with a smoking history was significantly higher in PLA (EPM or WOEPM) than in MA. This indicates that smoking plays a significant role in the increasing incidence of PLA for patients with or without a history of EPM, which has been well documented in the literature.⁸ In our patient cohort, a patient with a smoking history had a posterior probability of 87.8% of having PLA, while a patient without a smoking history had a posterior probability of 43.2%. The incidence of smoking history in PLA-EPM was less than that in PLA-WOEPM, although not significant (P was slightly greater than .05). An increase in case number may show a statistical difference. This result suggested that besides smoking, other factors, such as occupational exposure, hereditary factors, and genomic mutations of tumor suppressor genes, also play a role in the increased incidence of PLA in the patients with a history of EPM.^{8–10}

Our data showed that multiple nodules in the lung are more commonly seen in MA. However, multiple nodules were shown in 54.5% of patients with PLA as detected by a CT scan. In our patient cohort, the Bayesian posterior probabilities for multiple and single nodules were 73.3% and 66.2%, respectively. Therefore, multiple lung nodules might not be a good criterion for predicting MA.

In this study, we noted that one metastatic colonic and one metastatic pancreatic adenocarcinoma were focally positive for TTF-1, while one metastatic pancreatic adenocarcinoma was focally positive for napsin A. Our results showed that IHC for TTF-1 and napsin A has high sensitivity, specificity, positive predictive value, and negative predictive value in identifying PLA in patients with EPM/EPA. These findings are in accordance with the work of others except for sensitivity for napsin A in detecting PLA, which is higher in our study (93.3% vs 75%–82%).^{4,5} There is some evidence that TTF-1 immunostaining is occasionally positive in adenocarcinomas arising in different organs, including the thyroid, colon, gynecologic tract, ovary, urinary bladder, prostate, and breast.^{5,11–15} However, to our knowledge, the possible immunoreactivity of pancreatic adenocarcinoma to TTF-1 noted herein has not been reported. Napsin A expression has been reported occasionally in carcinomas of the endometrium, liver (hepatocellular carcinoma), pancreas, urinary tract (urothelial carcinoma), stomach, kidney, thyroid, esophagus, and colon.^{5,16–19} Notably, the possible immunoreactivity of breast carcinoma to napsin A reported herein is novel. Two situations that possibly cause false positivity in NCBs and cell blocks should be excluded by careful evaluation. One situation is the “edge effect,” with positivity seen at the edges of cores or cell blocks and negativity at the center of the tissue. Another situation is residue or contamination of benign respiratory epithelial cells, which could be eliminated by careful evaluation histomorphology of H&E-stained NCBs and cell blocks as a comparison.

Another major finding of this study is the use of TTF-1 and napsin A IHC staining of lung nodules to more accurately identify a PLA that might have been misclassified as originating from another organ outside the lung. The most common organ for patients with PLA-EPA was the breast (35.8%), followed by the colon (13.2%), prostate (11.3%), endometrium (5.7%), ovary (5.7%), and others. The most common organs resulting in metastatic pulmonary nodules in this series were the colon (32.8%), breast (28.1%), pancreas (7.8%), prostate (7.8%), endometrium (6.3%), ovary (6.3%), and others. Individually, our results firmly support that TTF-1 and napsin A IHC have a high diagnostic accuracy in identifying the lung as the origin of the adenocarcinoma. A lung nodule diffusely positive for both TTF-1 and napsin A, which occurred in 87% of our patients, is confirmative for PLA given a specificity approaching 100%. However, if a lung nodule is focally positive for either TTF-1 or napsin A, a comparison of cytomorphology and/or histomorphology with previous biopsy or surgical resection specimens and IHC for a broader panel of markers should be performed to distinguish PLA from MA. Based on the previous EPM, selected limited organ-specific IHC markers, such as gastrointestinal markers (CK20 and CDX2), breast markers (ER, PR, BRST-1, and mammaglobin), thyroid marker (thyroglobulin), and squamous cell and urothelial cell markers (p63, high-molecular-weight cytokeratin, and CK5/6), should be included in the IHC study.

In conclusion, TTF-1 and napsin A are excellent IHC markers for identifying PLA in patients with EPM who have a lung nodule. We reason that incorporating dual IHC staining with TTF-1 and napsin A in assessing lung nodules in patients with EPM will improve the diagnosis and management in these patients. Most important and interestingly, we found that close to half of the lung nodules in patients with EPM were PLA. Our findings warrant that all lung nodules in patients with EPM should be investigated to distinguish PLA from metastatic malignancy by comparison of cytomorphology and/or histomorphology with previous biopsy or surgical resection specimens, along with IHC evaluation that includes TTF-1 and napsin A as well as selected other suitable organ-specific IHC markers. This information should affect prognosis and management since surgical resection is effective and warranted in patients with PLA if they satisfy the usual criteria of operability after full assessment.⁷

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Image 1.

Cytomorphology, histomorphology, and immunohistochemistry (IHC) images of primary lung adenocarcinoma (**A**, **C**, **E**, and **G**) and metastatic breast adenocarcinoma (**B**, **D**, **F**, and **H**). **A** and **B**, Fine-needle aspiration cytomorphology (Diff-Quik; $\times 600$). **C** and **D**, Histomorphology of needle core biopsy (H&E; $\times 600$). **E** and **F**, IHC for thyroid transcription factor 1 ($\times 600$). **G** and **H**, IHC for napsin A ($\times 600$). **I** and **J**, IHC for estrogen receptor ($\times 600$).

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High Frequency of Primary Lung Adenocarcinoma in Patients With a History of Extrapulmonary Malignancy

Table 1

Group	No. of Patients	F/M, No. (F %)	Age, Range (Mean ± SD), y	Frequency 1, % ^a	Frequency 2, % ^b
PLA-EPA	41	32/9 (78.0)	41–91 (72.5 ± 13.1)	35.3	40.2
PLA-EPNAM	14	12/2 (85.7)	53–87 (68.7 ± 10.5)	12.1	
MA	61	43/18 (70.5)	29–86 (59.9 ± 13.8)		
Total	116	87/29 (75.0)	29–91 (65.4 ± 14.4)	47.4	

PLA-EPA, primary lung adenocarcinoma with a history of extrapulmonary adenocarcinoma; PLA-EPNAM, primary lung adenocarcinoma with a history of extrapulmonary nonadenocarcinoma malignancy; MA, metastatic adenocarcinoma.

^aFrequency of PLA in patients with a history of extrapulmonary malignancy.

^bFrequency of PLA in patients with a history of EPA.

Table 2

High Frequency of a History of Extrapulmonary Malignancy in Patients Diagnosed With Primary Lung Adenocarcinoma

Group	No. of Patients	F/M, No. (F %)	Age, Range (Mean $\pm$ SD), y	Frequency, % ^a
PLA-EPA	41	32/9 (78.0)	41–91 (72.5 $\pm$ 13.1)	28.7
PLA-EPNAM	14	12/2 (85.7)	53–87 (68.7 $\pm$ 10.5)	9.8
PLA-WOEPM	88	58/30 (65.9)	42–83 (67.7 $\pm$ 11.0)	
Total	143	102/41 (71.3)	41–91 (69.1 $\pm$ 11.7)	38.5

PLA-EPA, primary lung adenocarcinoma with a history of extrapulmonary adenocarcinoma; PLA-EPNAM, primary lung adenocarcinoma with a history of extrapulmonary nonadenocarcinoma malignancy; PLA-WOEPM, primary lung adenocarcinoma without a history of extrapulmonary malignancy.

^aFrequency of PLA in patients with a history of EPA, EPNAM, or extrapulmonary malignancy.

Table 3

Frequency of Extrapulmonary Malignancy

Organ	No. (%)			
	PLA-EPA	PLA-EPNAM	MA	Total
Bladder	2 (3.8)	1 (6.7)	0	3 (2.3)
Breast	19 (35.8)	0	18 (28.1)	37 (28.0)
Cervix	0	0	1 (1.6)	1 (0.8)
Colon	7 (13.2)	1 (6.7) ^a	21 (32.8)	29 (22.0)
Endometrium	3 (5.7)	0	4 (6.3)	7 (5.3)
Esophagus	1 (1.9)	0	1 (1.6)	2 (1.5)
Head, squamous carcinoma	1 (1.9)	2 (13.3)	1 (1.6)	4 (3.0)
Kidney	0	0	2 (3.1)	2 (1.5)
Liver	0	0	1 (1.6)	1 (0.8)
Lung, adenocarcinoma	4 (7.5)	1 (6.7)	0	5 (3.8)
Lung, squamous carcinoma	1 (1.9)	0	0	1 (0.8)
Lymph node, lymphoma	2 (3.8)	5 (33.3)	0	7 (5.3)
Skin, melanoma	1 (1.9)	3 (20.0)	0	4 (3.0)
Ovary	3 (5.7)	0	4 (6.3)	7 (5.3)
Pancreas	1 (1.9)	0	5 (7.8)	6 (4.5)
Pheochromocytoma	0	1 (6.7)	0	1 (0.8)
Prostate	6 (11.3)	0	5 (7.8)	11 (8.3)
Sarcoma	0	1 (6.7)	0	1 (0.8)
Stomach	1 (1.9)	0	1 (1.6)	2 (1.5)
Thyroid	1 (1.9)	0	0	1 (0.8)

MA, metastatic adenocarcinoma; PLA-EPA, primary lung adenocarcinoma with a history of extrapulmonary adenocarcinoma; PLA-EPNAM, primary lung adenocarcinoma with a history of extrapulmonary nonadenocarcinoma malignancy.

^aNeuroendocrine neoplasm.

Table 4Correlation of Primary Lung Adenocarcinoma With Smoking History and Multiple Nodules^a

Group	No. of Patients	Smoker	Multiple Nodules
PLA-EPM, No. (%)	55	37 (67.3)	30 (54.5)
PLA-WOEPM, No. (%)	88	71 (80.7)	48 (54.5)
MA, No. (%)	61	24 (39.3)	52 (85.2)
P1, <i>P</i> value		<.005	<.005
P2, <i>P</i> value		<.005	<.005

MA, metastatic adenocarcinoma; P1, comparison of PLA-EPM with MA; P2, comparison of PLA-WOEPM with MA; PLA-EPM, primary lung adenocarcinoma with a history of extrapulmonary malignancy; PLA-WOEPM, primary lung adenocarcinoma without a history of extrapulmonary malignancy.

^a A χ^2 test was used for statistical analysis.

Table 5

Bayesian Probabilities of Primary Lung Adenocarcinoma in Patients With a Smoking History, Pulmonary Nodules, and a History of Extrapulmonary Malignancy^a

Category	No. of Patients (n = 143)	Prior Probability, %	Posterior Probability, %
Smoker	108	75.5	87.8
Nonsmoker	35	24.5	43.2
Multiple nodules	78	54.5	73.7
Single nodule	65	45.5	66.2
EPM	55	38.5	59.5
WOEPM	88	61.5	78.9

EPM, extrapulmonary malignancy; WOEPM, without extrapulmonary malignancy.

^a Bayesian probability was used for statistical analysis. In this cohort, 70.1% of patients with adenocarcinoma (with or without EPM) had primary lung adenocarcinoma.