Relationship Between a History of Antecedent Cancer and the Probability of Malignancy for a Solitary Pulmonary Nodule*

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Study objectives: To determine the probability of malignancy for a solitary pulmonary nodule (SPN) as a function of cancer history.

Setting and design: Patients who had undergone resection of SPNs at Brigham and Women's Hospital between August 1989 and October 1998 were analyzed. The cohort was split into the following three groups: no history of cancer; history of lung cancer; and history of extrapulmonary malignancy. The histology of the SPN was determined after excision. Logistic regression was used to evaluate the effect of covariates on the probability of malignancy.

Measurements and results: A total of 1,104 patients (55% women; median age, 64 years; age range, 17 to 88 years) underwent removal of 353 benign lesions (32%), 638 non-small cell lung cancers (NSCLCs) [58%], and 113 metastases (10%). Antecedent cancer history was significantly associated with final diagnosis (p < 0.0001), with SPNs being malignant in 63% of patients with no previous cancer, 82% of those with a history of lung cancer (NSCLC, 80%; metastases, 2%), and 79% of patients with history of extrapulmonary cancer (NSCLC, 41%; metastases, 38%). There was no difference in the cause of SPNs between patients with a history of a single cancer and those with a history of multiple cancers. The probability of a benign cause ranged between 62% for nodules < 1 cm to 17% when nodules were > 3 cm, if the patient had no history of cancer (p < 0.0001). The probability of an SPN being benign was cut in half if there was a history of cancer. Among patients with previous extrapulmonary malignancy, age, smoking history, and histology were predictors of diagnosis (p < 0.0001). These variables were used to construct a clinical score to predict the probability of an SPN being a NSCLC or metastasis in these patients.

Conclusions: A history of cancer is an important predictor of the probability of malignancy in new SPNs. Metastases from previous cancer account for almost half of SPNs seen among patients in this subgroup. Diagnosis depends on the histology of previous malignancies, smoking history, age, and size of the SPN.

Key words: antecedent cancer; cancer history; clinical score; lung cancer; metastasis; solitary pulmonary nodule

Abbreviations: NSCLC = non-small cell lung cancer; SPN = solitary pulmonary nodule

Solitary pulmonary nodules (SPNs) represent a common problem, with > 130,000 new nodules recognized each year in patients in the United States. Furthermore, they entail a difficult diagnostic challenge. Although clinical characteristics and radiologic characteristics are used to estimate the probability of malignancy for a particular nodule, they have been unreliable.

An SPN in a patient with a history of cancer may be a metastasis from the previous known neoplasm. It also may be a primary non-small cell lung cancer (NSCLC) or a benign lesion. Lung cancer is currently so prevalent within the United States, that more SPNs will be primary lung cancers than metastases from extrathoracic primary tumors in patients with no history of malignancy. The corre-
spending probabilities for patients with a history of cancer, however, are not well-known. The risk of developing a new malignancy is 5 to 15 times higher in a patient with an unrelated previous cancer than in the general population, probably due to genetic predisposition and exposure to common carcinogens such as smoking. Thus, it is reasonable to expect that a significant number of new SPNs in patients with a history of other malignancies will prove to be new primary lung cancers.

This concept has been substantiated over the last 50 years by several studies that have suggested that SPNs occurring in the setting of a previous malignancy may more frequently represent primary lung neoplasms than metastases from the known malignancies. Furthermore, the chance of metastasis varies depending on the histology of the primary tumor.

However, the previous literature has become outdated. The databases used to calculate the probability of malignancy in an SPN depended on nodules excised by open thoracotomy in the 1960s and 1970s. CT scans were unavailable in most of that era, there were half as many new lung cancer cases diagnosed each year compared to the present, tuberculosis was more common, and slow-growing or small nodules were frequently not excised due to the morbidity from undergoing a thoracotomy. New CT scan techniques have made it possible to identify very small nodules that are <1 cm in diameter. Furthermore, the reduction in operative morbidity associated with thoracoscopic excision has reduced the clinical threshold to remove small nodules. For these reasons, it is appropriate to calculate the probability that a new SPN represents a malignancy based on data accumulated from the excision of nodules in the 1990s.

Contemporary knowledge of the probability of malignancy in a pulmonary nodule in the setting of a history of previous cancer, and the identification of the factors that may alter such a probability, would be helpful in defining the optimal diagnostic and therapeutic approach. A portion of this subgroup of patients with a history of malignancy has been specifically excluded from previous studies. We sought to determine the probability of malignancy for an SPN within the context of cancer history, and, in particular, to define the occurrence of metastases and primary lung malignancies among these patients.

Patients and Methods

The base population for this study was composed of 1,112 patients who underwent resection of an SPN at Brigham and Women’s Hospital between August 1989 and October 1998. Patients without a complete clinical history (six patients) or who had previously undergone resection of pulmonary metastases (two patients) were excluded. Therefore, 1,104 patients with an SPN undergoing an initial excisional biopsy were included in the analysis.

Preoperative information was collected prospectively for each patient on referral to the Division of Thoracic Surgery and was compiled into a computerized database by a full-time surgical nurse/data manager. The data included sex, age, smoking history, asbestos exposure, symptoms, and clinical history of previous malignancies, including site and histology. Medical records at our institution, when available, confirmed the history of cancer. Size and final diagnosis for each SPN were obtained from pathology reports.

Based on cancer history, patients were grouped into the following three categories: no history of malignancy; history of lung cancer; or history of extrapulmonary cancer that was potentially metastatic to lung. Those patients with a history of both lung neoplasms and extrapulmonary neoplasms, were included in the category of lung cancer. Individuals with a history of extrapulmonary cancer were further categorized according to their type of neoplasm into prostate, breast, GI, melanoma, renal, sarcoma, and others. Patients with multiple extrapulmonary neoplasms were included in a separate category, and those having only tumors that were not potentially metastatic to the lung (ie, nonmelanomatous skin cancer and brain/cerebellar tumors) were considered to have a negative history of cancer.

SPNs were classified as benign, lung cancer, or metastasis, according to the final pathologic diagnosis following excisional biopsy of a specimen. No distinction was made between apparent recurrence and new primary malignancy among patients with a history of lung cancer. For patients with a history of extrapulmonary neoplasms in which the nodule could histologically represent either a primary lung cancer or a metastasis, the pathologist would favor one of the diagnoses by immunostaining and reviewing the slides from the previous malignancy. When both diagnoses were equally favored, the SPN was classified as a metastasis.

Percentages were used to describe and compare the distribution of final diagnoses between groups by cancer history. Categoric predictors of final diagnosis were analyzed by χ² test or Fisher exact test, as appropriate. Analysis of variance and Kruskal-Wallis test were used for continuous predictors, depending on the normality of the variable. Significant covariates were modeled with logistic regression and were based on the coefficients from the model, and a clinical score was designed to predict the probability of lung cancer and metastasis for patients with a previous extrapulmonary malignancy. The fit of the model was evaluated with the C-statistic. The C-statistic is a measurement of the fitness of the logistic regression model to predict a certain outcome, equivalent to the area under a receiver operating characteristic curve, with 1.0 being complete concordance and 0.5 being the equivalent of tossing a coin. All analyses were performed using a statistical software package (SAS for Windows, version 8.1; SAS Institute; Cary, NC).

Results

One thousand one hundred four patients (women, 55%; men, 45%; median age, 64 years; age range, 17 to 88 years) were included in the study. The cohort was composed of 767 patients (69%) without a history of cancer, 49 patients (4%) with previous lung cancer; and 288 patients (26%) with a history of extrapulmonary malignancies. Of the 49 patients with a history of lung cancer, 13 also had a history of extrapulmonary neoplasms.
Cancer Probabilities

Most resected SPNs were malignant. Lesions were benign in 353 cases (32%), NSCLCs were present in 638 cases (58%), and metastases were present in 113 cases (10%). The distribution of patients according to cancer history and diagnosis is shown in Table 1.

Cancer history was significantly associated with final diagnosis (p < 0.0001). Among patients with no history of cancer, 37% of SPNs were benign, while 63% were malignant (NSCLC, 63%; metastases from previous unrecognized extrapulmonary primary tumor, three patients). However, those patients with a history of lung cancer had only a 16% probability of the SPN being benign and had an 82% probability of malignancy (NSCLC, 80%; metastasis, one patient). This shift toward a higher probability of malignant cause of a new lung nodule continued in patients with a history of extrapulmonary cancer, with only 21% of SPNs found to be benign and 79% malignant (NSCLC, 41%; metastases, 38%). Three patients with no cancer history had lesions that were compatible with metastases from unknown primary tumors. The only patient with a history of lung cancer in whom a nonlung metastasis was diagnosed had experienced a previous extrapulmonary malignancy.

To summarize, patients within this cohort with no history of cancer had a 63% chance of a malignant nodule. Patients with a history of lung cancer had an 82% chance of a malignant cause of the new nodule, with lung cancer being the most likely specific cause. Patients with a history of other types of cancer still had a 79% probability of malignancy but with a roughly even split in the odds of lung cancer vs a metastasis from the previous cancer.

We further analyzed the three subgroups as a function of the pathologic size of the nodule. In patients with no history of cancer, the probability of a diagnosis of a benign nodule ranged from 62% for nodules < 1 cm to 17% for nodules ≥ 3 cm (p < 0.0001) [Table 2]. The remaining nodules were nearly all lung cancers. For patients with a history of lung cancer, the probability of a benign nodule was approximately half as much for any given size compared to those patients with no history of cancer. Thus, there was a 30% chance that a nodule was benign if it was < 1 cm in size, decreasing to a 10% probability for nodules > 3 cm in size if there was history of lung cancer (difference not significant). Nearly all other nodules in this subgroup were lung cancers. Finally, for patients with a history of extrathoracic malignancy, the probability of a new benign SPN ranged from 33% for nodules < 1 cm to 9% for nodules > 3 cm (p = 0.002) [Table 3]. The remaining probabilities were split almost evenly between new lung cancers and metastases from the previous malignancy, unless the nodule was > 3 cm. These large nodules had a higher probability of being a new lung cancer.

Analysis of Predictors After Antecedent Extrapulmonary Cancer

Among patients with a history of extrapulmonary cancer (258 patients), age was associated with histology (p < 0.0001). The mean ages for patients with benign nodules, NSCLC, and metastatic disease were 60.1, 67.0, and 54.6 years, respectively. Smoking history also was related to final diagnosis, as a continuous variable (ie, No. of pack-years of total exposure), a categoric variable (ie, current, former, or never smoker), or a dichotomous variable (ie, heavy exposure as defined by a smoking history of ≥ 20 pack-years) [p < 0.0001]. The percentage of SPNs being NSCLCs was 65% for current smokers, 42% for former smokers, and 20% for nonsmokers. The mean (± SD) sizes of the SPNs were 1.3 ± 1.0 cm for benign tumors, 2.2 ± 1.6 cm for NSCLCs, and 1.8 ± 1.4 cm for metastases (p < 0.0001). Nei-

### Table 1—Distribution of Patients According to Cancer History and Final Diagnosis*

<table>
<thead>
<tr>
<th>Cancer History</th>
<th>Patients, No.</th>
<th>Benign</th>
<th>Lung Cancer</th>
<th>Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapulmonary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>19</td>
<td>4 (21)</td>
<td>12 (63)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Breast</td>
<td>54</td>
<td>13 (24)</td>
<td>29 (54)</td>
<td>12 (22)</td>
</tr>
<tr>
<td>GI</td>
<td>39</td>
<td>5 (12)</td>
<td>12 (31)</td>
<td>22 (56)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>19</td>
<td>3 (16)</td>
<td>4 (21)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Renal</td>
<td>11</td>
<td>2 (18)</td>
<td>2 (18)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>12</td>
<td>3 (25)</td>
<td>2 (17)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Others†</td>
<td>85</td>
<td>23 (27)</td>
<td>39 (46)</td>
<td>23 (27)</td>
</tr>
<tr>
<td>Several tumors</td>
<td>49</td>
<td>8 (16)</td>
<td>18 (37)</td>
<td>23 (47)</td>
</tr>
<tr>
<td>Lung‡</td>
<td>49</td>
<td>8 (16)</td>
<td>40 (82)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>None</td>
<td>767</td>
<td>254 (37)</td>
<td>480 (63)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Total</td>
<td>1,104</td>
<td>353 (32)</td>
<td>638 (58)</td>
<td>113 (10)</td>
</tr>
</tbody>
</table>

*Values given as No. (%). 
†Only patients with a single other malignancy are included. 
‡Patients with clinical history of lung cancer, regardless of previous extrapulmonary malignancies (13 patients included also had extrapulmonary malignancies).

### Table 2—Diagnosis as a Function of Size Among Patients With No History of Cancer*

<table>
<thead>
<tr>
<th>SPN Size, cm</th>
<th>No.</th>
<th>Benign</th>
<th>Lung Cancer</th>
<th>Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.0</td>
<td>159</td>
<td>99 (62)</td>
<td>59 (37)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>1.0–1.9</td>
<td>248</td>
<td>111 (45)</td>
<td>136 (55)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>2.0–2.9</td>
<td>154</td>
<td>35 (25)</td>
<td>115 (75)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>≥ 3.0</td>
<td>206</td>
<td>36 (17)</td>
<td>170 (83)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>767</td>
<td>254 (37)</td>
<td>480 (63)</td>
<td>3 (0.4)</td>
</tr>
</tbody>
</table>

*Values given as No. (%).
There was no significant difference in histology between patients with a history of a single extrapulmonary cancer and those with a history of several tumors. However, as summarized in Table 1, patients with history of breast, prostate, or "other" cancers had fewer metastases and more NSCLCs ($p < 0.0001$).

**Prediction Rule of Cancer With Antecedent Extrapulmonary Malignancy**

A logistic regression model to predict final diagnosis was constructed including age (dichotomous variable with a cutoff of 55 years), smoking history (categoric variable including current, former, or never smokers), and type of previous extrapulmonary cancer. The models were designed using all but 37 patients who had missing values for smoking history. The coefficients obtained from the regression model then were used to design a simple clinical rule (Table 4) to predict the probabilities of an SPN being a NSCLC or a metastasis in a patient with a history of extrapulmonary cancer that could potentially metastasize to the lungs.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>$&lt; 55$ yr</td>
<td>0</td>
</tr>
<tr>
<td>$\geq 55$ yr</td>
<td>2</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>0</td>
</tr>
<tr>
<td>Former</td>
<td>1</td>
</tr>
<tr>
<td>Current</td>
<td>2</td>
</tr>
<tr>
<td>Cancer history</td>
<td></td>
</tr>
<tr>
<td>Renal, GI, sarcoma, melanoma</td>
<td>0</td>
</tr>
<tr>
<td>Several malignancies</td>
<td>0</td>
</tr>
<tr>
<td>Breast, prostate, others</td>
<td>2</td>
</tr>
</tbody>
</table>

*The clinical score was constructed for patients with history of extrapulmonary cancer and no previous lung cancer.

†The total score for a patient is constructed by adding the numbers corresponding to the score for each variable.

Higher clinical scores translate into a higher probability of the SPN being an NSCLC, while lower scores indicate a higher probability of the SPN being a metastasis. Table 5 shows the distribution of patients by final diagnosis according to their clinical score. C-statistics for the prediction of metastasis and NSCLC were 0.801 and 0.775, respectively.

The incorporation of size into the predictive model increased its complexity and did not provide additional power. Therefore, it was decided not to include it as a variable in the model.

**DISCUSSION**

An SPN in this highly selected cohort was found to be from a malignant cause in at least 63% of cases, even with no history of cancer. A history of extrapulmonary neoplasms increased the overall risk of cancer in an SPN from 63 to 79%. Primary lung cancer remained the most important cause of malignancy (52%) in this subgroup of patients, although there was roughly an even chance that a malignant nodule within this group represented a metastasis (48%). Nodules were also malignant in 82% of patients with a history of lung cancer. However, as would be expected, almost all of these neoplasms corresponded either to recurrences of the lung cancer or to new primary lung tumors.

The incidence of malignancy in a patient with a history of cancer has changed dramatically with time. Several decades ago, some benign diseases like tuberculosis were significantly more prevalent, chemotherapeutic agents were less effective in controlling primary tumors, and some of the currently known risk factors for cancer were not recognized. This difference in incidence is confirmed when comparing the results of previous studies with those of more current ones, including ours. In the series by Cahan et al. in the 1960s, an SPN in a patient with a history of sarcoma or melanoma was metastatic in origin in $> 90\%$ of the cases. On the contrary, some
studies\(^1\) have shown that patients with a history of the same tumors have a 60% chance of their SPN being a metastasis and a 24% probability of it being a lung cancer. These numbers are in accordance with the results of our study (ie, approximately 60% of SPNs being metastases and 20 to 30% primary lung cancers in patients with history of sarcoma, melanoma, or GI cancer).

The probability of an SPN being a metastasis in a patient with a history of extrapulmonary cancer depends on the histology of the previous tumor. In this sense, our study confirmed the findings of the study by Quint et al.,\(^1\) in which the final diagnoses of the same tumors have a 60% chance of their SPN being a metastasis and a 24% probability of it being a lung cancer. In the 31 patients with a history of salivary gland, thyroid, thymic, or uterine cancer (metastases, 52%; lung cancer, 42%). Metastases were rare among patients with head and neck, urinary bladder, breast, uterine cervix, biliary tree, esophageal, ovarian, prostate, or stomach cancers, and they were nonexistent in patients with lymphoma or leukemia. Another study published by Cahan\(^1\) in the 1960s reported the ratio of metastases to primary lung cancers in 332 patients with a history of cancer to be higher for sarcomas (15:1) and melanomas (9:1), than for colon cancer (1:1), testicular cancer (0.8:1), renal cancer (0.8:1), breast cancer (0.5:1), prostate cancer, or head and neck cancer.

According to our study, the probability of metastasis in an SPN decreases from around 60% for melanomas, sarcomas, renal cancer, and GI cancer to 20% for prostate and breast cancers. No specific analyses were performed for other histologic diagnoses, since we considered the numbers for these malignancies to be too small to draw any definite conclusions. One interesting observation in our data was that the probability of metastasis in an SPN was the same whether there was a history of more than one extrapulmonary malignancy or a history of only one previous cancer.

In 1997, Swensen et al.\(^1\) published a clinical prediction model to predict the probability of malignancy in SPNs between 4 and 30 mm in size. This model was generated from the logistic regression of clinical and radiologic variables among a random sample of 419 retrospective cases. It was then tested on a separate retrospective group of 210 patients with moderate predictive value, as measured by 83% area under the receiver operating characteristic curve. Furthermore, they found that three clinical characteristics (ie, age, cigarette-smoking status, and history of cancer > 5 years ago) and three radiologic characteristics (ie, diameter, spiculation, and upper lobe location) were independent predictors of malignancy. We found the same three clinical characteristics and the diameter to have predictive value. We did not prospectively record other radiologic variables in our database.

Our analysis extends and updates the previous work by Swensen et al.\(^1\) in several ways. Although their model was published in 1997, the data were collected between 1984 and 1986. There were an estimated 150,000 new cases of lung cancer in 1984,\(^1\) compared to 170,000 in 1989 and 1998\(^1\) (a 13% increase). Our 1,112-patient database is nearly three times as large as that of Swensen et al.\(^1\) Patients in whom a diagnosis of any type of cancer had been made within the last 5 years were excluded from the database of the previous group, yet physicians are frequently asked to evaluate nodules in this patient population as well (eg, breast cancer survivors and prostate cancer survivors). Whereas Swensen et al.\(^1\) differentiated benign causes from all malignant causes, we have tried to further dichotomize the malignant group into primary lung cancer vs metastatic cancer from an extrathoracic source.

The overall probability of malignancy found by Swensen et al.\(^1\) (malignant, 23%; benign, 65%; indeterminate, 12%) is different from our overall probability of 68% malignant (primary lung cancer, 58%; metastases, 10%) and 32% benign. A part of this difference may represent a change in the actual probabilities that any given nodule is malignant over the past 2 decades. Lung cancer is more prevalent, tuberculosis is less common, and more aggressive surveillance programs are identifying lung nodules using CT scans. Furthermore, the difference may reflect a reduced threshold to excise these nodules by thoracoscopic techniques during the last 2 decades, instead of open thoracotomy, as was necessary in the mid-1980s. Additionally, it may represent a geographic difference since the rate of fungal nodules is different in the upper Mississippi River Valley compared to that in New England. Finally, and most likely, the increased probability of malignancy within our database may reflect a referral bias, since only those patients who are believed likely to have a malignancy are generally referred for excision. This may explain the higher rate of malignancy in other surgical series. However, when one considers that even patients who have been referred for evaluation with a nodule between 1 and 2 cm in size have at least a 55% probability of malignancy, it is hard not to recommend excision unless the patient lacks sufficient cardiopulmonary reserve. Since 1999, we have followed the Lung Cancer Action Project.
protocol\textsuperscript{19} in regard to newly diagnosed nodules. Namely, observing and repeating scans in 3 months for nodules ≤ 5 mm, biopsying all nodules > 1 cm, and evaluating nodules between 5 mm and 1 cm on a case-by-case basis.

Size, grouped into discrete categories, proved to be an important factor in defining the histologic diagnosis of SPNs. The probability of an SPN having a benign diagnosis in a patient without a history of cancer was 62% if the lesion was < 1.0 cm, 45% if it was between 1.0 and 1.9 cm, 25% if it was between 2.0 and 2.9 cm, and 17% if it was ≥ 3.0 cm. These numbers are in agreement with those of previous studies\textsuperscript{13} that have shown that the probability of a benign diagnosis decreases with the size of the nodule, while the probability of lung cancer increases. In patients with a history of extrapulmonary malignancy, the probability of a diagnosis of a benign nodule decreases to only 33% for nodules < 1.0 cm and 9% for those ≥ 3.0 cm. The probability of malignancy is shared by metastases and primary lung cancers, with the former tending to be more common in smaller nodules and the primary lung cancers being more common in bigger nodules.

An important smoking history and increasing age create a bias in favor of the SPN being a primary lung cancer instead of a metastasis.\textsuperscript{15,20} Based on this knowledge and the results of our own study, we constructed a clinical score to predict the probability of an SPN being a metastasis or a primary lung cancer. This score is based on the variables of age, smoking history, and histology of previous malignancies. It is not intended to substitute clinical evaluation and histologic diagnosis of the SPN by excisional biopsy, but to aid in the counseling of patients with previous cancer who are facing the diagnostic uncertainty of an SPN, and in planning the subsequent diagnostic and therapeutic strategy.

Diagnoses based on chest radiographs tend to be correct in only 20 to 30% of cases,\textsuperscript{8,9} and, although CT scan quantification of attenuation, size, shape, and texture of SPNs seems to be promising in differentiating malignant from benign lesions,\textsuperscript{3} the differentiation between metastases and lung primaries is not yet possible. A definitive diagnosis of an SPN is essential to design the most adequate therapeutic strategy to maximize survival. In our opinion, resection of the nodule currently represents the most reliable method for precise diagnosis. The data presented here highlight the need to differentiate primary lung malignancies from metastatic deposits, and this can be difficult with the limited tissue samples obtained from fine-needle biopsy.

Once an SPN is removed by wedge resection and is analyzed by the pathologist, the treatment strategy can be refined. If the resected nodule proves to be a primary lung cancer and the patient has sufficient pulmonary reserve, a lobectomy may be the adequate curative treatment. If, on the contrary, the lesion proves to be a metastasis from an extrapulmonary source, a metastasectomy may improve survival as long as the criteria for metastasectomy exist.\textsuperscript{21} In this case, a wedge resection is performed in order to retain as much pulmonary parenchyma as possible. Alternatively, the identification of recurrent metastatic disease may open additional treatment options such as chemotherapy or immunotherapy. If the nodule proves to be a benign lesion, its resection may remove the fear of a recurrent malignancy with acceptable morbidity.\textsuperscript{7} In this sense, an excisional biopsy aids in both the diagnosis and treatment of the patient with an SPN.

Although thoracoscopic techniques limit the morbidity associated with wedge excision of an SPN,\textsuperscript{22,23} they do not completely erase the operative consequences. Patients and physicians faced with a new SPN must consider that there will be a small chance of perioperative mortality, pain, hospitalization, and inconvenience associated with the procedure. The clinical score provided in this study may help to semiquantitatively assess the probability of malignancy.

An important limitation of all studies based on the surgical resection of SPNs is the potential for selection bias.\textsuperscript{24} A patient with an SPN that has been screened by a physician, referred to a thoracic surgeon, and has undergone resection of the SPN based on unquantifiable considerations by the surgeon may not have the same probability of malignancy as a patient with a nodule found by screening in the general population.\textsuperscript{25} Furthermore, patients with radiologic stability of the SPN or those with tiny nodules may be less frequently referred to the surgeon. Our institution is a strong advocate of lung metastasectomies\textsuperscript{21} and thoracoscopic excision of lung nodules for diagnosis,\textsuperscript{22,23} and, as such, patients with a history of malignancy who are found to have an SPN usually undergo wedge resections. This fact decreases the vulnerability of our study to such selection bias. However, we have to acknowledge that frail and elderly patients may be referred less often to our service, and may undergo resections less frequently than strong and younger patients, based on concerns about pulmonary reserve and life expectancy. In the analysis of this selected group, SPNs in elderly patients tend to have a higher probability of being a primary lung cancer. Therefore, our study would potentially be underestimating the total number of primary lung malignancies and overestimating that of metastases. This would strengthen the conclusion that an SPN in a patient with a history of cancer is most probably a primary lung neoplasm.
The occurrence of an SPN in the setting of a patient with a history of extrapulmonary cancer often represents a primary lung tumor rather than a metastasis. Even though the probability of malignancy depends on age, smoking history, size of the nodule, and histologic diagnosis of the primary neoplasm, the only reliable method to achieve a precise diagnosis and to plan the therapeutic approach accordingly is to perform an excisional biopsy. Since an SPN may represent either a primary lung cancer or a metastasis with almost equal probability, the pre-resection evaluation must consider both of these possibilities. To this end, our prediction rule can help to tailor a treatment strategy that is aimed at offering the best prognosis for each individual patient.

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