Evidence-Based Criteria to Help Distinguish Metastatic Breast Cancer From Primary Lung Adenocarcinoma on Thoracic Frozen Section

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Abstract

The distinction between primary lung adenocarcinoma and metastatic breast carcinoma in patients with a history of breast cancer is difficult by frozen section (FS) analysis. Our experience with 129 FSs from 121 patients with a pulmonary nodule and a history of breast cancer was reviewed. The pretest odds ratio of primary pulmonary carcinoma/metastatic breast carcinoma was 2.6. The incidence of 12 histopathologic features was assessed in a “training set” composed of 20 FSs, 10 with primary lung adenocarcinoma and 10 with metastatic breast cancer. A differential diagnosis model composed of significant pathologic features that favor the diagnosis of primary lung adenocarcinoma (acini, lepidic growth, nuclear pseudoinclusions, and scar) or metastatic breast carcinoma (comedonecrosis, solid nests, trabecular architecture, and cribriform growth) was identified. The external validity of this model was successfully tested by challenging 19 pathologists and trainees with a test set of 20 unknown FSs, supporting the clinical applicability of the diagnostic model.

Breast and lung carcinomas are the two most frequent malignancies in women.1 The most recent available data from the American Cancer Society estimates that breast cancer developed in 212,920 women in the United States in 2006.1 It is estimated that 81,170 primary neoplasms of the lung and bronchus developed in women during the same period. Adenocarcinoma is the most common form of lung cancer in women, and its incidence increased approximately 600% in US women from 1930 to 1997.2-6

The prognosis for breast cancer diagnosed at an early stage is very good, but these neoplasms can metastasize to the lungs in up to 12% of hospitalized cases.3-6 In the past, lung opacities in a patient with a history of breast cancer were usually presumed to be metastatic lesions based solely on radiologic data.7 However, several studies have shown that a pulmonary nodule in a patient with a history of breast cancer is more likely to represent a new primary lung carcinoma than a metastasis.7-10

The distinction between primary lung carcinomas and metastatic breast carcinomas in a patient with a solitary or multiple lung nodules and history of breast cancer is important for thoracic surgeons to determine the extent of resection but poses a difficult diagnostic dilemma for pathologists performing frozen section (FS). Metastases are usually treated with wedge or segmental resections, whereas patients with primary lung carcinomas undergo lobectomy, sleeve resection, or pneumonectomy.4 Inaccurate diagnoses of a particular specimen as primary lung carcinoma can lead to an unnecessary lobectomy, whereas patients with false-negative diagnoses of metastatic breast carcinoma may require a second thoracotomy for a completion lobectomy or more extensive surgery.

In an attempt to identify diagnostic criteria that would help distinguish primary lung adenocarcinoma, the most
frequent form of pulmonary neoplasia in our population, from metastatic breast carcinoma by FS, using the systematic approach favored by proponents of evidence-based pathology, we reviewed our experience with breast cancer cases that developed solitary and multiple pulmonary nodules during the course of the disease.11-13 This approach includes, in addition to the usual review of personal experience and information from the literature, the use of Bayesian and other statistics for the selection of evidence-based criteria and the evaluation of the external validity of the conclusions of a study by field testing them using groups of pathologists exposed to pretests and tests given after the new criteria are taught (posttests).

Materials and Methods

This project was reviewed and approved by the institutional review board at Cedars-Sinai Medical Center, Los Angeles, CA. The subsequently described systematic approach was followed.

The following specific questions are important to learn how to provide an accurate FS diagnosis of primary adenocarcinoma of the lung or metastatic breast carcinoma in patients with a lung nodule and a history of breast cancer: (1) What is the odds ratio (OR) of both entities in our population and others? (2) What is the specificity of this differential diagnosis in our population and others? (3) What is the clinical significance of a misdiagnosis of metastatic breast carcinoma as primary lung adenocarcinoma? (4) What diagnostic criteria are useful to distinguish both entities by FS? (5) What is the clinical usefulness of the diagnostic criteria: Can other pathologists make more accurate differential diagnoses between primary lung adenocarcinoma and metastatic breast carcinoma using the results of this study? (6) Are multiple pulmonary nodules in a patient with a history of breast cancer usually metastatic?

We queried for the answers to these 6 questions in several current textbooks of breast and pulmonary pathology.14,15 We also performed a review of the “English language” and “Human” literature using MEDLINE (National Library of Medicine) from 1970 to 2007. The following search terms and various combinations were used: “pulmonary nodules,” “metastatic,” “neoplasm,” “lung nodules,” “lung cancer,” “breast cancer,” “multiple,” “solitary,” and “pulmonary nodule.” The MEDLINE search identified 408 articles. Their abstracts were reviewed to determine whether they had information suitable to answer our 6 specific questions. A total of 28 articles were selected as potentially relevant.3-10,16-34 However, only 5 of these studies had sufficient level III and IV evidence about the results of pathologic evaluation of solitary pulmonary nodules in patients with a history of breast cancer.7-10,16 Levels of evidence have been categorized by Sackett et al35,36 and range from strongest (I) to weakest (V). Level IIIa includes systematic review of case-controlled studies, level IIIb is a case-controlled study, and level IV is a case series, poor cohort case controlled.

We reviewed the records of our surgical pathology laboratory from 1999 to 2006. A total of 129 biopsy specimens from 120 women and 1 man with a history of breast cancer who had undergone wedge biopsy and FS for the diagnosis of a lung nodule were identified. Of the 129 specimens, 92 involved a solitary pulmonary nodule and 37 involved multiple pulmonary nodules. The 129 FS diagnoses of lung nodules from these patients included 60 primary lung carcinomas, 38 metastatic breast carcinomas, 17 organizing pneumonias, 5 metastases from neoplasms other than breast cancer, 2 carcinoid tumors, and 7 other diagnoses. Primary lung carcinomas included 45 adenocarcinomas, 11 bronchioloalveolar carcinomas, and 4 squamous cell carcinomas. The diagnosis of primary lung adenocarcinoma was established by review of the clinical history and imaging findings and/or positive thyroid transcription factor-1 nuclear immunoreactivity of the tumor cells. The diagnosis of metastatic breast carcinoma was established by comparing the tumors with the original breast neoplasm or estrogen receptor nuclear immunoreactivity of the tumor cells.

All FS slides were reviewed, and 40 cases, including 20 each of primary lung adenocarcinoma and metastatic breast carcinoma, were selected for study using convenience samples. The best quality FS slide from each of the 40 cases was used for the organization of 2 sets, a training set to be used for the identification of the diagnostic criteria and a test set to validate the clinical applicability of the diagnostic criteria. Each of the 2 sets had 10 FSs each of primary lung adenocarcinoma and metastatic breast carcinoma. The incidence of 12 histopathologic features selected by us from personal experience as potentially useful to help differentiate primary lung adenocarcinoma from metastatic breast carcinoma was evaluated in all training cases. The presence of 10 of the 12 histopathologic features was evaluated at $\times$100 microscopy: acini, lepidic growth pattern, scar, subpleural location, lymphovascular invasion, papillary architecture, comedonecrosis, solid nests, trabecular architecture, and cribiform architecture. The presence of the 2 other histopathologic features was evaluated at $\times$400 microscopy: nuclear pseudo-inclusions and macronucleoli.

The diagnostic specificity and sensitivity of a differential diagnosis of primary lung adenocarcinoma vs metastatic breast carcinoma during the 7-year review period was calculated using the final pathologic diagnoses. The pretest OR of primary lung adenocarcinoma was calculated for the 5 studies from the literature that provided “best evidence” and in our cases.7-10,16 The incidence of each of the 12 histopathologic features in the 2 populations was compared with $\chi^2$ statistics. The ORs of primary lung adenocarcinoma/metastatic breast carcinoma were calculated for each histopathologic feature.
Pathologic features found to be statistically significant by \( \chi^2 \) were stratified by the ORs. The theoretical specificity of a differential diagnosis model composed of all significant diagnostic features was “retroactively” evaluated in all 40 FSs to estimate how good this set of criteria would be, should all features be present in an individual FS.

For the pretest, 19 pathologists, including 10 attending pathologists, 5 residents, and 4 pathology fellows, were asked to diagnose the 20 cases in the test set as primary lung adenocarcinoma or metastatic breast carcinoma. They were provided with no information other than the patient had a solitary lung nodule and a history of breast cancer. At the conclusion of the pretest, the participants were given a brief lecture, including typical examples and an explanation of how to use the 8 evidence-based diagnostic criteria identified in the study. Thereafter, they were asked to examine the 20 cases for a second time (posttest). To our knowledge, the test set did not contain easier cases than the training set. The diagnostic specificity of the pretest and posttest results was compared by using paired t test statistics.

**Results**

The average OR of primary pulmonary adenocarcinoma/metastatic breast carcinoma in 207 patients with pulmonary nodules and a history of breast cancer reported from multiple institutions is 2.4. The results are somewhat counterintuitive because in most series, primary pulmonary adenocarcinomas were more probable than metastatic lesions, except for the presence of breast metastases in 75% of the 23 cases reported by Tanaka et al. \(^1\)

The literature does not provide specific information about the sensitivity and specificity of the differential diagnosis between primary pulmonary adenocarcinoma and metastatic breast carcinoma in patients with a history of breast cancer who have a solitary lung nodule. The specificity of this differential diagnosis at Cedars Sinai Medical Center was 88% during the 7-year period and before this study. The total error rate was 6.2%, and the deferral rate was 15.5%. The distribution of cases for solitary pulmonary nodules in our population was as follows: primary lung carcinoma, 45; metastatic breast carcinoma, 25; organizing pneumonia, 16; indeterminate carcinoma, 4; and typical and atypical carcinoid tumor, 1 each.

One of our patients with metastatic breast carcinoma underwent an unnecessary lobectomy for an incorrect diagnosis of primary pulmonary adenocarcinoma. Seven patients with primary pulmonary adenocarcinoma were initially treated with wedge resection for a presumed diagnosis of metastatic breast carcinoma and had to undergo a second thoracotomy for completion lobectomy.

Sienko et al. \(^2\) list complex or cribriform architecture, cytologically bland or uniform cells, and relatively small nuclei as features favoring metastatic breast carcinoma over primary lung adenocarcinoma in FS. **Table 1** summarizes the results of \( \chi^2 \) analysis and the posttest ORs of primary pulmonary adenocarcinoma/metastatic breast cancer in the training set. Of the 12 criteria, 8 were significant at a \( P \) value of less than .05 value: acini, lepidic growth, nuclear pseudo-inclusions, scar, comedonecrosis, solid nests, trabecular architecture, and cribriform architecture. The OR allowed for the stratification of these criteria into those with an OR of more than 1 favoring a diagnosis of primary pulmonary adenocarcinoma (acini, lepidic growth, nuclear pseudo-inclusions, and scar) **Image 1** and those with an OR of less than 1 favoring a diagnosis of metastatic breast carcinoma (comedonecrosis, solid nests, trabecular architecture, and cribriform architecture) **Image 2**. These results are based on observations collected from a convenience sample, and the possibility of case selection bias cannot be entirely excluded. The ORs reported in Table 1 may not be entirely representative of a larger population of cases of primary pulmonary adenocarcinoma/metastatic breast cancer. The theoretical specificities of the use of these 8 diagnostic features for a differential diagnosis of primary pulmonary adenocarcinoma and metastatic breast carcinoma, calculated by assessing the incidence of these features in the 40 FSs selected for study, were 85% and 100%, respectively.

The results of the pretest and posttest scores are shown in **Table 2**, by testee category and by overall test results. Pretest and posttest specificities were 75% and 88%, respectively. All participants improved their posttest scores by a significant 10%. However, when the results were analyzed by testee group, they were statistically significant only for attending pathologists, perhaps because this group was larger.

During the 7-year period, we received 37 wedge biopsy specimens with multiple pulmonary nodules from patients

### Evidence-Based Diagnostic Criteria to Distinguish Primary Lung Adenocarcinoma From Metastatic Breast Carcinoma at Frozen Section

<table>
<thead>
<tr>
<th>Feature</th>
<th>Posttest Odds Ratio (Lung/Breast)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acini</td>
<td>34</td>
<td>.0001</td>
</tr>
<tr>
<td>Lepidic growth</td>
<td>17</td>
<td>.005</td>
</tr>
<tr>
<td>Nuclear pseudo-inclusions</td>
<td>14</td>
<td>.015</td>
</tr>
<tr>
<td>Scar</td>
<td>11</td>
<td>.033</td>
</tr>
<tr>
<td>Macronucleoli</td>
<td>3.02</td>
<td>.213</td>
</tr>
<tr>
<td>Subpleural location</td>
<td>0.20</td>
<td>.168</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>0.05</td>
<td>.174</td>
</tr>
<tr>
<td>Papillary architecture</td>
<td>Infinity</td>
<td>.163</td>
</tr>
<tr>
<td>Comedonecrosis</td>
<td>0.115</td>
<td>.0006</td>
</tr>
<tr>
<td>Solid nests</td>
<td>0.0087</td>
<td>.002</td>
</tr>
<tr>
<td>Trabecular architecture</td>
<td>0</td>
<td>.002</td>
</tr>
<tr>
<td>Cribriform architecture</td>
<td>0</td>
<td>.002</td>
</tr>
</tbody>
</table>

* Features in italics favor primary lung carcinoma; features in bold favor metastatic breast carcinoma.
with a history of breast cancer. Of the 37 patients represented, 15 had primary pulmonary adenocarcinoma, 13 had metastatic breast cancer, and 9 had multiple diagnoses. Table 3 lists the entirety of diagnoses of biopsied multiple pulmonary nodules. The OR of primary pulmonary adenocarcinoma/metastatic breast carcinoma in this group is 1.1, which is lower than for patients with solitary pulmonary nodules.

**Discussion**

Our results underscore the potential value of using a systematic evidence-based approach and simple Bayesian statistics to identify specific problems with FS diagnoses and propose diagnostic criteria that could improve the diagnostic quality of future intraoperative consultations. The proponents of evidence-based medicine have shown in multiple studies that the use of odds, probabilities, and other quantitative data can help physicians modify long-held beliefs that are based on tradition or empirical experience rather than evidence collected in well-designed scientific studies.

Pathologists could probably benefit from this approach as well. For example, before testing our colleagues with the test set of unknown FSs we conducted an informal opinion survey. Most participants opined that the differential diagnosis between metastatic breast cancer and primary lung cancer is very difficult by FS and that pathologists should probably equivocate by deferring the definitive diagnosis until the new nodules could be studied by immunohistochemical analysis and/or compared with the slides of the previous breast lesion.

**Image 1** Microscopic features favoring primary lung adenocarcinoma. **A**, Scar (H&E, ×100). **B**, Nuclear pseudoinclusions (H&E, ×400). **C**, Acini (H&E, ×100). **D**, Lepidic growth (H&E, ×100).
In addition, our colleagues were split almost 50-50 when asked about their belief regarding the origin of a new pulmonary neoplasm in a patient with a history of breast carcinoma.

In contrast with those beliefs, the specificity of this differential diagnosis in our department during the previous

**Image 2I** Microscopic features favoring metastatic breast carcinoma. A, Cribriform growth (H&E, ×100). B, Solid nests (H&E, ×100). C, Comedonecrosis (H&E, ×100). D, Trabecular growth (H&E, ×100).

**Table 2I**

<table>
<thead>
<tr>
<th>Participants</th>
<th>Pretest</th>
<th>Posttest</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residents (n = 5)</td>
<td>82</td>
<td>92</td>
<td>.108</td>
</tr>
<tr>
<td>Fellows (n = 4)</td>
<td>79</td>
<td>88</td>
<td>.116</td>
</tr>
<tr>
<td>Attending physicians (n = 10)</td>
<td>77</td>
<td>89</td>
<td>.005</td>
</tr>
<tr>
<td>All participants (n = 19)</td>
<td>78</td>
<td>89</td>
<td>.001</td>
</tr>
</tbody>
</table>

* Data are given as percentage of correct answers.

**Table 3I**

Frozen Section Diagnosis of Multiple Pulmonary Nodules in 37 Patients With a History of Breast Carcinoma

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary lung carcinoma</td>
<td>15</td>
</tr>
<tr>
<td>Metastatic breast carcinoma</td>
<td>13</td>
</tr>
<tr>
<td>Metastatic melanoma</td>
<td>2</td>
</tr>
<tr>
<td>Colonic adenocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Indeterminate carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Transitional cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Alveolar soft part sarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Inflammatory pseudotumor</td>
<td>1</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Granulomatous pneumonia</td>
<td>1</td>
</tr>
</tbody>
</table>
7-year period was 88%, with only 1 false-positive and 7 false-negative diagnoses for metastatic breast carcinoma, and the pretest OR of a new primary lung adenocarcinoma in our patient population is 2.6. These somewhat counter-intuitive results defy the previously held belief that “a new pulmonary nodule in a cancer patient represents a metastasis unless proven otherwise.” Posttest odds calculations helped to identify 8 diagnostic features that provide strong evidence for primary pulmonary adenocarcinoma or metastatic breast carcinoma. The use of the ORs and their interpretation in terms of levels of evidence using the suggestions by Sackett et al15,36 or similar semiarbitrary scales may provide a language that could help pathologists explain the degree of certainty of the criteria being used for an FS diagnosis. We are certainly not advocating the calculation of ORs during the performance of an FS, but general familiarity with this information could help improve communication during intraoperative consultations.

The interpretation of FSs from patients with a history of breast cancer who have multiple pulmonary nodules has not been studied previously in detail.10,16 Several studies have shown that in patients with a history of breast cancer, multiple primary pulmonary carcinomas can develop, in variable proportions. For example, Chang et al10 concluded that “our findings suggest the number of lung nodules does not appear to be reliable indicator of the histology of the disease,” and Khokar et al17 reported that lung cancer accounted for nearly half of all thoracic malignancies of patients with preexisting extrapulmonary malignancy and a new nodule or nodules. Patz et al18 reached a different conclusion in evaluating percutaneous needle biopsy specimens in patients with multiple pulmonary nodules and a single known primary malignancy. In the breast cancer group in that study, of 29 patients who underwent biopsy for multiple nodules, 26 cases were proven to be metastatic breast carcinoma, 2 cases were non-diagnostic and presumed positive, and 1 was nondiagnostic. Our data show that the odds of a new primary pulmonary carcinoma are similar to metastatic breast carcinoma in the patient population that underwent FS because of imaging studies demonstrating only pulmonary nodules and no evidence of extrapulmonary metastases.

Our conclusions suggest that the differential diagnosis between metastatic breast carcinoma and primary pulmonary adenocarcinoma can be made by FS with a high degree of accuracy. Pathologic features that provide moderate evidence for the possibility of a new primary lesion include the presence of acini, lepidic growth, nuclear pseudoinclusions, and central scar. Pathologic features that provide moderate evidence for the diagnosis of a breast metastasis include the presence of comedonecrosis, solid nests, trabecular architecture, and cribriform growth pattern. Future studies of patients with a history of breast carcinoma and multiple lung nodules are needed.

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References