Diagnostic Concordance of Histologic Lung Cancer Type Between Bronchial Biopsy and Cytology Specimens Taken During the Same Bronchoscopic Procedure

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Context.—The diagnosis of lung cancer is often confirmed by cytology and biopsy specimens obtained during a bronchoscopic procedure. At our institution, these specimens are read by different pathologists, and the rate of concordance was not known.

Objectives.—To evaluate the concordance rate in the diagnosis of lung cancer types between cytology and biopsy specimens and to correlate discordance with patient outcome.

Design.—Specimens obtained during the same procedure, between January 1, 2000, and December 31, 2005, were identified. Cases with cytology and biopsy specimens positive for cancer were evaluated for concordance of histologic type, small cell versus non–small cell lung carcinoma. Cases with different types were considered discordant, and slides were reviewed.

Results.—Of 231 cases, 225 (97.4%) had concordant diagnoses. Discordance was the result of misinterpretation of undifferentiated carcinoma, overinterpretation of squamous dysplasia, interpretation of suboptimal specimens with necrosis and crush artifact, and sampling error.

Conclusions.—Even though the cytology and biopsy specimens were reviewed by different pathologists, the concordance rate for histologic type at our institution was high, emphasizing that this is a safe practice. The few discordant cases did not affect the patient’s outcome.

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Table 1. Demographics, Radiologic Information, and Outcomes for Different Cytology/Biopsy Diagnosis Categories and Overall Group for Same Bronchoscopic Procedure Specimens

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cytology/Biopsy Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases, No. (%)</td>
<td>231 (27)</td>
</tr>
<tr>
<td>Positive/Positive</td>
<td>44 (5)</td>
</tr>
<tr>
<td>Positive/Negative</td>
<td>90 (10)</td>
</tr>
<tr>
<td>Negative/Positive</td>
<td>493 (57)</td>
</tr>
<tr>
<td>Negative/Negative</td>
<td>858 (100)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>67.0 (11.0)</td>
</tr>
<tr>
<td>Localized infiltrate</td>
<td>9 (3.9)</td>
</tr>
<tr>
<td>Bilateral infiltrates</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>7 (3.0)</td>
</tr>
<tr>
<td>NA</td>
<td>13 (5.6)</td>
</tr>
<tr>
<td>Size of lesion, mean (SD), cm</td>
<td>4.27</td>
</tr>
<tr>
<td>Location, No. (%)</td>
<td>148 (64)</td>
</tr>
<tr>
<td>Central</td>
<td>18 (41)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>24 (10)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Midlung or NS</td>
<td>57 (25)</td>
</tr>
<tr>
<td>Died, No. (%)</td>
<td>91 (39)</td>
</tr>
<tr>
<td>Of lung cancer</td>
<td>14 (32)</td>
</tr>
<tr>
<td>Of other causes</td>
<td>6 (2.6)</td>
</tr>
<tr>
<td>Of unknown cause</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Alive, No. (%)</td>
<td>114 (49)</td>
</tr>
<tr>
<td>With lung cancer</td>
<td>19 (43)</td>
</tr>
<tr>
<td>Without lung cancer</td>
<td>20 (9)</td>
</tr>
<tr>
<td>With unknown cancer status</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Died, No. (%)</td>
<td>168 (20)</td>
</tr>
<tr>
<td>Of lung cancer</td>
<td>25 (5)</td>
</tr>
<tr>
<td>Of other causes</td>
<td>66 (13)</td>
</tr>
<tr>
<td>Of unknown cause</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Alive, No. (%)</td>
<td>183 (21)</td>
</tr>
<tr>
<td>With lung cancer</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Without lung cancer</td>
<td>343 (70)</td>
</tr>
<tr>
<td>With unknown cancer status</td>
<td>36 (7)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>328 (38)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, nonspecific changes or no imaging studies; NS, not specified.

MATERIALS AND METHODS

With Mayo Clinic institutional review board approval, a computer search of pathology files was performed to identify all cases for which biopsy and cytology specimens were obtained during the same diagnostic bronchoscopic procedure between January 1, 2000, and December 31, 2005, at Mayo Clinic, Rochester, Minnesota, our institution.

The specimens included in this study were from patients who provided consent for their information to be used for research purposes. Cytology specimens were classified as negative, atypical, suspicious, or positive for malignancy. For the final analysis, atypical cases were considered negative, and suspicious cases were considered positive. Biopsy specimens showing dysplasia, carcinoma in situ, invasive carcinoma, or other malignancies were considered positive. Biopsy specimens with atypia (reactive or not otherwise specified) were considered negative. The positive cases were further evaluated for concordance of SCLC versus NSCLC between cytology and biopsy specimens.

Clinical and radiologic data were abstracted from computerized medical files and included age, sex, and clinical outcome. Outcome was based on the last clinical note or the reported date of death, and duration of follow-up was calculated from the date of the patient's bronchoscopic procedure. Abstracted radiologic information included lesion type, size, and location. Lesions were divided into infiltrates or nodule/mass and unilateral or bilateral. The location of lesions as central or peripheral was recorded when assessed.

Slides for discordant cases were reviewed independently by a cytopathologist (D.R.S.) and a pulmonary pathologist (M.C.A.) who were blinded to the clinical data and original diagnosis. Immunohistochemical studies were performed to support the diagnostic impression when there was disagreement on the original diagnosis or disagreement between the reviewing pathologists. Cytologic and histologic diagnoses were then compared, and cases with remaining discordance were submitted for independent evaluation to a second pulmonary pathologist (E.S.Y.) who was blinded not only to the clinical data and original diagnosis but also to the opinions of the other 2 pathologists. A consensus diagnosis was then made on the basis of all the available data. Factors contributing to the discordance were noted.

RESULTS

During the study period, 858 patients underwent a bronchoscopic procedure in which both cytology and biopsy specimens were obtained (Table 1). Of these, 493 patients (57%) had negative results for malignancy on both cytology and biopsy specimens. In a few patients, a positive result was detected either in the cytology specimens (44 patients [5%]) or in the biopsy specimen (90 patients [10%]) alone. The remaining 231 patients (27%) had both positive cytology and positive biopsy findings, and these composed our study group. Most patients were men (151 of 231; 65%) with a mean age of 67 years. The primary reason for biopsy in these patients was a central lung mass (198 of 231; 86%). For 225 of the 231 cases (97.4%), the cytology and the biopsy specimens yielded a concordant diagnosis. The findings in the 6 discordant cases are summarized in Table 2, and details of their clinical histories are provided as individual case reports. The effect of the discrepancy on each patient outcome was classified as harm, near-miss, and no-harm, using the scale proposed by the Institute of Medicine.13–15

Case 1

A 64-year-old woman presented with a 6-cm central lung mass. Original diagnoses were combined SCLC and NSCLC for the cytology specimen and SCLC for the
biopsy specimen. The patient was treated for SCLC and had an initial complete response to chemotherapy and radiotherapy, but liver metastasis developed 9 months later. She died of lung cancer 12 months after initial diagnosis.

The review diagnosis for the cytology specimen was SCLC, with a possible, but questionable, squamous cell carcinoma component (Figure 1, A). Review of the biopsy specimen concurred with the original diagnosis of SCLC. Squamous metaplasia with severe dysplasia was noted on the biopsy specimen (Figure 1, B). The consensus diagnosis was SCLC. The discordance was considered an interpretive error. The squamous dysplasia was interpreted as squamous cell carcinoma on the original cytology diagnosis. This was a no-harm type of error because it did not affect treatment; combined SCLC-NSCLC is treated as SCLC.

### Table 2. Discordant Cytology andHistology Types for the Same Bronchoscopic Procedure Cytology and Biopsy Specimens

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, y/sex</th>
<th>Original Diagnosis</th>
<th>Review Diagnosis</th>
<th>Cause of Discordance</th>
<th>Effect on Patient Outcome</th>
<th>Follow-up, mo</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64/F</td>
<td>Combined SCLC-NSCLC</td>
<td>SCLC</td>
<td>SCLC, moderate–severe dysplasia</td>
<td>No harm</td>
<td>12</td>
<td>DOD</td>
</tr>
<tr>
<td>2</td>
<td>62/M</td>
<td>Sec: NSCLC SQCC; TBNA: SCLC</td>
<td>SCLC</td>
<td>SCLC, dysplasia; TNBNA: SCLC NSCLC</td>
<td>Interpretation</td>
<td>12</td>
<td>AWD</td>
</tr>
<tr>
<td>3</td>
<td>76/M</td>
<td>NSCLC</td>
<td>SCLC</td>
<td>NSCLC</td>
<td>Harm</td>
<td>26</td>
<td>DOD</td>
</tr>
<tr>
<td>4</td>
<td>81/F</td>
<td>SCLC</td>
<td>NSCLC</td>
<td>NSCLC</td>
<td>No harm</td>
<td>18</td>
<td>DOD</td>
</tr>
<tr>
<td>5</td>
<td>39/M</td>
<td>NSCLC</td>
<td>NEC with SCLC features</td>
<td>NSCLC with possible SCLC component Carcinoid tumor</td>
<td>Suboptimal specimen</td>
<td>Harm</td>
<td>None NA</td>
</tr>
<tr>
<td>6</td>
<td>72/M</td>
<td>SCLC</td>
<td>Combined SCLC-NSCLC</td>
<td>Combined SCLC-NSCLC</td>
<td>Sampling error</td>
<td>None NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: AWD, alive with disease; DOD, died of disease; NA, not available; NEC, neuroendocrine carcinoma; NSCLC, non–small cell lung carcinoma; SCLC, small cell lung carcinoma; Sec, secretion; SQCC, squamous cell carcinoma; TBNA, transbronchial needle aspiration.

The effect of the discrepancy on each patient outcome was classified as harm, near-miss, and no-harm, using the scale proposed by the Institute of Medicine.1

### Case 2

A 62-year-old man presented with localized pulmonary infiltrates and a history of esophageal squamous cell carcinoma, treated with esophagogastrectomy the prior year. The original diagnoses were NSCLC favoring squamous cell carcinoma for the bronchial secretion specimen, SCLC for the transbronchial needle aspirate, and SCLC for the bronchial biopsy specimen. Nine months later, metastatic SCLC was diagnosed in a liver fine-needle aspiration biopsy specimen, and the patient underwent chemotherapy and radiotherapy, but the disease progressed, and metastasis developed in the right cerebellum. The patient was alive with persistent lung cancer after 12 months of follow-up.

The review diagnosis for the bronchial secretion specimen was SCLC with associated squamous dysplasia. The biopsy specimen showed extensive crush artifact and

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Figure 1. Case 1. Small cell lung carcinoma and squamous metaplasia with moderate to severe dysplasia. A, The cytology specimen shows small cell lung carcinoma (left) and clusters of squamous cells with dysplasia (right upper). B, Biopsy with small cell lung carcinoma and moderate squamous dysplasia in the overlying epithelium (Papanicolaou stain, original magnification ×400 [A]; hematoxylin-eosin, original magnification ×400 [B]).

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extensive necrosis. The histologic features of the viable cells suggested SCLC. Immunohistochemical studies performed on the biopsy demonstrated that the tumor was strongly positive for TTF-1, positive in a perinuclear dotlike pattern for cytokeratin AE1/AE3, and negative for cytokeratin 903, p63, and desmoglein 3, further supporting the diagnosis of SCLC and ruling out squamous cell carcinoma. The consensus diagnosis for this case was SCLC. This was considered an interpretive error, similar to that in case 1. Squamous dysplasia led to the interpretation of all the tumor cells as squamous cell carcinoma on the bronchial secretion specimen. This was a no-harm type error because it did not affect treatment for this patient.

**Case 3**

A 76-year-old man had a history of limited SCLC treated by chemotherapy and radiotherapy and had been free of disease for 8 years when he presented with a new lung mass and diffuse brain metastasis. The original bronchoscopic diagnoses of this new lung mass were NSCLC for the cytology specimen and SCLC for the biopsy specimen. Clinically, he was believed to have recurrent SCLC and was treated accordingly. The patient ultimately died of lung cancer 26 months later.

The review diagnoses for both the cytology and biopsy specimens were NSCLC (M.S., M.C.A., D.R.S.). The smears showed a few clusters of neoplastic cells, intermixed with benign bronchial epithelial cells. In some clusters, the neoplastic cells were stripped of their cytoplasm, showed hyperchromatic nuclei, and occasional molding. In other clusters, where the cells were better preserved, eosinophilic cytoplasm and distinct small nucleoli were visible. Some cells showed a finely granular chromatin pattern characteristic of neuroendocrine tumors (Figure 2, A). On the basis of the cytologic features observed in the preserved cells, this neoplasm was thought to be better characterized as an NSCLC.

Because of the discrepancy with the previous history and clinical assumption, both cytology and biopsy specimens were rereviewed along with material from the previous tumor (M.C.A., D.R.S.). On rereview, the biopsy specimen showed a poorly differentiated carcinoma. Atypical cells had a moderate amount of cytoplasm without nuclear molding, but the nuclei had a homogenous chromatin and no nucleoli, similar to the nuclear features observed in SCLC (Figure 2, B). Immunohistochemical studies of the biopsy specimen demonstrated that the tumor cells were positive for cytokeratin AE1/AE3, showing predominantly cytoplasmic staining. TTF-1, CD56, and synaptophysin results were also positive, and chromogranin staining was negative. The case was then reviewed by the third pathologist (E.S.Y.) who favored a diagnosis of SCLC. Interestingly, all 3 (M.C.A., D.R.S., E.S.Y.) pathologists believed that the original tumor was NSCLC and that it looked slightly different from the current tumor, although it had a similar immunoprofile (Figure 2, C). Ultimately, the 3 pathologists could not reach a consensus, and the differential diagnosis between SCLC and NSCLC with neuroendocrine differentiation was unresolved. Because differences in treatment could potentially affect the patient outcome, this was considered a harm type error.

Figure 2. Case 3. A, High-power photomicrograph of the cytology specimen. B, Corresponding biopsy specimen. Both specimens show an undifferentiated malignancy composed of moderate to large-sized cells with the presence of cytoplasm. Cytologically, the nuclei do not show extensive molding and have an open chromatin and a small punctate nucleoli. Histologically, the nuclei have more molding and more uniform, dark chromatin. C. The biopsy specimen taken 8 years previously when lung cancer was initially diagnosed (Papanicolaou stain, original magnification ×600 [A]; hematoxylin-eosin, original magnifications ×400 [B and C]).
Case 4

An 81-year-old woman presented with a large central lung mass. The original diagnoses were SCLC for the cytology specimen and NSCLC for the biopsy specimen. The patient was not a good candidate for surgery and was treated for NSCLC with radiotherapy. Bilateral adrenal masses developed, and the patient died of lung cancer 18 months after the initial diagnosis.

The review diagnoses for both the cytology and biopsy specimens concurred with their respective original diagnoses. Both specimens showed extensive necrosis. In the biopsy specimen, viable tumor cells contained a moderate amount of cytoplasm without nuclear molding (Figure 3, B through D), supporting a diagnosis of NSCLC. The cytology specimen was paucicellular, with rare clusters of cells, showing scant or no cytoplasm, and with elongated nuclei with no nucleoli, suggestive of SCLC (Figure 3, A). The cells seen in the cytology specimen were thought to correspond to the small hyperchromatic cells seen in the biopsy specimen. However, based on the well-preserved tumor cells in the biopsy, the final consensus diagnosis for this case was NSCLC. Rendering diagnosis in a suboptimal paucicellular specimen with extensive necrosis was identified as the cause of the discordance. This error did not affect patient care; the patient's treatment was based on the biopsy findings, which were confirmed in our review. Therefore, it was considered a no-harm type of error.

Case 5

A 39-year-old man, with a complex medical history, was first seen 4 years earlier for treatment of a thymic tumor, a diagnosis made outside our institution and not reviewed before treatment. Because of extensive regional invasion, he was treated with neoadjuvant therapy followed by surgery. A diagnosis of grade 3 (of 4) thymic neuroendocrine carcinoma was made on the surgical specimen, and the patient was treated with additional chemotherapy, followed by radiotherapy and chemotherapy for metastases in the left supraclavicular lymph nodes. A central lung mass then developed. The original diagnoses were NSCLC for the cytology specimen and a grade 3 (of 4) neuroendocrine carcinoma with SCLC features for the
biopsy specimen. Clinically, the patient was considered to have recurrent high-grade thymic neuroendocrine carcinoma.

The review diagnosis of the cytology specimen was NSCLC with a possible neuroendocrine (carcinoid or SCLC) component. On review, the lung biopsy was composed of a single, small fragment of bronchial wall involved by small, hyperchromatic, crushed tumor cells (Figure 4, A). No necrosis was seen. The differential diagnosis was between SCLC and carcinoid tumor. In immunohistochemical results, the neoplastic cells were strongly and diffusely positive for chromogranin and

**Figure 4.** Case 5. A, The biopsy specimen shows prominently crushed, small, hyperchromatic cells but no necrosis. The chromogranin is diffusely positive (image not shown). B, The MIB-1 labeling index is low. C, On review, the previous mediastinal specimen shows a marked artifact with crushing and a fixation effect. D, Focally, areas more typical of carcinoid tumor can be seen. E, The cytology specimen has scant cellularity, but the features are consistent with carcinoid tumor (hematoxylin-eosin, original magnifications ×200 [A], ×100 [C], and ×600 [D]; original magnification ×200 [B]; Papanicolaou stain, original magnification ×600 [E]).
synaptophysin and showed a low proliferation index of 15% on the MIB-1 tests (Figure 4, B). Therefore, the diagnosis of carcinoid tumor was favored, which prompted review of the prior mediastinal excision. This specimen also showed focal crushed areas, along with a fixation artifact that distorted the neuroendocrine architecture (Figure 4, C). The tumor had no extensive necrosis and few mitotic figures (<10/10 high-power fields), but cellular atypia was present. Areas with typical features of carcinoid tumor were few (Figure 4, D). Diffuse and strong positive immunoreactivity for chromogranin and synaptophysin was also present. These features supported a diagnosis of atypical thymic carcinoid tumor, including the mitotic count.

With this information, the cytologic specimen was rereviewed. The specimen was scant. The few tumor cell clusters did have neuroendocrine features and, in the absence of necrosis, were believed to be consistent with carcinoid tumor (Figure 4, E). The final consensus diagnosis was, therefore, carcinoid tumor. The error in this case was based on interpretation of scant material with a prominent artifact. The pitfall of distinguishing carcinoid tumor from SCLC was not avoided on initial diagnosis, possibly because of bias based on the historical diagnosis and no documentation of rereview of material. Furthermore, this error was compounded by not reviewing another institution's material before the initial surgery. Because of the aggressive nature of the tumor, treatment would not have differed for this patient, although confusing carcinoid tumor for SCLC is considered a harm type of error.

**Case 6**

A 72-year-old man presented with a 5-cm central mass. Original diagnoses were SCLC for the cytology specimen and combined SCLC-NSCLC for the biopsy specimen. Clinically, there was no reconciliation of the results, and the patient was considered by the oncologist as having SCLC and was treated as such. It was interesting to note in the clinical records that the pulmonologist thought this patient had NSCLC. No follow-up was available for this patient.

The review diagnosis for the cytology specimen was SCLC with extensive necrosis (Figure 5, A). Review of the biopsy specimen concurred with the original diagnosis of combined SCLC-NSCLC, further supported by the immunohistochemical study that showed strong TTF-1 immunoreactivity in the SCLC component, and CK903 highlighted the squamous cell carcinoma component (Figure 5, B through D). The consensus diagnosis was combined SCLC, with the NSCLC component not represented in the cytology specimen. The cause of discordance was considered to be attributable to sampling. This error did not affect patient care; therefore, it was considered a no-harm type error because the SCLC component, which determined treatment, was recognized.

**Summary of Cases**

In summary, 3 of these errors were interpretive: squamous dysplasia, interpreted as squamous cell carcinoma on cytology in cases 1 and 2; and distinguishing SCLC with larger-cell cytology from NSCLC with neuroendocrine differentiation in case 3. Poor quality of the material, either because of extensive tumor necrosis or crushing artifact, and the scantiness of the tumor cells were thought to be the causes of error in cases 4 and 5. Sampling error was the cause in case 6.

**COMMENT**

Our study showed that the concordance rate between the cytologic and histologic diagnoses distinguishing SCLC from NSCLC by different pathologists in our practice is high. This likely reflects that, in general, pathologists are highly accurate in the subtyping of lung cancer on cytology and biopsy bronchoscopic specimens. In a study done in the 1980s, Matsuda et al compared tumor types in specimens obtained from brushing and bronchial biopsy; the discordant rate for SCLC versus NSCLC was 2.57%. This similar discordance rate to our study, 2 decades later, suggests that, even with refinement in diagnostic tools and addition of ancillary studies, we have not improved on the rate of concordance.

The high rate of concordance on histologic type supports the practice as safe and adequate. Because of the retrospective nature of our study, we were unable to account for an inherent bias caused by informal, undocumented correlation occurring at the time of sign-out of difficult cases, although we suspect this undocumented correlation occurs infrequently.

Studies addressing cytologic-histologic correlation have more often been related to gynecologic than nongynecologic specimens. Classically, the discrepancies have been classified as the result of sampling or misinterpretation. In a recent study analyzing the root cause of error in cases detected by cytologic-histologic correlation, the authors proposed a no-fault system based on specimen interpretability. Discrepancies between cytology and biopsy specimens, considered either benign or malignant, were classified on the basis of the quality of the specimen and the amount of neoplastic cells present in the specimen. In our study, we focused on the discrepancies in the interpretation of tumor types; therefore, not all cases fell neatly into one of the subgroups proposed by those authors.

In our study, we believe that misinterpretation was the most common cause of discrepancy affecting 3 of 6 cases (50%). In cases 1 and 2, the interpretation of squamous dysplasia as NSCLC in the cytology specimen was the cause of the discrepancy. These 2 cases raise the issue of overinterpreting squamous dysplasia in cytologic specimens as squamous cell carcinoma. Several articles have addressed this issue of misinterpreting benign or atypical reactive cells as carcinoma in pulmonary cytology specimens. However, to our knowledge, squamous dysplasia has not been studied as having potential for misinterpretation. In our 2 cases, the finding of several squamous dysplastic cells made us overlook the other tumor cells present in the background. These were misinterpreted as poorly differentiated cells of invasive squamous cell carcinoma.

In case 3, a consensus could not be achieved; this lack of agreement represents a recognized challenge: the distinction between SCLC and NSCLC in some cases. Unfortunately, immunohistochemical study plays a small role in this distinction, with the exception of SCLC versus squamous cell carcinoma. In the latter, a panel of immunostains, comprising TTF-1, p63, and high-molecular-weight keratin, usually distinguishes these 2 carcinomas, with SCLC expressing TTF-1, but not p63 and high-
Otherwise, up to 25% of NSCLCs show expression of neuroendocrine markers, such as chromogranin, synaptophysin, and CD56, and by definition, all large cell neuroendocrine carcinomas should have expression of a neuroendocrine marker, thus overlapping with SCLC. A small percentage of SCLCs may be negative for all neuroendocrine markers. The pattern of staining with keratin markers may differ between SCLC and NSCLC, where the keratin in SCLCs often has dotlike perinuclear staining, whereas NSCLCs show more diffuse cytoplasmic staining, but otherwise, the distinction still relies mostly on cytologic and histologic features. This distinction is inherently subjective and can show overlap and thus lead to disagreements, even among experts. Fortunately, this lack of agreement occurs in only a small percentage of SCLCs.

In cases 4 and 5, the poor quality of the material caused the discrepancy. In case 4, the discordance was attributed to the poor quality of the specimen, which had extensive necrosis and prominent crush artifact on both the cytology and the biopsy specimens. However, the biopsy specimen had a cluster of viable tumor cells that allowed the diagnosis of NSCLC. Although pathologists recognize the shortcomings in making a diagnosis in specimens with necrosis and other artifacts, little data indicating how a marked artifact or necrosis affects the concordance rate between cytology and biopsy interpretation are available in the literature. Cataluña et al. showed that the presence of necrosis significantly affected the concordance rate between biopsy and surgical specimens. Indeed, 30% of the biopsy specimens harboring necrosis were discordant in contrast to 11% of biopsy specimens without necrosis (P = .02).

In case 5, misinterpretation was attributed to historical bias. Although the clinical history usually helps achieve the correct diagnosis, in this particular case, not reviewing the prior surgical specimens and being swayed by the prior diagnosis of grade 3 (of 4) thymic neuroendocrine carcinoma led to an incorrect diagnosis. Similar to the recommendations of other authors, we recommend that prior material, especially with unusual features or a rare

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**Figure 5.** Case 6. Combined small cell lung carcinoma and squamous cell carcinoma. A, Cytology specimen shows only the small cell lung carcinoma component. B, Both the small cell lung carcinoma component and the squamous cell carcinoma component are visualized on the biopsy specimen. C, High-molecular-weight keratin (CK903) is strongly positive in the squamous cell carcinoma component only. D, TTF-1 showed strong nuclear positivity in the small cell component only (Papanicolaou stain, original magnification ×600 [A]; hematoxylin-eosin, original magnification ×400 [B]; original magnifications ×400 [C and D]).
diagnosis, be reviewed in the current clinical context to avoid this type of misinterpretation.

In case 6, in which a sampling error occurred, the review biopsy diagnosis was combined SCLC-NSCLC; only SCLC was present in the cytology specimen. Combined SCLC-NSCLC is an uncommon diagnosis, and discordance between cytology and biopsy specimens is reported, to our knowledge, in only 2 prior studies. Matsuda et al reported 1 case of combined SCLC-NSCLC in which interpretation of the biopsy specimen was accurate, but the brushing cytology interpretation was not. Pilotti et al reported 2 cases of combined SCLC-NSCLC in which the cytology specimen was classified as “not otherwise specified” in both cases. Recognizing and confirming the presence of SCLC in at least one of the specimens, cytology or biopsy, in a possible combined SCLC or NSCLC, remains crucial because the standard of care for combined SCLC-NSCLC is to treat as SCLC.

Our study focused on discordances in distinguishing NSCLC from SCLC because pathologists have not been asked before to further classify the lung cancer type in cytology specimens. However, with the advent of novel therapies, we are facing the need to further subclassify NSCLC on cytology and biopsy specimens. Previous studies have shown that SCLC and NSCLC can be distinguished with high accuracy (94%-100%) in cytology specimens, but this accuracy drops to a range from 66% to 91% when subclassification of NSCLC into squamous cell carcinoma, adenocarcinoma, and large cell neuroendocrine carcinoma is performed. Ancillary studies may play a role as new biomarkers are discovered, and further studies to assess concordance in subclassification of NSCLC will need to be performed.

CONCLUSIONS

At our institution, the concordance rate for cytologic-histologic diagnosis regarding lung cancer type is high (97.4%), despite these specimens being interpreted independently by different pathologists. Therefore, we believe this practice is safe. Discordance was the result of interpreting suboptimal specimens, misinterpreting squamous dysplasia as squamous cell carcinoma on the cytology specimen, misinterpreting a poorly differentiated neoplasm, and not recognizing a second component of a combined SCLC-NSCLC. Challenging cases, an unusual diagnosis, and suboptimal specimens should prompt reconciliation of findings between cytology and biopsy specimens, as well as with pertinent, previous histologic specimens before finalizing the diagnosis.

References