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Misclassification of Bronchioloalveolar Carcinoma with Cytologic Diagnosis of Lung Cancer

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Abstract

Introduction: Cytology is commonly used to diagnose non-small cell lung cancer (NSCLC) but is an inaccurate means of diagnosis of bronchioloalveolar carcinoma (BAC). The aims of this study were to calculate the sensitivity and specificity of cytologic diagnosis of BAC and to estimate the misclassification of BAC as other subtypes of NSCLC.

Methods: Preoperative fine-needle aspiration cytology diagnoses were compared to histology diagnoses in 222 patients, including 51 patients with pure or mixed BAC, who underwent lung resection for NSCLC at our institution since 1999.

Results: The sensitivity and specificity of a cytologic diagnosis of BAC were 12% and 99%, respectively. Based on cytologic diagnosis, 63% of BAC was misclassified as adenocarcinoma, and 18% was misclassified as undifferentiated NSCLC. In this cohort, 35% of adenocarcinomas and 12% of undifferentiated NSCLC diagnosed by cytology had BAC histology.

Conclusions: Diagnosis of NSCLC by cytology alone results in significant misclassification of BAC, most commonly as adenocarcinoma or undifferentiated NSCLC. Because patients with BAC respond differently to certain treatments such as endothelial growth factor receptor inhibitors and surgical resection of multifocal lung cancer, misclassification of BAC may have important therapeutic implications.

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Keywords

bronchioloalveolar carcinoma; cytology; lung cancer; epidemiology; misclassification

Bronchioloalveolar carcinoma (BAC) is a subset of non-small cell lung cancer (NSCLC) associated with improved survival and distinct response to certain treatments compared with other subtypes of NSCLC.1 The 1999 World Health Organization criteria for the diagnosis of BAC require the absence of stromal, vascular, and pleural invasion. Tumors with BAC and invasive features are categorized as adenocarcinoma with mixed features (mixed BAC). Existing evidence strongly suggests that mixed BAC predicts improved survival and has distinct genetic changes compared with pure adenocarcinoma.2-6 BAC accounts for 4% to 30% of NSCLC, with surgical series reporting higher percentages of BAC and population-based studies reporting lower percentages of BAC. Much of this discrepancy is due to the inclusion of mixed BAC and earlier stage lung cancers in surgical series. Yet this discrepancy may also be related to the misclassification of BAC as other subtypes of NSCLC when cytology alone is used to diagnose lung cancer.

Cytology is often used to classify the two thirds of NSCLC that are unresectable, whereas lung resection histology is used to classify most early-stage NSCLC.7 Although cytologic criteria for the diagnosis of BAC have been described, recent reports have found that these criteria are inaccurate in differentiating pure BAC from mixed BAC and adenocarcinoma. 8-13 The diagnosis of BAC requires examination of the alveolar architecture and evaluation for histologic invasion not possible with cytology.14

There has been no published report of the sensitivity and specificity of cytology for the diagnosis of BAC, and this is important in estimating the misclassification of BAC that occurs when cytology alone is used to diagnose NSCLC. Correct classification of BAC may be important because patients with any BAC histology have improved survival compared with patients with pure adenocarcinoma.6 Moreover, patients with multifocal lung cancer with BAC histology benefit from surgical resection, and patients with BAC histology are more likely to respond to the endothelial growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) gefitinib (Iressa) and erlotinib (Tarceva).15-17

We set out to determine the sensitivity and specificity of cytology for the diagnosis of BAC and to estimate the misclassification that occurs when the diagnosis of BAC is made by cytology alone. To accomplish this aim, we studied patients who underwent a fine-needle aspiration (FNA) biopsy followed by surgical lung resection.

MATERIALS AND METHODS

Comparing Cytology and Histology

Between January of 1999 and June of 2006, 430 patients underwent lung resection for NSCLC at our institution. Twenty-three patients with carcinoid tumor were excluded from this analysis. Of the remaining 407 patients, 222 had preoperative FNA cytology results available for review. An additional 19 patients who underwent lung resection had a preoperative cytologic diagnosis of NSCLC made by bronchoscopic brushing, bronchial

lavage, Wang needle biopsy, or pleural fluid cytology. This relatively small group of patients was excluded because of varying quality of cytologic specimens and our inability to verify the number of patients who might have had nondiagnostic bronchoscopic or sputum cytology before being referred to our institution. An additional 15 patients were diagnosed by mediastinoscopic biopsy or by noncytologic endobronchial biopsy. Of the patients without preoperative tissue diagnosis, 102 patients underwent surgical biopsy with intraoperative frozen section examination. Reasons for performing a surgical biopsy rather than a FNA biopsy included positron emission tomography–positive nodule, high-risk radiographic features, history of NSCLC, history of nonlung primary cancer with suspected lung metastasis, a nodule that was inaccessible or too small for FNA, and patient preference. We were unable to obtain detailed information on the preoperative diagnosis in 49 patients.

Our institution's cytologists reviewed the cytology of 96 (43%) patients included in this study. In all cases, the pathologist assigned a diagnosis and then described the cytologic findings. The cytologic findings that suggest BAC includes monolayered sheets of cells; uniform, round nuclei; papillary fronds; fine nuclear chromatin and nuclear grooves; intranuclear cytoplasmic inclusion bodies; and the presence of mucin (Figure 1).11,12 Specimens assigned a diagnosis other than BAC, but described by the pathologists as suggestive of or consistent with BAC, were noted. Similarly, specimens diagnosed as undifferentiated NSCLC, but mentioning only adenocarcinoma in the report, were noted to be suggestive of adenocarcinoma.

Our institution's surgical pathologists reviewed all histologic specimens after lung resection. Neither existing pathology slides nor paraffin blocks were re-examined for this study. Samples were categorized as pure BAC, when the pathologist noted BAC features with no areas of stromal, lymphatic, or pleural invasion, and mixed BAC when the pathologist noted BAC features with foci of invasion. Staging was based on pretreatment clinical stage for patients who underwent neoadjuvant treatment and pathologic stage for all other patients.

Sensitivity and specificity were calculated for a cytologic diagnosis of BAC using the standard procedure of pure BAC on histology. These values were then recalculated using any BAC features on histology as the standard procedure. Sensitivity and specificity were then recalculated including cytology suggestive of BAC as a positive test. Finally, sensitivity and specificity were calculated separately for cytologic specimens reviewed by our institution's cytologists to determine whether there were differences in cytologic diagnosis of BAC between pathologists at a tertiary care hospital and pathologists at referring institutions.

Statistical Analysis

Comparisons of variables were performed using Pearson χ^2 statistic or Fisher's exact test for categorical variables and Student t test for continuous variables. Statistical analyses were conducted using STATA 9.1 (College Park, TX) statistical software. Statistical significance was assumed for a two-tailed p value <0.05.

Ethical Considerations

This research study involved analysis of existing data from the UCSF Thoracic Oncology clinical database with no subject intervention. No identifiers were linked to subjects. This

study was approved by the University of California San Francisco Institutional Review Board (IRB, approval H8714-11647-10).

RESULTS

A total of 222 patients with matched FNA cytology and lung cancer resection histology results were included in this study. A summary of the lung cancer stage and histologic diagnosis of these patients is listed in Table 1.

The sensitivity and specificity for the diagnosis of BAC by FNA cytology are listed in Table 2. The sensitivity and specificity for the diagnosis of pure BAC were 22% and 99%, respectively. The sensitivity and specificity for the diagnosis of BAC (combining pure and mixed BAC) were 12% and 99%, respectively. When we included specimens with a diagnosis other than BAC that had features suggestive of BAC as a positive test, the sensitivity increased to 50% for pure BAC and 35% for any BAC histology, but the specificity decreased to 93% and 97%, respectively. When analysis was restricted to specimens reviewed by cytologists at our institution, the sensitivities and specificities calculated were similar (Table 2).

Cytology results for patients with BAC and adenocarcinoma on final pathology are listed in Table 3. Had patients in our study been diagnosed by FNA cytology alone, 56% of pure BAC and 63% of all tumors with BAC features would have been classified as adenocarcinoma. In addition, 17% of pure BAC and 18% of all tumors with BAC features would have been classified as undifferentiated NSCLC. Moreover, 12% of tumors classified as adenocarcinoma by cytology and 4% of tumors classified as undifferentiated NSCLC by cytology were pure BAC on histology. Thirty-six percent of tumors classified by cytology as adenocarcinoma and 12% of tumors classified by cytology as undifferentiated NSCLC had BAC features on histology. In our cohort of patients, among the 22 excluded patients that had non-FNA cytology diagnostic of NSCLC and subsequent lung resection, only one patient had BAC on histology (mixed BAC).

We compared the clinical characteristics of patients with BAC who were diagnosed by cytology as adenocarcinoma or undifferentiated NSCLC with all other patients diagnosed by cytology as adenocarcinoma or undifferentiated NSCLC. There were no significant differences in the proportion of patients who were women or nonsmokers between the two groups. Among patients with a diagnosis of adenocarcinoma by cytology, 18 patients (30%) without BAC had mediastinal metastases, but no patient with pure BAC had mediastinal lymph node metastases ($p = 0.05$), and two patients (9%) with mixed BAC had mediastinal metastases ($p = 0.05$). Among patients with a cytologic diagnosis of NSCLC, 18 (22%) patients without BAC had mediastinal metastases, but none of the four patients with pure BAC and only one patient (17%) with mixed BAC had mediastinal metastases, although these values were not statistically significant ($p = 0.61$ and 0.57). As reported in Table 4, among patients without mediastinal lymph node involvement who were diagnosed as adenocarcinoma by cytology, 15% had pure BAC and 30% had mixed BAC. Among patients without mediastinal lymph node involvement who were diagnosed as NSCLC by cytology, 6% had pure BAC and 8% had mixed BAC.

CONCLUSIONS

Our findings indicate that the diagnosis of BAC based on FNA cytology is inaccurate and frequently leads to the misclassification of BAC, most commonly as adenocarcinoma or undifferentiated NSCLC. While the specificity of cytology for a diagnosis of BAC was 99% in this study, the sensitivity was only 22% for pure BAC. The sensitivities and specificities were similar when our institution's pathologist or the referring institution's pathologists reviewed cytology. When cytology suggestive of BAC was included as a positive test, the sensitivity for pure BAC rose to 50% and was 63% among specimens reviewed by our institution's pathologists. These numbers are similar to the 60% sensitivity for BAC that we calculated based on data reported by Macdonald and Yazdi,11 who reviewed 49 cytology and histology specimens diagnosed as BAC. That report had insufficient information to calculate sensitivity, but there were nine false-positive cytologic diagnoses of BAC, suggesting that liberal criteria were used in the cytologic diagnosis of BAC. Although the sensitivity of cytologic diagnosis of BAC was poor, the specificity was in our study was high. This suggests that when cytologic findings strongly suggest BAC, the diagnosis is likely.

According to World Health Organization criteria for the diagnosis of BAC, there must be an absence of visceral, pleural, and lymphatic invasion. Accordingly, patients with hilar or mediastinal nodal metastases, chest wall and mediastinal invasion, or distant metastases do not have pure BAC. Yet BAC is still possible in patients with stage IIIb disease due to satellite nodules, or stage IV disease from multilobar disease. Moreover, adenocarcinoma with BAC features is possible in all disease stages, and it is unclear whether patients with advanced adenocarcinoma with BAC features have improved survival or differential response to EGFR-targeted therapy. Our findings suggest that BAC histology may be more common in advanced-stage NSCLC than previously believed.

In this study, had the diagnoses of lung cancer been made by FNA alone, 63% of patients with pure or mixed BAC would have been classified as adenocarcinoma, and 18% of patients with pure or mixed BAC would have been classified as having undifferentiated NSCLC. Moreover, 36% of adenocarcinomas diagnosed by FNA cytology would have had BAC histology, and 12% of undifferentiated NSCLC would have had BAC histology. This latter calculation is based on the prevalence of BAC features in this cohort of patients that disproportionately represented patients with early-stage NSCLC. Recently, a population-based analysis of advanced-stage BAC patients demonstrated that stage IIIb BAC patients due to satellite nodule in the same lobe and stage IV BAC patients due to intrapulmonary spread have significantly improved overall survival compared to patients with stage IIIb due to other T4 descriptors or N3 nodal stage or stage IV due to distant metastasis.18 Similarly, in our institutional cohort, patients who underwent lung resection were staged IIIb or IV most commonly because of satellite nodules or multifocal lung cancer, respectively. These patients are probably not representative of other patients with stage IIIb due to other T4 descriptors or N3 nodal stage or stage IV due to distant M1 disease who are less likely to undergo lung resection. Although the true prevalence of adenocarcinoma with BAC features among patients with advanced NSCLC is elusive, making it difficult to precisely calculate

the degree of misclassification of BAC, we can conclude that FNA cytology results in significant misclassification of BAC as adenocarcinoma and undifferentiated NSCLC.

Our findings have several therapeutic implications for patients with multifocal BAC and locally advanced or metastatic adenocarcinoma with BAC features. First, existing evidence indicates that patients with multifocal lung cancer with BAC histology benefit from complete surgical resection.16,17,19 Although patients with multifocal BAC are classified as stage IV according to the American Joint Committee on Cancer classification, complete resection of multifocal BAC is associated with a 64% 5-year survival.16 It is unclear whether patients with multifocal mixed BAC also benefit from complete surgical resection. A cytologic diagnosis of adenocarcinoma or undifferentiated NSCLC should not necessarily preclude surgical resection of multifocal lung cancer, especially when there is no evidence of mediastinal lymph node metastasis.

Patients with NSCLC with BAC histology are more likely to respond to the EGFR-TKIs gefitinib and erlotinib, although there is currently insufficient evidence supporting first-line treatment of patients with advanced BAC with EGFR-TKIs.20 Although it is unclear whether patients with mixed BAC histology have similar response rates to EGFR-TKIs compared with patients with pure BAC, recent studies suggest that EGFR-TK domain mutations are common in patients with mixed BAC, suggesting that these patients are more likely to respond to EGFR-TKIs.21,22 More investigation on the response of patients with mixed BAC to EGFR-TKIs is needed. There is also insufficient evidence of whether patients with BAC histology respond differently to cytotoxic chemotherapy compared with pure adenocarcinoma, and the frequent use of cytology for diagnosis among patients with advanced or metastatic lung cancer makes the study of treatment of unresectable BAC or advanced stage adenocarcinoma with BAC features difficult.15

The diagnosis of BAC can also be suggested by certain radiographic findings. Radiographic findings on computed tomography scanning suggesting BAC include ground glass opacities (GGOs), nonresolving consolidation, and a tumor with satellite nodules.6 An overwhelming majority of peripheral GGOs <2 cm in size are BAC. Very few patients at our institution with small GGO-predominant tumors underwent cytologic biopsy, and so we cannot draw conclusions on the accuracy of FNA cytology in this population or the accuracy of combining cytologic findings with radiographic findings of GGO in the diagnosis of BAC. As previously mentioned, patients without radiographic or positron emission tomography evidence of regional invasion, mediastinal metastases, or distant metastases are significantly more likely to have BAC features on histology, and this information should be used in conjunction with cytologic information to estimate the likelihood of BAC histology.

A limitation of this study is that we did not review pathologic specimens but rather used pathology reports to classify tumors. We did not review specimens because we were trying to estimate the misclassification of BAC that occurs when cytology is used to diagnose NSCLC in clinical practice. Although review of specimens might have improved the validity of the diagnosis of BAC on histology as the gold standard to which cytology is compared, our results are more generalizable to clinical practice. The similar sensitivities and specificities for diagnosis of BAC by our institution's pathologists and referring institution's

pathologists support the generalizability of our findings. Our findings also offer important information for interpreting population-based classification of lung cancers, which rely on the diagnosis assigned at the time of pathologic review.

Another limitation is that our conclusions on the degree of misclassification of BAC are limited to results of FNA cytology. Although 91% of cytologic diagnoses were made by FNA in our institution, many patients with NSCLC undergo other cytologic analysis during their evaluation including bronchoscopic brushing, lavage, and Wang needle biopsy. Other patients are diagnosed by sputum or pleural fluid cytology. We chose to restrict our analysis to patients with FNA because cytology specimens obtained by other methods were relatively infrequent and were of variable quality. We also could not verify whether patients had nondiagnostic bronchoscopic or sputum cytology during their evaluation by referring physicians, which might introduce significant bias in the calculation of sensitivity and specificity. In addition, patients with pure or mixed BAC are less likely to be diagnosed by non-FNA cytology because lesions almost never have endobronchial extension and are less likely to be associated with bulky mediastinal adenopathy or pleural effusion.

A meaningful proportion of patients with unresectable lung cancer without mediastinal nodal or distant metastases may have pure or mixed BAC and may respond to systemic agents differently from other subtypes of NSCLC. Clinical trials of systemic therapies for advanced NSCLC might decrease the amount of misclassification between undifferentiated NSCLC, adenocarcinoma, and BAC with the use of core biopsy for diagnosis.15 Although it seems likely that the sensitivity of core needle for BAC would be better than cytology, the diagnostic accuracy of core needle biopsy for BAC is currently unknown. An ongoing study at Memorial Sloan-Kettering Cancer Center on the treatment of early stage BAC with gefitinib incorporating core needle biopsy followed by surgical resection will provide valuable information on the diagnostic accuracy of core needle biopsy for BAC.23 Core biopsy may be an important diagnostic tool in patients with advanced or metastatic lung cancer who might be given certain treatments if diagnosed with BAC, such as resection of multifocal lung cancer or treatment with EGFR-TKIs. Although EGFR mutations, polymorphisms, and gene copy number predict response to EGFR-TKIs, more investigation is needed to identify the molecular markers that predict outcome and response to therapy in patients with adenocarcinoma and BAC. A molecular marker, detectable in a cytology specimen, might then obviate the need for classification based on histologic findings.

Although a clear pathologic definition of pure BAC exists, a standardized classification of tumors with mixed BAC and adenocarcinoma histology is essential for comprehensive population-based research on BAC. The presence of any BAC features is associated with improved survival compared with pure adenocarcinoma, but it is controversial whether an increased proportion of BAC features predicts an incrementally improved survival.6 This controversy has led to variability in classification of BAC in the literature and a lack of reporting of mixed BAC to cancer registries, limiting population-based research to pure BAC. A standardized classification scheme including mixed BAC is crucial to adequately study the epidemiology and treatment of this unique subset of lung cancer.

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REFERENCES

1. Raz DJ, He B, Rosell R, Jablons DM. Bronchioloalveolar carcinoma: a review. Clin Lung Cancer. 2006; 7:313–322. [PubMed: 16640802]
2. Higashiyama M, Kodama K, Yokouchi H, et al. Prognostic value of bronchiolo-alveolar carcinoma component of small lung adenocarcinoma. Ann Thorac Surg. 1999; 68:2069–2073. [PubMed: 10616979]
3. Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. Cancer. 1995; 75:2844–2852. [PubMed: 7773933]
4. Raz DJ, He B, Rosell R, Jablons DM. Current concepts in bronchioloalveolar carcinoma biology. Clin Cancer Res. 2006; 12:3698–3704. [PubMed: 16778095]
5. Sakurai H, Dobashi Y, Mizutani E, et al. Bronchioloalveolar carcinoma of the lung 3 centimeters or less in diameter: a prognostic assessment. Ann Thorac Surg. 2004; 78:1728–1733. [PubMed: 15511463]
6. Travis WD, Garg K, Franklin WA, et al. Evolving concepts in the pathology and computed tomography imaging of lung adenocarcinoma and bronchioloalveolar carcinoma. J Clin Oncol. 2005; 23:3279–3287. [PubMed: 15886315]
7. Lathan CS, Neville BA, Earle CC. The effect of race on invasive staging and surgery in non-small-cell lung cancer. J Clin Oncol. 2006; 24:413–418. [PubMed: 16365180]
8. Lozowski W, Hajdu SI. Cytology and immunocytochemistry of bronchioloalveolar carcinoma. Acta Cytol. 1987; 31:717–725. [PubMed: 2827409]
9. Saleh HA, Haapaniemi J, Khatib G, Sakr W. Bronchioloalveolar carcinoma: diagnostic pitfalls and immunocytochemical contribution. Diagn Cytopathol. 1998; 18:301–306. [PubMed: 9557268]
10. Silverman JF, Finley JL, Park HK, Strausbauch P, Unverferth M, Carney M. Fine needle aspiration cytology of bronchioloalveolar-cell carcinoma of the lung. Acta Cytol. 1985; 29:887–894. [PubMed: 2996275]
11. MacDonald LL, Yazdi HM. Fine-needle aspiration biopsy of bronchioloalveolar carcinoma. Cancer. 2001; 93:29–34. [PubMed: 11241263]
12. Ohori NP, Santa Maria EL. Cytopathologic diagnosis of bronchioloalveolar carcinoma: does it correlate with the 1999 World Health Organization definition? Am J Clin Pathol. 2004; 122:44–50. [PubMed: 15272529]
13. Morishita Y, Fukasawa M, Takeuchi M, Inadome Y, Matsuno Y, Noguchi M. Small-sized adenocarcinoma of the lung. Cytologic characteristics and clinical behavior. Cancer. 2001; 93:124–131. [PubMed: 11309778]
14. Atkins KA. The diagnosis of bronchioloalveolar carcinoma by cytologic means. Am J Clin Pathol. 2004; 122:14–16. [PubMed: 15272525]
15. Miller VA, Hirsch FR, Johnson DH. Systemic therapy of advanced bronchioloalveolar cell carcinoma: challenges and opportunities. J Clin Oncol. 2005; 23:3288–3293. [PubMed: 15886316]
16. Roberts PF, Straznicka M, Lara PN, et al. Resection of multifocal non-small cell lung cancer when the bronchioloalveolar subtype is involved. J Thorac Cardiovasc Surg. 2003; 126:1597–1602. [PubMed: 14666039]
17. Battafarano RJ, Meyers BF, Guthrie TJ, Cooper JD, Patterson GA. Surgical resection of multifocal non-small cell lung cancer is associated with prolonged survival. Ann Thorac Surg. 2002; 74:988–994. [PubMed: 12400733]
18. Zell JA, Ou SH, Ziogas A, Anton-Culver H. Long-term survival differences for bronchioloalveolar carcinoma patients with ipsilateral intrapulmonary metastasis at diagnosis. Ann Oncol. 2006; 17:1255–1262. [PubMed: 16766595]
19. Volpino P, D'Andrea N, Cangemi R, Mingazzini P, Cangemi B, Cangemi V. Bronchioloalveolar carcinoma: clinical, radiographic, and pathological findings. Surgical results. J Cardiovasc Surg (Torino). 2001; 42:261–267.

20. Miller VA, Kris MG, Shah N, et al. Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. J Clin Oncol. 2004; 22:1103–1109. [PubMed: 15020612]

21. Haneda H, Sasaki H, Lindeman N, Kawano O, Endo K, Suzuki E, et al. A correlation between EGFR gene mutation status and bronchioloalveolar carcinoma features in Japanese patients with adenocarcinoma. Jpn J Clin Oncol. 2006; 36:69–75. [PubMed: 16449241]

22. Haneda H, Sasaki H, Shimizu S, et al. Epidermal growth factor receptor gene mutation defines distinct subsets among small adenocarcinomas of the lung. Lung Cancer. 2006; 52:47–52. [PubMed: 16503085]

23. Kris MG. How today's developments in the treatment of non-small cell lung cancer will change tomorrow's standards of care. Oncologist. 2005; 10(suppl 2):23–29. [PubMed: 16272456]

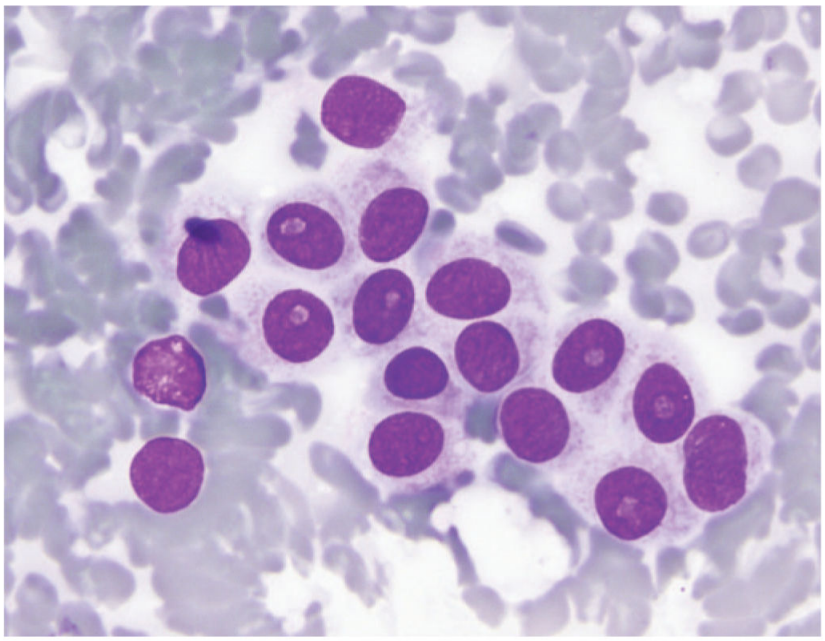

FIGURE 1.

Cytology specimen from a patient with bronchioloalveolar carcinoma (BAC) (x40, May-Grunwald-Giemsa stain). Features that suggest the diagnosis of BAC include monolayered sheet of cells; uniform, round nuclei; fine nuclear chromatin; and intranuclear cytoplasmic inclusion bodies.

TABLE 1

Lung Cancer Stage, Histologic Diagnosis, and Cytologic Diagnosis of Participants ($n = 222$)[a]

	No. (5)
Stage at diagnosis[b]	
I	116 (52)
II	28 (13)
IIIa	34 (15)
IIIb	33 (15)
IV	10 (5)
Histologic subtype	
Adenocarcinoma	89 (40)
Mixed BAC	33 (15)
Pure BAC	18 (8)
Squamous	48 (22)
Large cell	7 (3)
Undifferentiated	26 (12)
Benign[c]	1 (0.4)
Cytology results	
Adenocarcinoma	88 (40)
BAC	7 (3)
Squamous	32 (14)
Large cell	8 (4)
Undifferentiated	76 (34)
Benign or nondiagnostic	10 (5)
Metastatic cancer[d]	1 (0.4)

BAC, bronchioloalveolar carcinoma.

[a] Stage represents pretreatment clinical stage among patients undergoing neoadjuvant among patients not undergoing neoadjuvant therapy. Histologic subtype is the pathologic diagnosis made after lung resection. Cytologic diagnosis is based on fine-needle aspiration (FNA).

[b] Excludes one patient with benign disease on final path.

[c] Patient with BAC features on FNA found to be benign on lung resection histology.

[d] Cytologic diagnosis was metastatic papillary thyroid carcinoma. Histology showed lung adenocarcinoma.

TABLE 2

Sensitivity and Specificity of Cytologic Diagnosis of BAC

	Pure BAC (n = 18)			Pure or Mixed BAC[a] (n = 51)		
	All Specimens	**UCSF Reviewed**	***p* Value[b]**	**All Specimens**	**UCSF Reviewed**	***p* Value[b]**
Cytologic diagnosis of BAC[c] (n = 7)						
Sensitivity	22.2%	25.0%	0.80	11.8%	8.7%	0.54
Specificity	98.5%	98.9%	0.73	99.4%	98.6%	0.25
Cytology suggestive of *BAC*[d] (n = 24)						
Sensitivity	50.0%	62.5%	0.34	35.3%	43.5%	0.27
Specificity	92.6%	89.8%	0.17	96.5%	94.5%	0.23

BAC, bronchioloalveolar carcinoma.

[a] Disease includes both histologically pure and mixed BAC.

[b] *p* Value is for the χ^2 test comparing sensitivity and specificity for University of California, San Francisco (UCSF)– and non-UCSF reviewed specimens.

[c] A positive test is defined as a cytologic diagnosis of BAC.

[d] A positive test includes both cytology specimens final diagnosis of BAC and specimens described as suggestive of BAC.

TABLE 3

Cytologic Diagnosis in Patients with BAC and Adenocarcinoma

FNA Cytologic Diagnosis	Lung Resection Histology, no. (%)			
	BAC (Pure and Mixed) (*n* = 51)	**Pure BAC (*n* = 18)**	**Mixed BAC (*n* = 33)**	**Adenocarcinoma (*n* = 89)**
BAC	6(12)	4 (22)	2 (6)	0
Adenocarcinoma	32 (63)	10 (56)	22 (67)	52 (58)
Suggestive of BAC[a]	12 (24)	6 (32)	6 (18)	5 (6)
NSCLC, not differentiated	9(18)	3 (17)	6 (18)	27 (30)
Suggestive of adenocarcinoma[b]	3 (6)	1 (6)	2 (6)	3 (3)
Large cell	0	0	0	4 (5)
Benign or nondiagnostic	3 (6)	0	3 (9)	6 (7)
Metastasis	1 (2)	1 (5)	0	0

BAC, bronchioloalveolar carcinoma; FNA, fine-needle aspiration.

[a]The subcategory suggestive of BAC is not a cytologic diagnosis, but rather signifies that the pathologist described the cytologic findings as suggestive of BAC.

[b]As above, this subcategory represents cytologic specimens diagnosed as undifferentiated non-small cell lung cancer (NSCLC) where the pathologist indicated that the findings were suggestive of adenocarcinoma.

TABLE 4

Patients without N2 Disease Diagnosed by Cytology[a]

Cytologic Diagnosis	Any BAC Features, No. (%)	Pure BAC, No. (%)	Mixed BAC, No. (%)
Adenocarcinoma	30 (45)	10 (15)	20 (30)
Undifferentiated NSCLC	9 (14)	4 (6)	5 (8)

[a]Patients without mediastinal lymph node involvement on final pathology.