Review

Noninvasive Bronchoscopic Specimens in the Diagnosis of Lung Cancer

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Abstract: One of the most useful applications of flexible bronchoscopy has been in the diagnosis of lung cancer. The diagnostic yield of peripheral lesions, however, is much lower than endobronchially visible lesions, despite the use of multiple sampling techniques. We review the experience with noninvasive bronchoscopic specimens—bronchial aspirates, washings, and bronchoalveolar lavage (BAL)—in the diagnosis of peripheral lung cancers. In addition, the use of BAL tumor markers in the diagnosis of lung cancers is also reviewed. The overall diagnostic yield of noninvasive bronchoscopic specimens is just less than 50% for peripheral lung cancers. Limited study numbers have not shown a significant increase in diagnostic yield when added to more invasive biopsy specimens and brushings. However, the general consensus from studies suggests that BAL should be included in the evaluation of peripheral lesions, and that the diagnostic yield is likely to improve when combined with biopsy and brushing. BAL appears to have its highest yield in infiltrative malignancies, such as bronchoalveolar carcinoma and lymphangitic carcinomatosis. A limitation of BAL is the consistent finding that the cytologic diagnosis of malignancy does not always correspond to the histologic pattern. The average correlation rate was 80%; however, most discrepancies occurred among the subtypes of non-small cell lung cancers. Tumor markers, despite extensive research efforts, remain primarily a research tool. Sufficient data do not exist to justify their use in routine clinical practice. Key Words: Lung cancer—Bronchoalveolar lavage—Bronchial washings—Cytology


FFB, flexible bronchoscopy; BNA, transbronchial needle aspiration; BAL, bronchoalveolar lavage; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; PGE2, prostaglandin E2.

One of the most useful applications of flexible bronchoscopy (FFB) has been in the diagnosis of lung cancer. FFB is especially valuable when an endobronchial malignant lesion can be visualized. In such cases, the diagnostic yield may exceed 90% when multiple types of specimens are obtained, including forceps biopsy specimens, bronchial needle aspiration (BNA), bronchial brushing, and bronchial washing. The diagnostic yield for lesions that cannot be visualized directly has been substantially lower, even when a combination of specimens is taken. These types of lesions pose obvious technical challenges when using forceps, BNA, and brushes, and during the years since the inception of FFB, many bronchoscopists have conjectured about the possible value of sampling techniques that extend beyond the view of the bronchoscope.

The most frequent bronchoscopic approaches to sampling the distal lung have included the noninvasive methods of bronchial aspiration, bronchial washing, and bronchoalveolar lavage (BAL); and the more invasive procedures of distal bronchial brushing, transbronchial biopsy, and BNA. The noninvasive techniques have, for the most part, provided smears that are stained via cytologic methods, although occasional studies have examined the usefulness of tumor marker assays. These methods have the advantages of ease and safety during the bronchoscopic procedure. Indeed, bronchial secretions or “aspirates” can be collected simply by inserting a suction trap, and bronchial washings require only the instillation of small volumes of saline (usually less than 20 mL). Even BAL, which involves instillation of larger volumes of saline, has been shown repeatedly to add little or no morbidity to FFB procedures. However, each of these procedures adds expense if they require specimen processing and interpretation.
We review the experience with the noninvasive bronchoscopic specimens—bronchial aspirates, bronchial washings, and BAL—in the diagnosis of lung cancer. In particular, we concentrate on the role of these specimens in the evaluation of lesions that are apparent radiographically, but are not visualized endoscopically.

BRONCHIAL ASPIRATES AND WASHINGS

Investigation of noninvasive bronchoscopic techniques for the diagnosis of malignancy began with the widespread acceptance of FFB as an important diagnostic modality. Early on, these studies dealt primarily with bronchial aspirates and washings. The initial results were disappointing. The diagnostic yield was often lower than that of sputum examinations.\(^3\) In 1974, however, Skitarelic and von Haam\(^3\) presented favorable results for both bronchial brushings and washings in patients for whom the clinical suspicion of malignancy was not confirmed by sputum examinations. Bronchial washings were positive in 64 of 104 cases of malignancy (63%), and bronchial brushings were positive in 40 of 47 (85%).\(^3\) Skitarelic and von Haam\(^3\) did not correlate results with peripheral versus central location of the lesion. The correct cell type matching between the cytologic specimen and confirmed histologic diagnosis for bronchial washings was 81%.

Subsequent studies that have distinguished peripheral from central lesions specifically have reported mixed diagnostic usefulness of bronchial aspirates and washings. Kvale et al.\(^4\) and Solomon et al.\(^5\) failed to show any notable benefit of bronchial washing in diagnosing peripheral lesions. Kvale et al.\(^4\) defined peripheral lesions as those not visible through the bronchoscope. The diagnostic yield in peripheral tumors with fluoroscopic guidance for biopsy, brushings, and washings was 3 of 6 (50%), 1 of 5 (20%), and 2 of 6 (33%) respectively.\(^4\) In no case did washings provide the only positive finding. Solomon et al.\(^5\) reported similar findings in 36 patients. Bronchial washings identified included 8 of 36 washings (22%), and were the only positive bronchoscopic specimen in only one patient.\(^5\)

Other studies have had more positive results in supporting the use of bronchial aspirates and washings in peripheral lesions. Funahashi et al.\(^6\) reported an overall diagnostic yield of aspirates, brushings, and biopsy specimens of 25 of 41 (61%) in endoscopically nonvisible tumors. Aspirates were positive in 17 of 40 (43%) but were solely diagnostic in 4 patients. They concluded that in peripheral or nonvisible tumors, aspirates should be collected and are likely to enhance the overall diagnostic yield. These bronchoscopists did not instill saline into the bronchial tree because of concern about the risk of hypoxemia and questionable contribution to the overall diagnostic yield.\(^6\)

Several studies have also reported results supporting the role of bronchial washings as a useful component in a “routine diagnostic specimen bundle” obtained during bronchoscopy of patients with peripheral lesions. In a prospective study by Jay et al.\(^7\) of 240 consecutive patients who underwent FB, 69 were eventually diagnosed with lung cancer. For 18 of these patients with nonvisible peripheral lesions, bronchial washings were positive in 44%, but they were the only positive specimen for 3 patients. By comparison, bronchial brushings were performed in 10 patients and were positive in only three (33%). The cytologic correlation with histologic examination was 54 of 58 (94%).\(^7\) Lam et al.\(^8\) reported an overall diagnostic yield of bronchial washings, brushings, and biopsy in 13 of 155 patients (86%) with peripheral tumors. The yield for bronchial washings, bronchial brushings, and biopsy specimens was 52%, 52%, and 61% respectively. Bronchial washings, brushings, and biopsy specimens were the sole diagnostic specimens in 13 (8%), 6 (4%), and 32 (21%) patients respectively. Cytologic–histologic accuracy for bronchial washings was 76%. They concluded all three procedures were valuable in diagnosing lung cancer and were complementary to one another.\(^8\) Lundgren et al.\(^9\) compared the diagnostic value of BNA, biopsy, bronchial aspirates, bronchial washings, and bronchial brushings in the diagnosis of lung cancer. They performed all five procedures on 60 patients with tumors. There were 13 endoscopically nonvisible tumors. The overall diagnostic yield was 9 of 13 (69%). Bronchial washings or aspirates, brushings, biopsy specimens, and BNA were positive in 6 (46%), 5 (38%), 2 (15%), and 2 (15%) patients respectively. These authors concluded that the diagnostic accuracy of combining forceps biopsy and bronchial aspiration or washing was higher than that of any single method for both visible and nonvisible tumors, whereas no appreciable benefit was achieved by using three or more procedures.\(^9\)

The concept of bronchial washings as an important adjunctive specimen to forceps biopsy in the diagnosis of peripheral tumors has been the subject of some controversy. In 1990, Mak et al.\(^10\) performed a retrospective analysis of the diagnostic effectiveness of combining cytologic and histologic procedures compared with a single technique in 188 patients with pulmonary malignancies: 125 visible endoscopically and 63 nonvisible endoscopically. These patients had bronchoscopic biopsy specimens, brushings, and bronchial washings without fluoroscopic guidance. The overall diagnostic yield for the
nonvisible lesions was 55.6%. Bronchial washings accounted for 38.1%, the highest yield of all when compared with brushings and biopsy, and provided the sole diagnosis in 9.5% of patients. Cytologic–histologic matching was 76%. Most discrepancies occurred with large cell and adenocarcinoma. Cytologic matching for small cell carcinoma was 20 of 22 (91%). The optimal combination of procedures was biopsy and bronchial washing. These authors suggested obtaining both washings and brushings, in addition to forces biopsy specimens, but holding one specimen initially to reduce cost and work.  

Trevisani et al.11 responded to the report by Mak et al.10 with a similar retrospective analysis using their own data. In 32 endoscopically nonvisible cases, biopsy specimens and bronchial washings were positive in 53% and 59% respectively. Bronchial washings provided the only positive result in 7 of 32 patients (22%). However, because the Fisher exact test showed no statistical difference between the diagnostic sensitivity of using biopsy alone and the combination of biopsy and washing, they concluded that bronchial washings should not be carried out routinely for suspected lung cancers.11  

Mak12 suggested that lack of significance in the study by Trevisani et al.11 was the result of type 2 error, and reinforced the clinical importance of bronchial washings that were the only diagnostic specimens for a total of 13 patients in the two studies. In another report, Semple12 related his findings in a similar population of patients, and his conclusion was that, in agreement with Mak et al.,10 all three techniques—biopsy, brushing, and washing—were required for maximum diagnostic yield.

**BRONCHOALVEOLAR LAVAGE**

In the early 1980s, BAL became widely recognized as an effective means of sampling the distal lung parenchyma. Initially, its application focused primarily on characterizing types of local lung inflammatory responses in patients with diffuse lung diseases and identifying opportunistic pulmonary infections in immunocompromised patients. But in 1983, Springmeyer et al.14 reported a case of bronchioloalveolar cell carcinoma diagnosed by BAL. Bronchoalveolar lavage was performed with 100 mL normal saline (20-mL aliquots) in a patient with progressive, diffuse infiltrates on chest radiograph. Clusters of adenocarcinoma cells characteristic of bronchioloalveolar cell carcinoma were seen in the BAL specimen, whereas bronchial washings and brushings were negative. The diagnosis was confirmed at thoracotomy by wedge biopsy. Sestini et al.15 followed up with two more case reports of bronchioloalveolar cell carcinoma diagnosed by BAL. Bronchoalveolar lavage was performed with 120 mL saline (30-mL aliquots) and was filtered through gauze. Both patients had diffuse infiltrates on chest radiography. Underlying carcinoma was not suspected initially in either patient, BAL having been performed for the evaluation of interstitial pulmonary disease in both patients. For both patients, transbronchial biopsy specimens were negative for evidence of malignancy. These two reports resulted in the recognition that BAL can be useful in the diagnosis of diffuse lung tumors, and introduced the concept that bronchoalveolar cells should be examined carefully for malignant features in patients with diffuse pulmonary shadowing.

Subsequently, Fedullo and Ettenson14 reported a case of lymphangitic spread of adenocarcinoma of unknown primary diagnosed by BAL. The patient underwent BAL with 150 mL normal saline for evaluation of interstitial lung disease. Lavage cytology revealed tumor cells, and transbronchial biopsy revealed poorly differentiated adenocarcinoma in the lymphatic channels. Levy et al.17 were also able to demonstrate the value of BAL as a safe and reliable noninvasive method of confirming lymphangitic carcinomatosis in a retrospective analysis. Twelve patients with chest radiographs suggestive of lymphangitic carcinomatosis underwent FFB and BAL with 200 mL normal saline in 20-mL aliquots. The yield for BAL, washings, brushings, and transbronchial biopsy specimens was 5 of 5 (100%), 4 of 7 (57%), 2 of 5 (40%), and 4 of 7 (44%) respectively. BAL was able to confirm lymphangitic carcinomatosis in all patients in whom brushings and biopsy specimens were precluded because of coagulopathy or inability to cooperate.

In 1987, Linder et al.18 evaluated the sensitivity of BAL for the diagnosis of discrete lung cancers. Thirty-five patients with biopsy-proved lung carcinoma were included, but chest radiographic abnormalities were not described, and identification of patients with central versus peripheral lesions was not provided. BAL was performed with 120 mL normal saline in six aliquots of 20 mL. The first aliquot was considered a “bronchial specimen,” and all aliquots were filtered through mesh to remove mucus and debris. Cells diagnostic of malignancy were found in 24 of 35 patients (68.6%). The cytologic–histologic accuracy was 79.1% and there were no incorrect diagnoses of small cell carcinoma. Of the 24 positive cases, the bronchial sample, the alveolar sample, and both accounted for 7 (29%), 4 (17%), and 13 (54%) cases respectively.18

Recognition that BAL may play a useful role in the diagnosis of primary lung cancer was subsequently extended to include Hodgkin’s and non-Hodgkin’s lymphoma by two case reports. Morales and Matthews19 reported a patient with known Hodgkin’s disease who
presented with a nodular infiltrate 14 months after initial diagnosis and treatment. FFB revealed normal airways. Bronchial brushings were nondiagnostic, but BAL revealed binucleated cells with the characteristic features of Reed–Sternberg cells. The diagnosis of recurrent Hodgkin’s disease was confirmed by left upper lobectomy. Davis and Gadek20 reported a case of non-Hodgkin’s lymphoma diagnosed by BAL that was performed to evaluate progressive bilateral interstitial infiltrates. The lavage revealed a lymphocytic alveolitis with elevated B-cell proliferation consistent with non-Hodgkin’s lymphoma. The transbronchial biopsy was suggestive of lymphoma, and the diagnosis was confirmed by open lung biopsy.

In 1988, Shiner et al.21 examined the value of BAL under fluoroscopy in the diagnosis of peripheral lung lesions larger than 2 cm in diameter in 71 patients, 51 of whom were found to have malignancies. The nonvisible lesions were grouped according to location: central zone (<4-cm radius of hilum) and peripheral zone (>4-cm radius of hilum.) Bronchoalveolar lavage was performed with 100 mL normal saline in 20-mL aliquots. Brushings, washings, and four to six transbronchial biopsy specimens were also taken. Overall, 38 patients (74.5%) were diagnosed by FFB. The diagnostic yields for central and peripheral zones were 83% and 64% respectively. Transbronchial biopsy was diagnostic in 33 of 38 patients (87%), BAL in 9 of 38 patients (24%), and brushings in 19 of 38 patients (50%). Bronchoalveolar lavage provided the sole diagnosis in 3 patients, as did brushings (n = 2). The investigators recommended FFB with transbronchial biopsy and brushing under fluoroscopic control as the best initial procedure for peripheral tumors larger than 2 cm in diameter, and suggested that BAL also be performed to improve the diagnostic yield.21

BAL would be expected to have even lower diagnostic value for peripheral lesions of less than 2 cm. Studies have indicated that bronchoscopic specimens have low diagnostic yields for peripheral lesions of less than 2 cm regardless of technique. Radke et al.22 found that the yield of transbronchial biopsy and brushings for lesions larger than 2 cm in diameter was 64% compared with 28% in lesions smaller than 2 cm. This marked difference is likely the result of the relationship between bronchial anatomy and tumor size. According to a study by Tsuboi et al.23 that correlated bronchograms with pathologic examination in surgically resected lung carcinomas, three or more bronchi supply lesions larger than 3 cm, whereas lesions smaller than 3 cm may be supplied by only one or two bronchi. Therefore, peripheral lesions smaller than 2 cm may be substantially less accessible by bronchoscopic techniques.

Studies have suggested that the radiographic pattern of peripheral lesions can predict the likelihood that BAL will provide diagnostic information. Bellmunt et al.23 studied 30 patients to determine whether the diagnostic yield of bronchial washings and postbronchoscopic sputum was increased by addition of BAL. The diagnostic yields of BAL, wash/sputum, and combined were 26%, 40%, and 53% respectively. The addition of BAL did not result in a significant increase in diagnostic yield, but 4 patients were diagnosed solely by BAL. Three of four infiltrative lesions were positive by BAL, and two of these were diagnosed solely by BAL. From these findings, it was concluded that BAL seemed especially valuable in the diagnosis of lung cancers with infiltrative patterns on chest radiograph.24

The higher diagnostic yield for BAL for infiltrative lesions has been confirmed by De Gracia et al.25 in a study of 39 patients with nodular tumors and in 28 patients with infiltrative tumors in which a consistent sequence of procedures was performed: bronchial washing followed by BAL, and then post-BAL aspirate. Malignant disease was found in 55 of these patients, and the diagnosis was made by FFB in 31 (56.3%). The diagnostic yields for BAL and washings and aspirate obtained after BAL were each 18 of 55 patients (32.7%), but BAL was the sole diagnostic specimen for 6 patients. The yield was higher for infiltrative lesions than nodular lesions. The high yield of washings was attributed to the fact that aspirate obtained after BAL was added to the same sample as washings. BAL provided additional useful diagnostic information in patients with infiltrative lesions by identifying nonmalignant processes, including pulmonary tuberculosis.25

In recent years, the number of studies evaluating the usefulness of BAL in diagnosing peripheral lung cancers has remained small. This is consistent with the recent national survey of bronchoscopists by Prakash et al.26 who found that the respondents rarely used BAL in nonimmunocompromised patients. Yet, during the last decade, several reports have lent further support to the use of BAL in this setting.

In 1992, Pirozynski27 evaluated the usefulness of BAL in the diagnosis of 145 peripheral malignant neoplasms in a retrospective analysis. Bronchoalveolar lavage was performed with 200 mL normal saline in 20-mL aliquots after other sampling procedures were done. BAL had the highest diagnostic yield of 96 of 145 (64.8%), compared with brush biopsy (37 of 124, 29.8%), catheter biopsy (30 of 112, 26.8%), BNA (14 of 24, 58.3%), and forceps biopsy (35 of 107, 32.7%). Only BNA was comparable, but only 24 patients underwent BNA. Correct cell typing with BAL, however, was only 35.2% overall and 55%
for positive BAL specimens. The diagnostic efficacy of BAL was affected by tumor size. In patients with correct cell typing, the average tumor size was 4.9 ± 1.8 cm. Nondiagnostic BAL was most frequent, with a smaller tumor size of 2.6 ± 1.2 cm. It should be noted that in that study, BAL was performed after other sampling techniques were used. The impact of this sequence remains unclear and may potentially have increased the diagnostic yield of BAL.

Lam et al. reported a relatively high diagnostic yield for BAL in diagnosing lung cancers in 100 patients, for whom lesions were not grouped specifically into endobronchially visible or nonvisible lesions, although only 13 patients had no abnormalities seen on FFB. The diagnostic yield of BAL and biopsy was 69 of 100 patients (69%) and 50 of 64 patients (78.1%) respectively. The cytologic–histologic correlation was only 24 of 37 (65%), but no misclassification of small cell carcinoma and nonsmall cell carcinoma occurred.

Poletti et al. has recently affirmed the value of BAL in patients with extensive neoplastic involvement of the lung in a study of 162 patients with infiltrates involving more than one lobe on chest radiograph. BAL was performed with 100 to 200 mL of normal saline in 20-mL aliquots. The first aliquot was processed separately, and all aliquots were filtered through gauze. BAL was positive in 123 of 162 patients (76%) and was diagnostic solely in 8 patients. Endobronchial and transbronchial biopsy specimens were positive in 80%. The overall diagnostic yield of biopsy specimens and BAL was 85%. The overall cytologic–histologic correlation for BAL was 155 of 162 patients (71%), and 93% for positive BALs. Yields for BAL in bronchoalveolar cell carcinoma and carcinomatous lymphangitis were particularly high at 41 of 44 patients (93%) and 57 of 69 patients (83%) respectively. In both cases, the high diagnostic yield was attributed to the consistent involvement of the centrilobular spaces and the ease of BAL in collecting diagnostic material from these areas. In hematogenous metastases described as sharply circumscribed nodules, yield for BAL was much lower (10 of 22, 45%), because tumor involvement was interstitial and outside the centrilobular spaces.

THE USE OF TUMOR MARKERS IN NONINVASIVE BRONCHOSCOPIC SPECIMENS

The use of various biochemical and immunologic markers in BAL fluid has been suggested as adjuncts to FFB to aid in the diagnosis of bronchogenic carcinoma. This practice, although studied thoroughly and promoted for research purposes over the years, has not gained clinical acceptance. The application of tumor markers has been of particular interest for the diagnosis of peripherally situated tumors that are poorly accessible to bronchoscopic evaluation.

Numerous investigations have examined the levels of carcinoembryonic antigen (CEA) in BAL fluid. In 1978, Concannon et al. reported that blood levels of CEA correlated with the clinical evolution of bronchogenic carcinoma. In addition, CEA levels in pleural fluid and bronchial secretions have also been proposed as adjunctive diagnostic tests. In 1980, Lemarie et al. compared levels of CEA in the blood and BAL fluid in four distinct groups of patients that included normal volunteers, those who did not have cancer but who were to have bronchoscopic evaluations for various reasons (e.g., postinfection, endotracheal sarcoid), those with bronchogenic carcinoma, and those who had pulmonary metastases of different origins. They noted that an elevated CEA level in BAL fluid was more sensitive than serum CEA in detecting those patients with bronchogenic carcinoma and pulmonary metastases from different origins.

Goldstein et al. evaluated the usefulness of a panel of four tumor markers (CEA, calcitonin, creatinine kinase-BB, and deoxyribonucleic acid) in serum and BAL fluid from patients with bronchogenic carcinoma or benign disease and in normal volunteers. CEA was the only serum marker elevated significantly in malignancy. All markers in BAL fluid were abnormally high in lung cancer patients. There was no correlation between levels in lavage fluid and those in serum. They found that high concentrations of three assays, including CEA in BAL fluid and serum and calcitonin in BAL fluid, combined with cytologic and histologic analysis of specimens from bronchoscopy best discriminated bronchogenic carcinoma from benign lung disease. The sensitivity of bronchoscopy increased from 45 to 89% when combined with a diagnostic criterion of elevation of two of the three markers, but specificity was only 71%. However, no cancer patient was found with negative bronchoscopy and all three markers were negative, yielding a negative predictive value of 100% for this combination.

Another study by de Diego et al. suggested the diagnostic usefulness of BAL CEA in combination with other endoscopic methods, particularly transbronchial biopsy. They measured CEA levels in serum and BAL fluid from patients with peripheral bronchogenic carcinoma and pneumonia. CEA levels in BAL fluid from patients with bronchogenic carcinoma were significantly higher than in serum. Additionally, CEA levels in BAL fluid were significantly higher in patients with bronchogenic carcinoma than in patients with pneumonia, or in healthy smokers and nonsmokers. BAL CEA levels re-
Neuron-specific enolase (NSE) is a biochemical marker proposed as a tumor marker for several types of malignancies, including bronchogenic carcinoma. Although it has a role in monitoring the response to therapy and detecting early recurrences, its usefulness as a diagnostic test has not been clearly established. Prados et al. analyzed NSE levels in BAL fluid from normal smokers and nonsmokers. They discovered that smokers tended to have higher levels than nonsmokers. In addition, several studies have implied that the diagnostic value of various tumor markers, including BAL CEA levels, may vary depending on the histologic subtype of tumor.

Several studies have cast doubt on the diagnostic specificity of CEA in BAL fluid. Merrill et al. reported CEA levels in BAL fluid from normal smokers and nonsmokers. They concluded that smokers tended to have higher levels than nonsmokers. In addition, several studies have implied that the diagnostic value of various tumor markers, including BAL CEA levels, may vary depending on the histologic subtype of tumor.

Numerous other tumor markers such as CA-125, CA-72–4, CA-19–9, CA-15–3, SCC Ag (Squamous Cell Carcinoma Antigen), neutral endopeptidase, bombesin-like peptides, and immunoglobulins (secretory immunoglobulin A) have been studied in BAL fluid, but none have proved to be diagnostic and reliable enough to justify routine clinical application. The K-ras oncogene, which is found in the BAL fluid of some patients with nonsmall cell carcinoma, appears to be promising.

CONCLUSION

Noninvasive bronchoscopic specimens have the advantage that they can be collected during FFB without any additional time or effort and little additional risk to the procedure. Furthermore, in addition to the more invasive methods of forceps biopsy and brushings, they represent a means of sampling peripheral tumors that may not be visualized endoscopically. However, the additional expense of processing and reporting results raises the question of whether the diagnostic yield is sufficiently high to warrant routine collection of these specimens during bronchoscopy for suspected malignancy.

The usefulness of bronchial aspirates and washings in diagnosing peripheral malignancies has been mixed, depending on the clinical setting in which it has been studied (Table 1). The major role of these specimens has been as an adjunctive specimen that can occasionally increase the yield of the FFB procedure by yielding a positive cytologic diagnosis when other specimens such as forceps biopsy are negative.

The role of BAL in the diagnosis of a peripheral lung lesion suspicious for cancer remains undefined. The paucity of studies addressing this application of BAL is reflective of its limited use in nonimmunocompromised patients, as noted by Prakash et al. There is little doubt that BAL can diagnose peripheral cancers. However, the average yield for diagnosing cancers by BAL cytology remains just less than 50% (range, 24–100%). The overall consensus from studies suggests that BAL should be included in the evaluation of peripheral lesions, and it is likely to improve the diagnostic yield of forceps biopsy and brushings. Available data would suggest that BAL...
has its highest yield in infiltrative malignancies such as bronchoalveolar carcinoma and lymphangitic carcinoma-tosis. The relative safety of BAL compared with biopsy in patients with increased bleeding risk further supports the use of BAL in evaluating lesions suspicious for malignancy. A potential limitation of BAL is the consistent finding that the cytologic diagnosis of malignancy does not always correspond to the histologic pattern. The overall average correlation rate between cytologic and histologic diagnoses among the studies reviewed was 80% (range, 55–94%). However, the majority of documented discrepancies occurred within the subtypes of nonsmall cell lung cancers and not between small and nonsmall cell lung cancers. Thus, from a treatment perspective, this discrepancy would appear to have a minimal outcome effect. Further investigation of the usefulness of BAL in this setting is warranted because several questions remain: How much does BAL add to the diagnostic yield of forceps biopsy and brushings? Should BAL replace brushings in diagnosing peripheral cancers? Would the diagnostic yield of BAL be improved if it were performed routinely after forceps biopsy specimens and brushings?

Tumor markers, despite extensive research efforts, remain primarily a research tool. Sufficient data do not exist to justify their use in routine clinical practice, although if high sensitivity and specificity assays could be developed, there would be substantial potential for their use in the diagnosis of peripheral lung neoplasms.

### REFERENCES


### Table 1. Results of diagnostic techniques in peripheral lesions

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<th>Series</th>
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<th>BAL (%)</th>
<th>Brush (%)</th>
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BW, bronchial washing; BAL, bronchoalveolar lavage; Bx, biopsy; dx, diagnosis; cyto-hist, cytologic-histologic accuracy.
fiberoptic bronchoscopy in the diagnosis of lung cancer [letter].

alveolar cell carcinoma diagnosed by bronchoalveolar lavage.

nosis of bronchiolo-alveolar carcinoma. Eur J Respir Dis

16. Fedullo AJ, Ettensohn DB. Bronchoalveolar lavage in lymphang-

17. Levy H, Horak DA, Lewis MJ. The value of bronchial washings
and bronchoalveolar lavage in the diagnosis of lymphangitic car-

the cytologic diagnosis of carcinoma of the lung. Acta Cytol
1987;31:796–801.

19. Morales FM, Matthews JJ. Diagnosis of parenchymal Hodgkin’s

20. Davis WB, Gadek JE. Detection of pulmonary lymphoma by bron-


22. Radke JR, Conway WA, Eyler WR. Diagnostic accuracy in pe-
ripheral lung lesions: factors predicting success with flexible fi-

for diagnosis of peripheral pulmonary carcinomas. Cancer 1967;
20:687–98.

bronchoalveolar lavage specimens: a diagnostic technique for lung
neoplasms with a peripheral location [letter]. Chest 1990;98:
513–4.

bronchoalveolar lavage in peripheral lung cancer. Am Rev Respir

26. Prakash UBS, Offord KP, Stubbs SE. Bronchoscopy in North

27. Pirozynski M. Bronchoalveolar lavage in the diagnosis of per-

sampling methods in bronchial carcinoma. Respirrology 2000;5:
265–70.

the diagnosis of disseminated lung tumors. Acta Cytol 1995;39:
472–7.

30. Goldstein N, Lipmann ML, Goldberg SK, et al. Usefulness of
tumor markers in serum and bronchoalveolar lavage of patients
undergoing flexible fiberoptic bronchoscopy. Am Rev Respir

of preoperative carcinoembryonic antigen (CEA) plasma levels in

titers on effusion fluid: a diagnostic tool? Arch Intern Med 1977;
137:875–9.

33. Blair OM, Goldenberg DM. A correlative study of bronchial cy-
tology, bronchial washing carcinoembryonic antigens, and plasma
carcinoembryonic antigen in the diagnosis of bronchogenic cancer.

34. Lemarie C, Lavandier M, Renoux M, et al. Carcinoembryonic

35. de Diego A, Compte L, Sanchis J, et al. Usefulness of carcinoem-
byronic antigen determination in bronchoalveolar lavage fluid: a
comparative study among patients with peripheral lung cancer,

36. Merrill WW, Goodman M, Matthey RA, et al. Quantitation of
carcinoembryonic antigen in the lung lining fluid of normal smok-

markers in serum and bronchial washings of patients with suspi-

38. Burghuber OC, Worofka B, Schernthaner G, et al. Serum neuron-
specific enolase is a useful tumor marker for small cell lung cancer.
Cancer 1990;65:1386–90.

neuron-specific enolase as a tumor marker in bronchoalveolar la-

specific enolase, SCC and CA-125 determination in bronchoalve-
olar lavage fluid from patients with lung cancer [abstract]. Am Rev

41. Funahashi A, LeFever A. Evaluation of prostaglandin E2 content
of bronchoalveolar fluid in the diagnosis of lung cancer [abstract].

42. LeFever A, Funahashi A. Elevated prostaglandin E2 levels in bron-
choalveolar lavage fluid of patients with bronchogenic carcinoma.

43. Cohen AJ, Franklin WA, Magill C, et al. Low neutral endopepti-
dase levels in bronchoalveolar lavage fluid of lung cancer patients.

44. Petruzelli S, Di Tomassi M, Menconi GF, et al. Tumor markers in
bronchial fluid of patients with lung cancer are they tumor maker
[abstract?] Eur Respir J 1994;7(suppl 18):229s.

study evaluating the effectiveness of secretory IgA measurements
in bronchoalveolar lavage to detect non-small cell cancer. Chest

46. Mills NE, Fishman CL, Scholes J, et al. Detection of K-ras onco-
gene mutations in bronchoalveolar lavage fluid for lung cancer

Journal of Bronchology, Vol. 8, No. 4, October 2001