

## RESEARCH ARTICLE

# Comparative Assessment of the Diagnostic Value of Transbronchial Lung Biopsy and Bronchoalveolar Lavage Fluid Cytology in Lung Cancer

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### Abstract

**Background:** This study was designed to determine the accuracy of bronchoalveolar lavage fluid cytology (BAL) using histopathologic examination of transbronchial biopsy specimens as the gold standard in diagnosis of lung carcinoma at our center. **Materials and Methods:** A retrospective study was conducted to investigate a total of 388 patients who were suspected of having lung cancer and had undergone fiberoptic bronchoscopy in Shahid Sadoughi hospital from 2006 to 2011. Lung masses were proven to be malignant by histology. **Results:** Transbronchial lung biopsy (TBLB) identified malignancy in 183 of the 388 cases, including 48 cases (26.2%) with adenocarcinoma, 4(2.1%) with bronchioloalveolar carcinoma, 47(25.6%) with squamous cell carcinoma, 34(18.5%) with well-differentiated neuroendocrine carcinoma, 35(19.1%) with small cell carcinoma, 14 (7.6%) with non-small cell carcinoma, and 1 (0.54%) with large cell carcinoma. A total of 205 cases were correctly classified as negative. BAL was also performed in 388 patients; 86/103 cases were consistent with the final diagnosis of lung cancer and 188/285 cases were correctly classified as negative. The sensitivity of BAL was 46.9% (CI:41.9%, 51.8%) and its specificity was 91.6% (CI:88.8%, 94.3%). BAL had a positive predictive value (PPV) of 83.4% (CI:79.7%, 87.1%) and a negative predictive value (NPV) of 65.8% (CI:61%, 70.5%). The overall accuracy of BAL was 70.5% and the exact concordance was 39%. **Conclusions:** Our findings suggest that BAL cytology is not sensitive but is a specific test for diagnosis of lung carcinoma. If transbronchial lung biopsy is combined with bronchoalveolar lavage, the positive diagnostic rate will be further elevated.

**Keywords:** Lung cancer - diagnosis - bronchoalveolar lavage - transbronchial lung biopsy - cytology

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### Introduction

Increased investigation on patients with malignant disease has led to significant developments in its treatment and handling of these patients. Despite this improvement, cancer remains the disease with the heaviest financial burden and highest mortality in many regions (Cho et al., 2013). Carcinoma of the lung is the most common malignant neoplasm and the leading cause of cancer-related death in the Asian Pacific Area (Luqman et al., 2014). Genetic, environmental characteristics and late detection are important factors for high mortality rates related to lung cancer (Ahmed et al., 2013). The prognosis of lung cancer is closely related to the administration of early efficient interventions. Due to the limitations of detection procedures and the particular characteristics of the tumor, it is difficult to make confirmed diagnosis of some carcinomas of the lung. The ability to take the lung tissue without the need for the patient to undergo surgery

is an important step. Flexible bronchoscopy is one of the main methods used in diagnosis of suspected lung cancer (Li et al., 2013). It represents a major progress in the diagnosis and treatment of lung diseases. Since the 1970s, as the evolution of transbronchoscope, TBLB has been widely used in the pulmonary medicine. Bronchial forceps biopsies can be carried out in two principal settings: biopsy of a visible bronchial lesion and biopsy of more a distal one, not visible endobronchially. Compared with open lung biopsy, TBLB has lower complications. However, in peripheral pulmonary lesions, TBLB has a variable and often trivial diagnostic yield as these lesions are often difficult to ascertain without a guidance materiel. In other words the precision of bronchoscope for pathological diagnosis is reported to be only 50 to 70% and the size of samples capture by bronchoscope is usually small and often not sufficient for ancillary methods in linkage with pathological diagnosis (Yasuda et al., 2011). In the case of peripheral pulmonary lesion which

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is inaccessible to bronchoscopic biopsy, a diagnosis of malignancy may be possible by cytological examination of the bronchoalveolar lavage fluid, but this method is much less sensitive than the assay of a biopsy specimen. Bronchoalveolar lavage is a minimally invasive procedure and it may also be used for molecular analysis in seek of diagnostic and prognostic marker (Myron et al., 2009). In order to determine the accuracy of BAL cytology using histopathologic examination of transbronchial biopsy as gold standard at our center, we made a retrospective study of a total of 388 patient, all of whom underwent examinations for both TBLB and BAL at the same time.

**Materials and Methods**

*This research was approved by the university ethics committee*

We retrospectively reviewed the records of the bronchoscopic procedures performed between 2006 and 2011, related to patients who thought to have clinical and radiologic features highly suggestive of lung cancer. All procedures were performed at a single institution (Department of Broncoscopy at Shahid Sadoughi Hospital). Combined BAL and TBLB were carried out. All the procedures of asepsis, premedication, sedation and anesthesia were the same as the formal bronchoscopy. After informed consent, transnasal standard flexible fibreoptic bronchoscopy was performed. A flexible fibreoptic bronchoscopy was performed with an Olympus CV-260SL bronchoscope, following the application of topical lidocaine. BAL was performed in 388 patients by the instillation of 150 mL of 0.9% saline. Lavaged specimens were processed with standard methodology. Two cytospin slides were fixed in alcohol and stained with the Papanicolaou method and were screened for neoplastic cells. The BAL findings were classified as positive for malignant cells if they showed malignant-looking cells. After that forceps were inserted through the channel of the bronchoscope, the forceps were inserted into the bronchial trees to the level of subsegmental bronchi by to-and-fro movement. In this approach, the bronchoscope was wedged into appropriate segmental bronchi and the biopsies were performed repeatedly in this area. At least five to six specimens were obtained. Histological specimens were collected in a 10% buffered formalin solution and embedded in paraffin. Then the slides were stained with hematoxylin and eosin for further histological

examination. Diagnosis of lung cancer was defined by the presence of malignant cells in histological specimens. All BAL data and biopsy slides were evaluated independently, without any knowledge of clinical data. Exclusion criteria were: 1) patients with severe coagulopathy and 2) patients with haemodynamic instability.

**Results**

This study included 388 patients investigated for lung mass on chest X-ray. The median age of these cases was 61.3±13.7 years (ranged from 19 to 89 years), including 128 males (50.4%) and 55(41%) females (male: female=2.3:1). TBLB was performed in 388 patients. It correctly identified lung cancer in 183 cases including 48 with adenocarcinoma, 47 with squamous cell carcinoma, 35 with small cell carcinoma, and 34 with well differentiated neuroendocrine carcinoma, 4 with bronchioloalveolar carcinoma and 1 case with large cell carcinoma (Table 1). BAL was performed in 388 patients; 86 (86/103) cases were consistent with the final diagnosis of lung cancer (Table 2) including 21 with adenocarcinoma, 18 with squamous cell carcinoma, 23 with small cell carcinoma, and 14 with well differentiated neuroendocrine carcinoma, 3 with bronchioloalveolar carcinoma and 7 cases with large cell carcinoma. On the other hand 188/284 cases were correctly classified as negative. The sensitivity of BAL was 46.9% (CI:(41.9%,51.8%)) and its specificity was 91.6% (CI:(88.8%,94.3%)). BAL had a positive predictive value (PPV) of 83.4% (CI:(79.7%,87.1%)) and a negative predictive value (NPV) of 65.8% (CI:(61%,70.5%)). The overall accuracy of BAL was 70.5% and the exact concordance was 39%.

**Table 1. Frequency of Lung Carcinoma According to Histological Type**

	TBLB+	
	Percent	No.
Squamous cell carcinoma	25.60	47
Small cell carcinoma	19.10	35
Adenocarcinoma	26.20	48
Well-differentiated-neuroendocrine carcinoma	18.50	34
Bronchioloalveolar carcinoma	2.10	4
Non-small cell carcinoma	7.60	14
large cell carcinoma	0.54	1
Total	100	183

**Table 2. A Comparative Assessment of the Diagnostic Value of Transbronchial Lung Biopsy and Bronchoalveolar Lavage Fluid Cytology in Lung Cancer**

		Total	TBLB		Kapa	p- value
			Non-malignant	Malignant		
BAL	Malignant	103	17	86	0.39	0.00%
		100%	16.50%	83.50%		
		26.60%	8.30%	47.30%		
	Non-malignant	285	189	96		
		100%	66.20%	33.80%		
		73.60%	91.70%	52.70%		
Total	Number	388	205	183		
	BAL	100%	53%	47%		
	TBLB	100%	100%	100%		

## Discussion

This article was designed to determine the accuracy of BAL cytology using histopathologic examination of transbronchial biopsy as gold standard in the diagnosis of lung carcinoma at our center. The critical topic of ameliorating the prognosis of lung cancer is early discovery, diagnosis and therapy. The diagnostic rate of peripheral lung cancer applied by transbronchial lung biopsy is still low. For peripheral pulmonary lesions TBLB has a sensitivity that varies pursuant to the number of biopsy specimens taken and to the size of the lesion (Dionisio, 2012). In addition, distribution of the lesion (focal or diffuse), small size of the obtained samples, confounding due to crush artifacts and failure to penetrate beyond the peribronchial sheath are also important (Margaritopoulos et al., 2012).

One review article illustrated the usefulness of volatile organic compounds in the early detection of lung cancer, however, lots of problems still exist in the application of this technique (Wang et al., 2014). Another work showed that combination detection of some tumor markers such as CEA, CA19-9, NSE and CYFRA21-1 could significantly improve the sensitivity and specificity in diagnosis of lung cancer, and could be important in early detection (Wen-Jing et al., 2013). However, this suggestion should be confirmed by further studies.

BAL is a noteworthy diagnostic and research instrument in pulmonology. It is an easily performed and well tolerated procedure that is useful in routine evaluation of patients with lung cancer. A number of studies have examined various combinations of assays with BAL to improve its diagnostic precision, but this does not mean that BAL alone is invaluable. In special clinical status, BAL is an important procedure for the physician who manages a patient in whom lung cancer is highly suspected. In the current study the sensitivity of BAL was 46.9% and its specificity was (91.6%). In one research BAL alone revealed malignant cells in 18 of 37 cases (sensitivity=48.6%), and the diagnostic value increased to 73.0% with BAL+TBLB. (Tang et al., 2000). Another study showed that TBLB had overall diagnostic sensitivity of 62%, BAL of 29%, bronchial brushing of 16% and washing of 6% (Russell et al., 2003). Lam et al. (2000) caught sufficient specimens via BAL in 69% of patients with lung cancer, and the addition of endobronchial brushings, endobronchial biopsies, and postbronchoscopic sputum analysis did not significantly increase the diagnostic yield. Wongsurakiat et al. (1998), retrieved malignant cells in 47% of patients with peripheral lung carcinoma, whereas transbronchial biopsy was diagnostic in only 17%. Schwarz revealed that bronchial brushings, BAL analysis, or bronchoscopic lung biopsies showed either or both positive cytology and histopathology when lymphangitic carcinomatosis was present (Schwarz, 2003).

In a comparative study of BAL and open lung biopsy Yamamoto (1994) found that the results of these two had a parallel relation except in few cases. In a recent study BAL showed the sensitivity of (69.6%) (Pradeep et al., 2014). Ahmed et al. (2004) found the sensitivity of BAL

cytology to be 93.44% as compared with transbronchial biopsy. Its specificity was 100%. These discrepancies between different studies may be explained by sampling error or the presence of benign process that simulates malignancy. The limitations of BAL examination are the possibility of false positivity in benign conditions and false negativity in the early stage of malignant diseases. Poor distribution of BAL specimens, infrequent exfoliation of malignant cells and interpretive errors contribute to relatively high false negative rate in some works. It should be noted that cytological sampling by BAL relies mainly on cells exfoliated from malignant tumor, and from long experience, it is now known that some lung cancers, for reasons yet unknown, do not exfoliate diagnostic cells regardless of the number of specimens collected. In the current study there was 16.50% false positivity. The reasons for false positive results can be misinterpretation of the cytological findings by the cytopathologist due to cellular changes in inflammatory diseases, squamous metaplasia and epithelial cell atypia in the background of fibrosis. On the other hand, some studies (Ahmed, 2004; Pradeep et al., 2014) had no false positivities. In a study conducted by Lachman et al. (1995) there were no false positivities. Ninety four percent (94%) of patients with a suspicious cytologic report had a final diagnosis of malignancy. There was no false positivity in the study of Rennard (1990). Similarly Linder et al. (1989) found no false-positive diagnosis in 386 patients. These results suggest that rare false positivity in some studies is power of BAL cytology.

However, in the current study there was 33.8% false negativity. False negativity in another study was 6.55% (Ahmed, 2004). The reasons for false negative results can be confounding inflammation, non representative specimen or hypocellular lavage. Similarly, the study of Wongsurakiat et al. (1998) had a significant false negative result. In the present study BAL had a positive predictive value of 83.4%. The positive predictive value of BAL cytology in one study was 100% (Ahmed, 2004). Saenghirunvattana et al. (1991) showed that patients whose first bronchial washing cytology was reported "suspicious for malignancy" had 82 per cent positive predictive value for malignancy. In the present study BAL had a negative predictive value of 65.8%. The negative predictive value of another study was 75%, while the diagnostic efficacy was 94.5% (Ahmed, 2004). A study conducted by Rennard (1990) had 35 patients with biopsy-proven lung cancer. In 24 (68.6%) of these, BAL showed malignant cells. There was no false positivity. Wongsurakiat et al. (1998) found that the diagnostic yield of BAL was affected by the size and segmental location of the tumor. In the study of Pirozynski the result of BAL was influenced by the type of cancer and size of the lesion. Highest yields were seen in adenocarcinoma (59.2%) and bronchioloalveolar carcinoma (80%). In our study the highest yield was seen in small cell carcinoma. In another study majority of the cases were of squamous cell carcinoma followed by adenocarcinoma and other types (Pradeep Kumar L et al. 2014). Pirozynski (1990) stated that the average size of the tumor in the group with accurate cell typing was  $4.9 \pm 1.8$  cm; in patients with non diagnostic BAL,

the average size was 2.6±1.2 cm. We did not evaluate this matter in this study. According to a study by Piaton et al. (1995) exact concordance could be captured in cytological and biopsy results in 87.3% cases. In our study the overall accuracy of BAL was 70.5% and exact concordance was 39%. We should note that examination of BAL cells via surface marker analysis can be used to identify special types of malignant lesions. The results of one study suggest a combination of cytologic approaches with molecular methods is useful for the diagnosis of lymphoproliferative disorders (Kido et al., 2012).

In conclusion, our study showed that BAL cytology is not sensitive but is a specific tool for diagnosis of lung carcinoma. The indication to perform TBLB procedure in lung cancer is the need for tissue examination which is considered necessary for correct diagnosis. The addition of BAL to the procedure, despite its apparent low yield, may be useful because it may save time. In addition, in the case of peripheral pulmonary lesion which is inaccessible to TBLB, a diagnosis of cancer may be possible by examination of the BAL fluid. If TBLB is combined with BAL, the positive diagnostic rate will be further elevated.

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