COMPARISON OF BRONCHOALVEOLAR LAVAGE CYTOLOGY AND TRANSBRONCHIAL BIOPSY IN THE DIAGNOSIS OF CARCINOMA OF LUNG

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Background: The objectives of this study were to compare bronchoalveolar lavage (BAL) cytology and transbronchial biopsy in the diagnosis of carcinoma lung and to determine accuracy of BAL cytology using histopathologicexamination of transbronchial biopsy as gold standard at our center. **Methods:** This study was carried out at Department of Histopathology, Ayub Medical College, Abbottabad, from 1-9-2000 to 28-2-2003. BAL fluid and bronchial biopsy were received and processed simultaneously. Four cytology and a set of histopathology slides were prepared. These were screened and diagnosis recorded. Sensitivity, Specificity, False Positive, False Negative, Positive predictive value and Negative predictive value of BAL cytology were determined using histopathology of transbronchial biopsy as gold standard. **Results:** We found the sensitivity of BAL cytology to be 93.44% as compared with transbronchial biopsy. The specificity was 100%. There was no false positive while false negative results were 6.55%. The positive predictive value was 100%, while the negative predictive value was 75%. The overall diagnostic efficacy of BAL cytology was 94.52%. **Conclusion:** BAL cytology is a highly sensitive and specific test for diagnosis of carcinoma lung. It can be used as a quick and reliable diagnostic method for diagnosis of lung malignancy.
Keywords: bronchoalveolar lavage, cytology, lung, carcinoma, biopsy

INTRODUCTION

Carcinoma lung is a leading cause of cancer death. It is the commonest malignancy in male population of Pakistan.[1] The only hope of combating the disease successfully remains in diagnosing the disease at the earliest possible stage, preferably before the lesion has reached the stage of a visible and palpable tumor.[2] A long-standing goal of cancer researchers has been to develop techniques that would facilitate earlier diagnosis and treatment of carcinoma lung and thereby decrease its mortality.

Patients who are suspected of having lung cancer undergo a thorough physical examination. A battery of diagnostic methods is available to diagnose lung cancer. However it is difficult to use all these techniques in every patient.

Before start of treatment a clear distinction between small cell and non small cell carcinoma must be made, for that histopathology remains the mainstay of treatment. Bronchial biopsies cannot be performed in more peripheral site or in patients at risk of hemorrhage. So alternative methods for obtaining a diagnosis are sometimes required. Bronchoscopic washing, brushing and fine needle aspirations may complement tissue biopsies in the diagnosis of lung cancer.[3]

Cytologic techniques are more safe, economical and provide quick results. The diagnostic yield for cytologic examination is comparable to that of other widely used endoscopic techniques such as transbronchial biopsy.[4] Pulmonary cytology and histopathology are valuable tools in the diagnosis of lung malignancies. The first realization that cancer of the lung could be accurately diagnosed and typed by the microscopy of expectorated cells is generally attributed to Dudgeon and Barret.[5]

Bronchoalveolar lavage (BAL) is a diagnostic and therapeutic procedure conducted by placing a fiberoptic scope into the lung of a patient, then wedging the tip of a bronchoscope into a bronchus (subsegmental), and instilling a known volume of saline (sterile water) solution into the distal airway, then aspirating up this volume. The sterile water removed contains secretions, cells, and protein from the lower respiratory tract. BAL can provide diagnostic information in cases of primary and metastatic lung cancer. It is a valuable diagnostic tool in detecting peripheral, primary pulmonary malignant neoplasm.[6] The efficacy of BAL is comparable with transbronchial biopsy both in central and peripheral lesions.[7] The sensitivity of BAL for the diagnosis of lung carcinoma is similar to that of transbronchial biopsy.[8] The diagnostic yield of BAL for cytological examination is comparable to that of other widely used endoscopic techniques such as transbronchialbiopsy (TBB). It is an easily performed and well tolerated

procedure that is useful in routine assessment of patients for carcinoma lung. It is a procedure that is non-invasive, easily performed, cost effective and less hazardous.

In Northern Pakistan including Hazara where lung malignancies are as common as in the rest of the country but population is comparatively poor, there is a need to adopt cheaper, safer and accurate procedures. This study was first of its kind in our setup. It was designed to compare the diagnostic efficacy of BAL cytology in diagnosis of primary lung carcinoma using histopathological examination of transbronchial biopsy as the gold standard.

MATERIAL AND METHODS

This study was carried out at the Department of Pathology, Ayub Medical College, Abbottabad in collaboration with the Department of Pulmonology, Ayub Teaching Hospital. The sample collection was carried out from 1st September 2000 to 28thFebruary, 2003. The study consisted of clinically diagnosed (suspected) cases of lung malignancy.

The BAL cytology and biopsy specimens were taken by the pulmonologist. The clinical, radiological and bronchoscopic data was also provided by the pulmonologist. Only the cases where BAL and bronchial biopsy were received simultaneously were included. Autolysed specimens with disturbed cellular morphological details, any case in which either of the tests was non conclusive and cases without proper history, provisional diagnosis and radiological findings were excluded. A total of 94 cases were received during this period out of which only 76 fulfilled all the criteria. Three out of these 76 were then dropped due to technical reasons (procedural faults). The results were therefore based upon 73 absolutely fit cases.

The bronchial wash fluid was sent to the laboratory within half an hour along with a proforma that had the presenting complaints, relevant history, provisional diagnosis and radiological findings. It was then immediately centrifuged for 5 minutes at 1500 revolutions per minute. Four slides were prepared from the sediment. Three of the slides were fixed in absolute alcohol (wet slides) for half an hour and one was air-dried. Two of the alcohol fixed slides were stained with H & E and the third with Papinoculou stain. The air dried slide was stained with Geimsa stain. All the slides were thoroughly screened with light microscope and the diagnosis was confirmed by cytopathologist. The cytologic diagnosis was grouped into four categories (Malignant, Suspicious/Atypical, Benign and Unsatisfactory/Inadequate) according to the World Health Organization classification using Willis and Ramzay criteria

The biopsy specimen was processed in an automatic tissue processor for paraffin block preparation. From each block 2-3 micron thick sections were prepared by using rotatory microtome. All the slides were then stained with routine H & E staining methods. All the slides were thoroughly screened and the diagnosis was confirmed by histopathologist. The tumors were classified according to WHO classification.[9]

The test performance characteristics were calculated using the predictive value model of Galen and Gambino. Histopathology of bronchial biopsy was taken as diagnostic reference "Gold Standard". A 2 x 2 table (table-2) was used to determine sensitivity, specificity, Positive predictive value, Negative predictive value and diagnostic efficacy. The test performance characteristics of BAL cytology as compared with the gold standard (biopsy) shown in table 3 were calculated based upon table-2.

RESULTS

The results presented are based upon 73 cases. Male to Female ratio in our study population was 7:1. The mean (±SD) age of our subjects was 64±3.42 years.

Table-1 gives diagnosis of malignancy or otherwise by BAL cytology and on histopathology. Table-2 (2x2) gives comparison of BAL cytology with the gold standard histopathology. Table-3 gives results of test performance characteristics of BAL cytology as compared with histopathology based upon the cells of table-2. Sensitivity of BAL cytology was 93.44 %, Specificity 100 %, False Positive 0 %, False Negative 6.55%, Positive predictive value 100 %, Negative predictive value 75 % and Diagnostic efficacy 94.52 %

Table-1: Diagnosis based on BAL cytology and histopathology (n=73)

	BAL Cytology	**Histological Diagnosis**
Diagnosis	**Cases (%)**	**Cases (%)**
Malignant	57 (78.08%)	61 (83.56 %)
Non Malignant	16 (21.91%)	12 (16.44%)

Table-2: 2 X 2 Table for comparison of BAL cytology with histopathology of biopsy

Histopathology of Bronchial Biopsy

		Malignancy	No Malignancy	
BAL cytology	**Malig-Nancy**	**57** (a)	**00** (b)	57 a + b
	No Malig-nancy	**04** (c)	**12** (d)	16 c + d
		61 a + c	12 b + d	73 N

DISCUSSION

Different diagnostic modalities are available for diagnosis of bronchogenic carcinoma in early stage. It has been suggested that a combination of various techniques may give the best results.[1,4] A lot of variation in results is observed from center to center, as most of these techniques depend on the expertise of the specialist. It is very rare that a center excels in all the techniques.[11] It is not possible to perform all techniques in each patient, therefore a search for the single best and reliable technique will continue.

Table-3: Test performance characteristics of BAL cytology as compared with histopathology of biopsy (gold standard)

Characteristic	Calculation based upon 2 x 2 table	Score
Sensitivity	a / a +c x 100	93.44 %
Specificity	d / b + d x 100	100 %
False Positive	b/b + d x 100	0 %
False Negative	c/a + c x 100	6.55 %
Positive Predictive Value	a / a + b x 100	100 %
Negative Predictive Value	d / c + d x 100	75 %
Diagnostic Efficacy	a+d/a+b+c+d x100	94.52 %

BAL is a valuable diagnostic and research tool in pulmonology.[12] In a comparative study of BAL and open lung biopsy Yamamoto[13] found the results of these two to have an almost parallel relationship with a few exceptional cases. A number of studies have tried different combinations of tests with BAL to improve the diagnostic accuracy, but this does not mean that BAL alone is of no use. In selected clinical situations, BAL is an important tool for the physician caring for patients in whom malignancy of the lung is suspected.[4,14]

Tang et al[7] suggested that BAL + TBLB is a safe and valuable procedure to achieve a high sensitivity rate in the diagnosis of peripheral lung cancer, especially of the infiltrative type.

The diagnostic yield of BAL is influenced by the size and segmental location of the lesion. Bronchoalveolar lavage provided a higher diagnostic yield (46.7%) than transbronchial biopsy (16.7%) in a study by Wongsurakiat et al.[15]

Our study shows a sensitivity of 93.44 % and a specificity of 100 % for BAL cytology. This is comparable with contemporary studies from various centers discussed below.

Ovchinnikov and Chernishova reported in 1987 after a 10 years study of transbronchial lung biopsy and diagnostic bronchoalveolar lavage in patients suffering from diffuse lung disease that it was possible to determine the histopathologicaldiagnosis with the help of bronchological investigation for 71.6 % patients.[16]

Linder et al found the sensitivity of bronchoalveolar lavage for the diagnosis of lung carcinoma to be similar to that of transbronchial biopsy and Wang needle biopsy.[8] In a study by Fend BAL alone showed a sensitivity of 73.9%.[17] Debeljaket al tried to establish the sensitivity of BAL in comparison with both transbronchial lung biopsy (TBB) and brushing. The sensitivity of the three methods was equal for primary as compared to metastatic tumors and for interstitial infiltrates as compared to coin lesions.[18]

In a study by Tang BAL alone revealed positive malignant cells in 18 of 37 cases (sensitivity 48.6%), and the diagnostic value significantly increased to 73.0% ($p < 0.05$) with BAL + TBLB.[7]

Pirozynski reported from a large study to determine the usefulness of BAL in the diagnosis of peripheral, primary lung cancer that in 145 patients with biopsy-proven cancer BAL was diagnostic in 64.8% revealing malignant cells. In 35.9% of these patients, the cytologic diagnosis agreed with the final pathologic diagnosis of the resected tumor.[6]

Rennard[4] found that BAL revealed cells diagnostic of malignancy in 68.6 % of thirty-five patients with biopsy-proven lung cancer. In another study de Gracia reported that BAL was positive in 33% carcinomas, and it gave the only positive result in 11%.[19]

BAL was positive for malignant cells in 14 of the 30 patients (46.7%) in a study by Wongsurakiat. In seven (50%) of these patients, the cell type diagnosed by BAL agreed with the final diagnosis.[15] Specificity for BAL was a low 60.7% due to contamination by inflammatory cells from upper airways in the study of Fend.[17]

Luckily our study had no false positives however false positive can be reported due mainly to misinterpretation of the smears by the cytologist due to cellular changes in chronic inflammatory disorders such as chronic pneumonia (atypical histiocytes), tuberculosis (epitheloid cells), bronchiectasis, pneumonitis (misinterpretation of cuboidal alveolar cells as small cell carcinoma),squamous metaplasia and alveolar cell polymorphism in lung fibrosis. False positives have very unfortunate consequences for the individual patients, therefore some advise "under reporting" instead of "over reporting" in suspicious cases. If cytology is positive for malignancy or suspicious cells repeat biopsy, clinical correlation with radiological/bronchoscopic findings is necessary. In a study by Lachman et al[20] there were no false positive cytologic diagnoses. The majority (94%) of patients with a suspicious cytologic report had a final diagnosis of malignancy. There were no false positives in study of Rennard.[21] Similarly Linder et al found no false-positive diagnoses of lung cancer occurred in 386 patients. This comparison suggests that rare false positive is a strength of BAL cytology.[8]

False Negatives in our study was 6.55%. The reasons for false negative results can be superadded inflammation, non represenatitive material or hypocellular aspirates. However the study of Wongsurakiat et al[15] had a lot of false negative results. They report that in five patients with metastatic lung cancer BAL gave negative results in all.

The positive predictive value of BAL cytology in our study is 100 %. Saenghirunvattana et al[22] showed that patients whose first bronchial washing cytology was reported "suspicious for malignancy" had 82 per cent positive predictive value for malignancy. The negative predictive value of our study is 75 %, while the diagnostic efficacy was 94.5 %.

In a study report of 100 cases of bronchogenic carcinoma held at the Institute of chest Medicine, Mayo Hospital, Lahore the biopsy specimens gave positive results in 52 %, brushings in 63 % and washings in 89 %.[23]

A study by Rennard had 35 patients with biopsy-proven lung cancer. In 24 (68.6%) of these, BAL revealed cells diagnostic of malignancy. There were no false positives. Six out of 50 Hodgkin's disease patients in the same study had Reed Sternberg cells detected on BAL, and 7/20 breast cancer patients had malignant cells on BAL prior to chemotherapy.[21]

In a study Poletti et al reported their experience with bronchoalveolar lavage (BAL) and its value in the diagnosis of malignant lung infiltrates. A total of 162 patients with biopsy- or autopsy-proven cancer had an analysis of BAL fluid performed. Cytologic examination showed malignant cells in 76% patients. BAL disclosed cancer cells in 93% of 44 bronchioloalveolar carcinomas.[24]

Amongst the earlier studies Linder et al[8] studied BAL fluid of 35 cases of biopsy-proven lung carcinoma. Of these, 24 (68.6%) had cells diagnostic of malignancy on cytologic preparations of the bronchoalveolar lavage fluid. Radio SJ reported from a study on metastatic breast carcinoma that no patients with chest roentgenogram suggestive of metastatic cancer or transbronchial biopsy positive for metastatic cancer had a negative lavage.[25]

A study examined the value of bronchoalveolar lavage (BAL) in diagnosing lymphangitic carcinomatosis. Bronchoalveolar lavage correctly identified 100% out of five patients, while no complications of BAL occurred. This study suggested that BAL should be performed to confirm the diagnosis of lymphangitic carcinomatosis before proceeding to a biopsy, especially when the risks of pneumothorax and hemorrhage are excessive.[26]

In the study of Pirozynski the result of BAL was affected by the type of cancer and size of the tumor. Highest yields were seen in adenocarcinoma (59.2 %) and alveolar cell lung cancer (80 %). The average size of the tumor in the group with correct cell typing was 4.9 +/- 1.8 cm; in patients with nondiagnostic BAL, the average size was 2.6 +/- 1.2 cm.[6]

According to a study by Piatin et al exact concordance could be obtained in cytological and biopsy results in 87.3 % cases.[11]

Wongsurakiat et al[15] found that the diagnostic yield of BAL was influenced by the size and segmental location of the lesion. They found in their study to evaluate the value of bronchoalveolar lavage (BAL) and postbronchoscopic sputum cytology in diagnosing peripheral lung cancer found that in the primary lung cancer

group, BAL was positive for malignant cells in 46.7% patients. In 50% of these patients, the cell type diagnosed by BAL agreed with the final diagnosis.

In a study by Pirozynski in 94 patients (64.8 percent), BAL was diagnostic, revealing malignant cells. In 52 (35.9 percent) of these patients, the cytologic diagnosis agreed with the final pathologic diagnosis of the resected tumor. The result of BAL was affected by the type of cancer and size of the tumor. Highest yields were seen in adenocarcinoma (59.2 percent) and alveolar cell lung cancer (80 percent).[6]

These results and their comparison indicate that BAL cytology carried out at our center for the diagnosis of bronchogenic carcinoma is comparable with the results of other centers.

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