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Research Article

DIAGNOSTIC UTILITY OF BRONCHOALVEOLAR LAVAGE IN DETECTING LUNG MALIGNANCIES

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ABSTRACT:

Introduction: Lung cancer is one of the most common cancers in both males and females globally, with similar trends in India. In this era of personalised medicine, minimally invasive methods like bronchoscopy, bronchoalveolar lavage (BAL) and biopsy are gaining importance. The role of BAL in non neoplastic conditions has already been proven, whereas, its role in diagnosing malignancies shows varying results with sensitivity ranging from 35.5% to 80.9% in various studies. Aims: To determine the efficacy of bronchoalveolar lavage in diagnosing malignancies in suspected cases of lung carcinoma.Methods: A retrospective study done for a period of three years (2015-2017), yielded 125 samples ofbronchoalveolar lavage out of which 75 cases had concurrent samples of biopsy. Cytology slides of BAL samples and histopathology slides of lung biopsy were retrieved from archives and reviewed. Results: Mean age of patients was55.3 years with male preponderance. The most common malignancy was squamous cell carcinoma. Out of 75 cases, 32 were diagnosed as malignancy on histopathology. 8 out of 32 (25%)of these cases were picked up by BAL cytology. The sensitivity of BAL is 25% and specificity is 86%. Conclusion: Bronchoalveolar lavageis a test with good specificity and varying sensitivity for diagnosis of lung carcinomas.

Keywords: Bronchoalveolar lavage, bronchoscopy, cytology, diagnostic efficacy, lung carcinoma.

INTRODUCTION

Lung cancer is the second most common cancer in both males and females in the United States. In India, it is the second most common in males and sixth most common carcinoma in females based on incidence rates.[1] Lung cancer related mortality is also rising, thus increasing disease burden in India. In this era of personalised medicine, minimally invasive methods like bronchoscopy followed by bronchoalveolar lavage (BAL), bronchial brushings, washings and lastly biopsy are gaining more importance.

Also, earlier detection is of utmost significance because the prognosis strongly depends on stage of the disease at diagnosis.[2]

Biopsies are time consuming and may not always be possible in patients with a risk of haemorrhage or in peripheral lesions. In such cases, cytology in the form of BAL maybe useful. BAL, done before any surgical procedure can help one glean more information about the diagnosis. The role of BAL in diagnosing non neoplastic conditions have already been proven,[3,4] whereas its role in diagnosing malignancies shows varying results.

MATERIALS AND METHODS

A cross sectional study was done in the Department of Pathology at ESICMC, Rajajinagar, Bengaluru from 2015 to 2017. 125 samples of bronchoalveolar lavage were received, out of which 75 cases had concurrent samples of biopsy and hence were included in the study. Patient details were collected from hospital records wherever available.

BAL samples received were documented, physical characteristics noted, and then routinely processed by centrifugation at 1500 rpm (rotations per minute) for 5 minutes. Smears were prepared from the sediment. Air dried smears were stained with Leishman stain and alcohol fixed smears with Haematoxylin and eosin stain and PAP stains. Biopsy specimens were routinely processed in histopathology section by formalin fixation, processed in automatic tissue processor and stained with haematoxylin and eosin stain. These archived slides were retrieved and reviewed. BAL reports were categorised as- Unsatisfactory, Non-neoplastic, Suspicious for malignancy and Positive for malignancy.

Data was entered onto a masterchart and sensitivity and specificity of BAL was determined considering histopathology as the gold standard.

RESULTS.

This study included only those cases which had both BAL and concurrent biopsy samples. (75 cases).

The mean age was 55.3 years with maximum cases occurring in the age group of 51-60 years. There was a male predominance with a male: female ratio of 4.3:1. The mean age for females was 52.4 and the mean age for males was 56.1 years.

The study of BAL revealed 56(74.7%) non-neoplastic cases out of the total. 8 cases were suspicious for malignancy and 6 cases were positive for malignancy(Table 1). Out of these 6 cases, one was diagnosed as adenocarcinoma, one as squamous cell carcinoma(SCC) and 4 were positive for malignancy (subtype not discernible).

Table 1: Diagnosis on BAL

Diagnosis	**No of cases (total = 75)**	**Percentage**
Unsatisfactory	5	6.6%
Non neoplastic	56	74.7%
Suspicious for malignancy	8	10.7%
Positive for malignancy	6 Positive for malignancy - 4 Adenocarcinoma -1 Squamous cell carcinoma -1	8%

On the other hand, the diagnosis of biopsies by histopathology revealed 23(30.6%) cases as unsatisfactory, 20 (26.6%) cases as non-neoplastic and 32 (42.6%) as neoplastic. Out of the 32 malignant cases, majority of them - 20 (62.5%) cases, were of squamous cell carcinomafollowed by 5 cases (15.6%) of adenocarcinoma, 4 cases (12.5%) of small cell carcinoma and 3 cases (9.3%) of undifferentiated or poorly differentiated carcinoma. (Table 2)

Table 2: Diagnosis on histopathology

Diagnosis	**No of cases (total = 75)**	**Percentage**
Unsatisfactory	23	30.7%
Non neoplastic	20	26.6%
Neoplastic	32 Squamous cell - 20 Adenocarcinoma - 5 Small cell - 4 Undifferentiated/ Poorly differentiated - 3	42.7%

On comparing results of BAL and that of histopathology, it was found that BAL picked up 8 out of 32(25%) cases of malignancy (true positive). It could also identify 37 true negative cases out of 43 (86%). Additionally, a concordance of 30.6% in 23 cases was calculated where the BAL and HPE diagnoses were concurrent with each other. These included 2 unsatisfactory cases, 13 non neoplastic and 8 neoplastic cases. (Table 3)

Table 3: BAL diagnosis vs Histopathological diagnosis

Nature of lesion on BAL	**No of cases**	**Histopathology diagnosis**		
		Unsatisfactory	Non neoplastic	Neoplastic
Unsatisfactory	5	2	2	1
Non neoplastic	56	20	13	23
Neoplastic (suspicious/Positive)	14	1	5	8
		23	20	32

Thus, the sensitivity and specificity of BAL with respect to lung malignancies was determined to be 25% and 86% respectively (Table 4). BAL had a positive predictive value of 57% and a negative predictive value of 60.6% The diagnostic accuracy of BAL was 60%.

Table 4: BAL and HPE diagnoses of lung malignancies

	Biopsy positive	**Biopsy negative**	**Total**
BAL Positive	08 (True positive)	06 (False Positive)	14
BAL negative	24(False negative)	37 (True negative)	61
Total	32	43	75

DISCUSSION

Lung cancer is a leading cause of mortality in both sexes, for which numerous additional etiological factors (other than smoking) are being researched. Earlier, most patients used to present in advanced stages of lung carcinoma. Now however, the advent of flexible bronchoscopy has revolutionised the diagnosis and treatment options available for lung lesions.

Various procedures have come up, some better thanmany. These include cytological methods like bronchoalveolar lavage (BAL), bronchial brushings and histopathological methods like endobronchial and transbronchial forceps bronchial biopsy (EBB and TBB). Though the term bronchial wash and BAL are frequently used interchangeably, bronchial wash is considered a therapeutic procedure in the ICU setting and BAL is a diagnostic procedure. BAL includes instillation of aliquots of saline and aspiration of these aliquots, which are then centrifuged, smears are prepared and examined under the microscope.

Though histopathology is the gold standard of diagnosis, BAL confers some advantages. For example, it is known to pick up some peripheral lesions, even if not visualised by bronchoscopy. It is a relatively safer procedure compared to biopsy, especially in patients with a risk of bleeding. It requires lesser expertise and also helps to tamponade bleeding, if any, caused by biopsy.[5] Additionally, the use of immunocytochemistry permits the delineation of primary lung tumours (TTF-1 and CK7 positive) from metastatic tumours.[6]

Age, sex and subtype distribution: In the present study, a total of 32 cases were diagnosed as malignancy by histopathology out of which 28 were male and 4 were female, with a male to female ratio of 4.3:1. A study conducted by Bhat et al[5] had a M:F ratio of 6:1 and a study done by Pradeep et al[7] (M:F = 4.3:1) which coincided with that of the present study. All studies showed a male preponderance. Majority of the studies (including present study) showed a mean age in the 5th decade. (55-59 years). All the studies also found that the most common malignancy was squamous cell carcinoma, followed by adenocarcinoma contrary to western countries where adenocarcinoma has surpassed squamous carcinoma as the most common lung carcinoma.

Diagnostic accuracy: The diagnostic accuracy of BAL in the present study was 60%. It was calculated as (TP+TN/Total cases). Studies done by Tomar et al[8], Bhat et al[4] and Raiza et al[9] had diagnostic accuracies of 44.8%, 42.2% and 80.5% respectively(Table 5).

The accuracy of BAL can be improved dramatically by concordant use of other techniques, many of which could be done in the same sitting. In a study conducted by Pradeep et al,[7] diagnostic yield by BAL alone was 81.1% whereas yield with all three techniques was 100%. Biopsy was the most diagnostic procedure in their study. On the other hand, in a study done by Tuladhar et al,[10] BAL was found to surpass bronchial biopsy in the diagnosis of tuberculosis.

Table 5: Diagnostic accuracy of BAL

Study	**Diagnostic accuracy**
Bhat et al[5]	42.2%
Tomar et al[8]	44.8%
Raiza et al[9]	80.5%
Present study	60%

Specificity and sensitivity: Literature review reveals variable specificity and sensitivity with respect to BAL cytology. In our study, the specificity (true negativity) of BAL was 86%. This was comparable to the studies conducted by Gaur et al[11] and Binesh et al[12] (89.6% and 91.6% respectively).

On the other hand, the sensitivity of BAL in present study is 25%. Other studies showed a wide variation with sensitivity ranging from 35.5% (Bhat et al[5]) to 69.6% (Pradeep et al[7]). The sensitivity measures the true positivity of the disease and BAL has a low sensitivity thus ruling it out as a screening test. (Table 6)

Table 6: Comparison of characteristics of BAL with other studies.

Study	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Bhat et al[5]	35.5%	78.2%	89.7	18.46
Gaur et al[11]	39.4%	89.6%	68.3	72.3
Binesh et al[12]	46.9%	91.6%	83.4	65.8
Pradeep et al[7]	69.6%	-	-	-
Present study	25%	86%	57%	60.6%

Predictive values: Bronchoalveolar lavage has modest positive predictive and negative predictive values of 57%and 60.6% respectively. Other studies show comparatively higher predictive values, especially positive predictive value.

False negative: In the present study, a diagnosis of malignancy could not be established on BAL in 24 (32%) cases, thus yielding a false negative index of 75%. This was comparable to the study done by Bhat et al[5]. (Table 7)

Table 7: False negative and false positive indices

Study	False negative index	False Positive index
Sareen et al[2]	27.3%	0
Binesh et al[12]	52.7%	8.2%
Bhat et al[5]	64%	21.8%
Present study	75%	13.9%

This may be attributed to the low cell yield in BAL due to sampling limitation. The yield can be improved by increasing the number of aliquots and preventing the discard of the first aliquot as practiced at some institutions. Some groups practice physical filtering of the sample with gauze to filter out blood clots and mucus. This may also lead to loss of cells and is best avoided.

There is also the fact that BAL picks up only the exfoliated cells from the tumours. Firstly, only the poorly differentiated carcinomas exfoliate cells more readily than well differentiated ones. Secondly, these cells, which have been in the lumen for quite some time, tend to show degenerative changes thus making it difficult to discern the accurate morphology.[8] It is also difficult to diagnose malignancies when there is presence of necrotic tissue or superadded secondary inflammation.

It is imperative to mention here that biopsy and brush techniques can pick up well differentiated tumours also.

False positive: In the present study, 6 cases were diagnosed as malignant on BAL. However, histopathology proved otherwise, yielding a false positive index of 13.9%. This was closest to a study conducted by Binesh et al[12] with a false positive index of 8.2%. Other studies like Sareen et al[2] and Bhat et al[5] had extremely variable values of 0% and 21.8% respectively. (Table 7)

False positivity in BAL maybe the result of benign reactive changes in BAL secondary to pneumonia, squamous metaplastic cells or chemotherapy in previously treated patients. It may be missed on biopsy due to causes like inadequate biopsy, biopsy from a necrotic area or crush artefacts.

All in all, the yield in BAL can be improved by increasing the number of aliquots, radiological correlation and employing a combination of more than one bronchoscopic

methods. The discarding of the first aliquot should not be practiced, neither should the use of physical filters.

Conclusion:

Bronchoalveolar lavage is a test with good specificity (86%) and varying sensitivity for diagnosis of lung carcinomas. Though biopsy enables final diagnosis and typing of lung malignancies, bronchoalveolar lavage proves to be a good ancillary technique and should be performed before any surgical intervention.

Figure 1: Microphotograph of BAL smears suspicious for malignancy showing few large atypical cells. a) – Leishman stain, (10x). b) and c) - H and E, (40x).

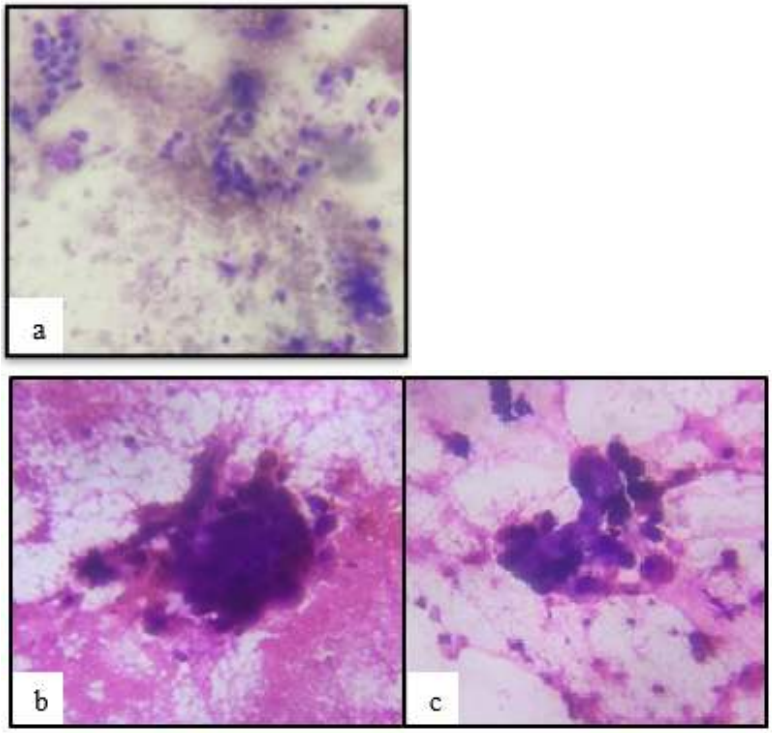


Figure 2: Microphotograph of BAL air dried smears showing high cellularity with malignant cells in clusters, sheets and scattered singly. Leishman, (10x)

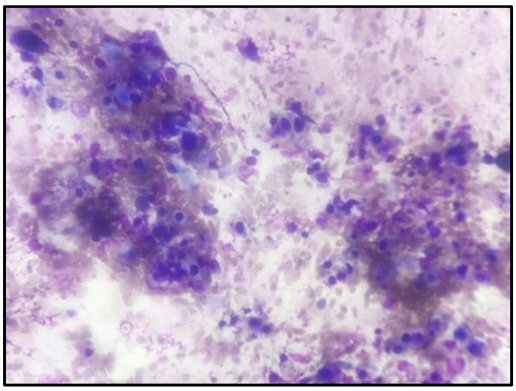


Figure 3: (a, b) Microphotograph of BAL smears showing neoplastic cells showing high N:C ratio, hyperchromatic pleomorphic nucleus and moderate eosinophilic cytoplasm.H an E. (40x)

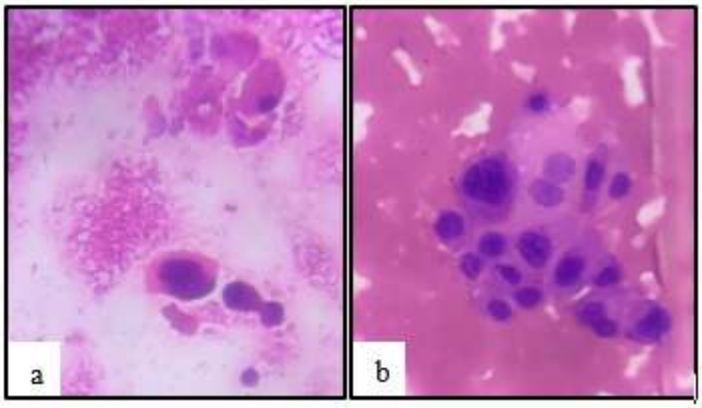


Figure 4: (a, b) BAL smears showing neoplastic cells showing high N:C ratio, hyperchromatic pleomorphic nuclei, few showing nucleoli. Leishman. (40x)

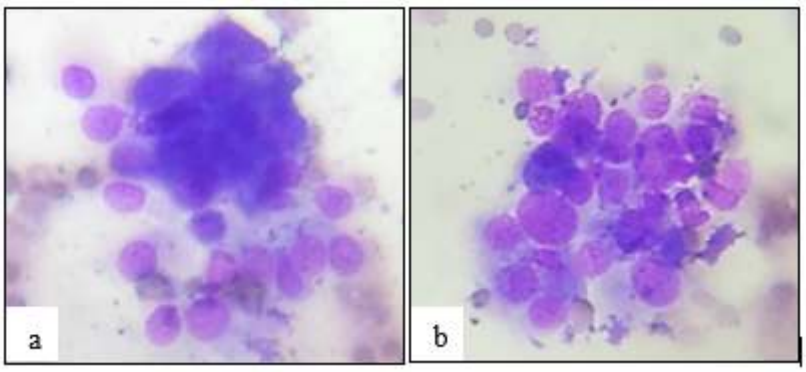


Figure 5: (a, b) Microphotograph of histopathological section of squamous cell carcinoma on bronchoscopic biopsy, showing neoplastic cells in sheets, with hyperchromatic, pleomorphic nuclei and eosinophilic cytoplasm. H and E, (4x, 40x)

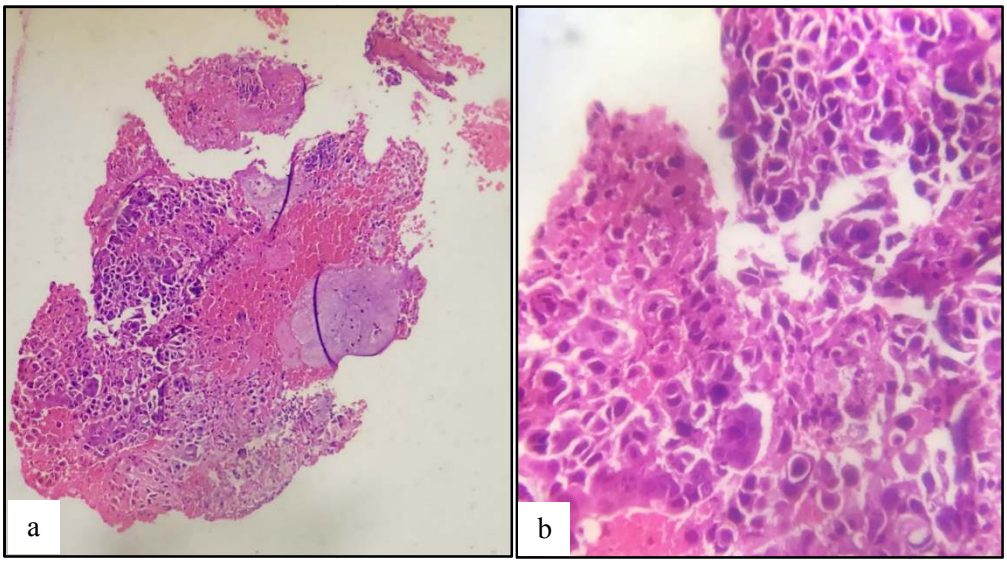
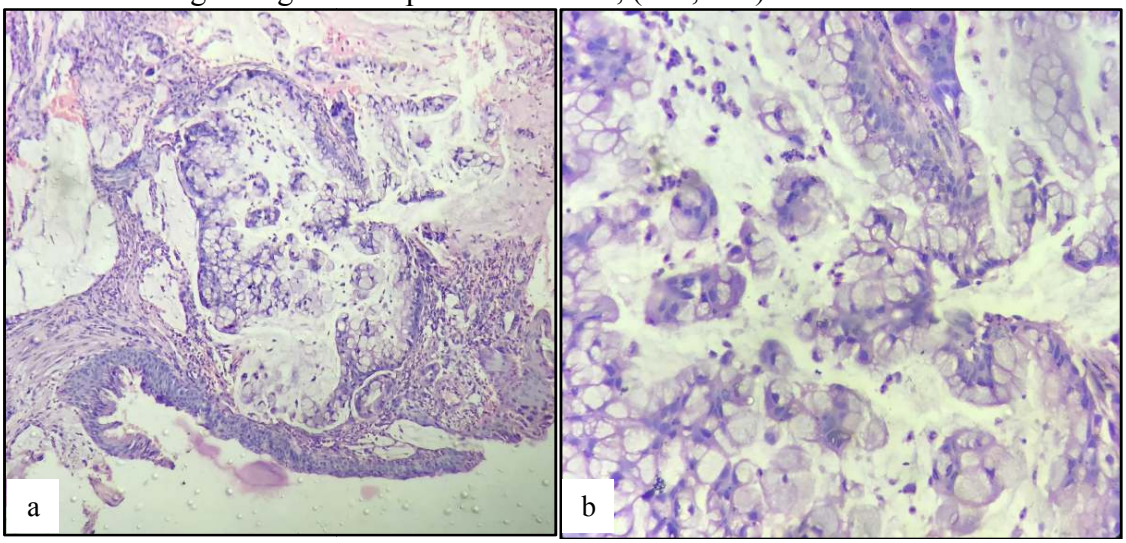


Figure 6: (a, b) Microphotograph of biopsy showing mucin secreting adenocarcinoma cells few arranged in glandular pattern. H and E, (10x, 40x)



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