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Diagnostic Role of Bronchoscopy guided Endobronchial Needle Aspiration cytology Exophytic endobronchial lesions: A single-center study in a tertiary care setting in India

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ABSTRACT

Objective: In present study, various conventional diagnostic techniques (CDTs) such as endobronchial forcep biopsy (FB), bronchial washing (BW) and endobronchial needle aspiration cytology (EBNA) are employed during fiber-optic bronchoscopy for diagnosis of exophytic endobronchial lesions (EEL) and special emphasis is given to EBNA.

Material and method: Prospective, observational study, screened 1280 cases with suspected lung malignancy on clinical and radiological basis. Bronchoscopy guided techniques such as EBNA, BW, FB is used in exophytic endobronchial lesions (EEL) in confirming the diagnosis of lung cancer and to find additive yield over other techniques such as BW and FB. Rapid on-site evaluation (ROSE) analysis of all EBNA samples done in pathology lab allied center. Finally, histopathology proven 810 lung malignancy cases are included in study. Statistical analysis is done by using chi-test.

Results: In present study, 810 diagnosed lung cancer patients between 29-85 age group predominant males 59.25% (480/810) and smokers by addiction in 63.20% (512/810) cases. Presented with cough in 82.09% (665/810), clubbing in 56.17% (455/810) cases & mass lesion in chest radiograph in 42.22% (342/810) cases. Anatomical location is documented on right side of tracheobronchial in 59.01% (478/810) cases during bronchoscopy. Yield of forcep biopsy & forcep biopsy plus bronchial wash in EEL is 89.25% (723/810) & 93.08 % (754/810) respectively. Yield of EBNA, EBNA plus bronchial wash & EBNA plus forcep biopsy in EEL is 64.56% (523/810), 67.28% (545/810) & 97.65% (791/810) respectively. Total yield of all fiberoptic bronchoscopy guided procedures (EBNA+FB+BW) in EEL is 100%. Additional yield of EBNA in EEL over other CDTs is 6.92%. Sensitivity of forcep biopsy & EBNA in diagnosing lung malignancy in EEL is 89.25% & 64.56% respectively. Forcep biopsy is more sensitive technique than EBNA in EEL. ($p < 0.00001$). Sensitivity of forcep biopsy plus bronchial wash in EEL is 93.08% (754/810). Sensitivity of EBNA plus bronchial wash in EEL is 67.28% (545/810). Sensitivity of EBNA plus forcep biopsy in EEL is 97.65% (791/810) ($p<0.00001$)

Conclusion: Endobronchial needle aspiration has documented very crucial role in diagnosing lung cancer in comparison to other conventional diagnostic techniques. Although Forcep biopsy is more sensitive test then EBNA in EEL in diagnosing disease, we have documented EBNA has significant additive yield in proportionate number of cases. EBNA is safe, sensitive and cytology samples can give comparable results to histopathology.

Key Words: EBNA, Bronchoscopy, bronchial wash, forcep biopsy, cytology

INTRODUCTION

Lung cancer is the most often diagnosed cancer and leading cause of cancer-related deaths worldwide. In India, lung cancer accounts for 5.9% of all cancers and 8.1% of all cancer-related deaths.[1] Bronchoscopy dates back to the late 18th century where rigid illuminating tubes were used to examine the tracheobronchial tree.[2] Subsequently, with the introduction of the fiberoptic bronchoscope by Ikeda et al.,[3] bronchoscopy has revolutionized the practice of pulmonary medicine. In lung cancer, because of advances in real-time imaging and catheter-based techniques, bronchoscopy not only remains pivotal in diagnosis and staging but also allows therapeutic intervention for airway restoration in patients with central airway obstruction and treatment of early detected central airway cancers.[4]

Conventional bronchial washing, brushing, and endobronchial and transbronchial biopsy have variable yields depending on tumor location and accessibility. For endobronchial tumor, forceps biopsy gives the highest yield (74%) compared with brushing (59%) and washing (48%). The yield is increased further to 88% when these modalities are combined.[4] Addition of needle aspiration for endobronchial, submucosal, peripheral pulmonary lesion, or Peribronchial lymph node has been demonstrated to enhance diagnostic yield and is cost effective by obviating further need of invasive interventions.[4]

Transbronchial needle aspiration via flexible bronchoscopy is a well-established sampling tool for diagnosis of lung malignancies.[5] TBNA is superior to all other sampling modalities in peribronchial and submucosal lesions and is on par with bronchoscopic forcep biopsy in endobronchial tumor with an average diagnostic yield of 80 %.[6] Dasgupta et al.[5] & Govert et al [6] used flexible bronchoscopy and TBNA to diagnose carcinoma of the bronchus in endobronchial lesions, which may manifest as exophytic masses. They concluded that the diagnostic yield appeared to be further enhanced when this technique was combined with other conventional methods.

TBNA improves the yield of FOB when added to bronchial washing, brushing and forcep biopsy. [7,8] Despite all these positive aspects, however, TBNA is underutilized.[9] This has been ascribed to lack of formal training, difficulties with needle handling, poor success rate and insufficient cytological laboratory support.[10] Although a combination of all these techniques has been shown to increase the diagnostic yield, it is not always possible to perform all these sampling techniques in the same patient.[10] In present study, we have utilized all fiberoptic bronchoscopy guided all conventional diagnostic modalities including EBNA in diagnosing lung malignancies.

METHOD

Prospective, observational study conducted during January 2016 to December 2021 in chest diseases department in Venkatesh chest hospital & MIMSR Medical College Latur to find the role of EBNA in exophytic endobronchial lesions (EEL) in confirming the diagnosis of lung cancer and to find additive yield over other techniques such as BW and FB. Total 1280 suspected lung malignancy on clinical and radiological basis are screened and finally 810 confirmed lung cancer cases were included in study after hospital's ethical committee approval and written informed consent of patient (Figure 1).

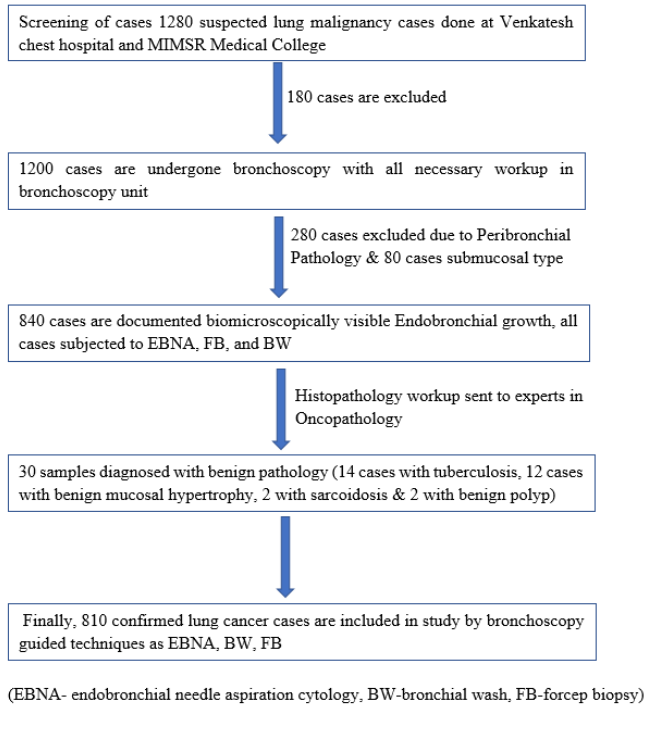

Figure 1: Flow of study

All of the cases with unexplained paralysis of vocal cord (hoarseness of voice) or stridor, chest X-ray with radiological features of malignancy (coin lesions, mass lesions, mediastinal widening, unilateral high hemidiaphragm, segmental/complete lung collapse and non-resolving pneumonia). Normal chest X-ray with high clinical suspicion, localized monophonic wheeze, endobronchial disease or growth symptoms such as hemoptysis, persistent cough, cases with suspected recurrent post-obstructive pneumonia, suspicious sputum cytology, unexplained and recurrent pleural effusion were included to the study.

Patients with coagulopathy which cannot be corrected and platelets 3, mechanical ventilation with high PEEP, refractory hypoxemia, recent myocardial infarction or unstable angina, significant dysrhythmia and hemodynamic instability, poor ability to cooperate with procedure were excluded.

The Fiber-optic Video Bronchoscope FUJINON EPX 201H is used during procedures in all patients enrolled in study and procedure performed by two operators. The upper airway is anesthetized with 2 ml of 10 % lignocaine solution. An additional small quantity of 1 % lignocaine is instilled through the bronchoscope for topical bronchial anesthesia, as needed. Patients if he or she is apprehensive are sedated with intravenous midazolam. Bronchoscope is inserted transnasally in about 85 % of cases, while in the remaining cases, the transoral route is used. Fluoroscopy facility is also available in our unit. During bronchoscopy we observed characteristic features of exophytic endobronchial lesions such as cauliflower like, polypoidal-like or nodular or multinodular endobronchial growth. In order to avoid contamination, EBNA is performed prior to other procedures such as bronchial brush, forcep biopsy and bronchial wash. EBNA procedure is done first to avoid false positive, and then, other techniques are performed. EBNA and forcep biopsy performed in most of the cases and other conventional diagnostic techniques such as bronchial wash and bronchial brush decision taken by operator doing bronchoscopy. Transbronchial needle aspiration is performed using MW 522 needle catheters (Mill-Rose Laboratories). During bronchoscopy, the catheter is passed through the biopsy channel with the needle retracted. Under direct vision, the needle is advanced into the endobronchial lesion; once the needle is appropriately placed within the lesion, it is minimally advanced, so that the entire length of the needle will be in the tissue. Then, the inner 22-gauge needle is retracted and locked in position. The needle is moved to and fro, under applied suction from a 20-ml syringe. The pressure is released before the needle is taken out from the tissue, to avoid false-positive aspirates. The aspirated material is blown into four or five slides, smeared, fixed with 95 % alcohol and sent for cytological examination at Pathology Department (Figure 2).

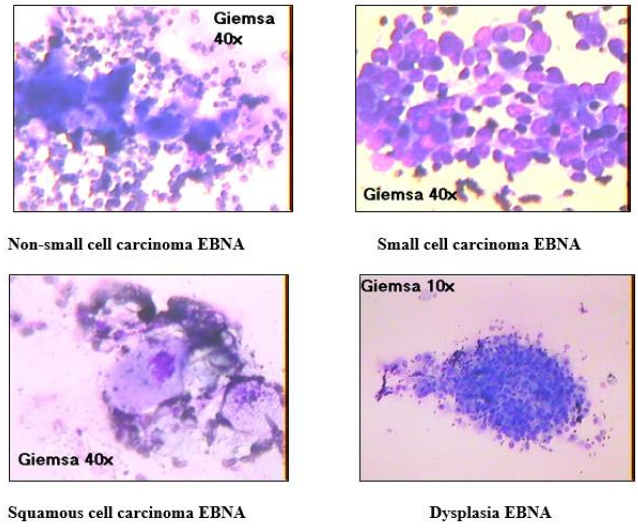

Figure 2: EBNA Cytology images

The statistical analysis is done using single proportion test (Chi test) in R-3.4 software. Significant values of x2 are seen from the probability table for different degrees of freedom required. A value of p is considered significant if it is below 0.05 and highly significant in case it is less than 0.001.

RESULTS

In present study, 810 diagnosed lung cancer patients between 29-85 age group, male are 59.25% (480/810) and females are 40.74% (330/810). In addiction history, we have observed 63.20% (512/810) cases are smoker and 43.25% cases with smoking index more than 20 pack years. Commoner symptoms are cough in 82.09% (665/810), Shortness of breath in 46.91% (380/810), hemoptysis in 30.37% (246/810) & chest pain in 16.79% (136/810) cases.

Clubbing on general physical examination is documented in 56.17% (455/810) cases. Commoner radiological presenting features are mass lesion in 42.22% (342/810) cases, Hilar opacity in 34.07% (276/810) cases & collapse segmental/lobar in 12.09% (98/810) cases. During bronchoscopy, anatomical location is documented on right side of tracheobronchial in 59.01% (478/810) cases as compared to left side of tracheobronchial wall 32.46% (263/810) & growth at carina documented in 8.51% cases (69/810) cases. Upper lobe bronchi are commoner site on both the sides as compared to other segmental bronchi (Table1).

Table 1 Clinical Evaluation, radiological patterns &anatomicall sites during bronchoscopy

Symptoms/signs	N	%
Cough	665	82.09
SOB	380	46.91
Hemoptysis	246	30.37
Chest Pain	136	16.79
Weight loss	123	15.18
Hoarseness of voice	41	5.06
Clubbing	455	56.17
SVC Syndrome	40	4.93
Lymphadenopathy	32	3.95
Radiological feature		
Mass lesion	342	42.22
Hilar Opacity	276	34.07
Collapse (lobar/segmental)	98	12.09
Consolidation	88	10.86
Pleural effusion	72	8.88
Mediastinal Widening	70	8.64
Site of Lesion		
Right side	478	59.01
Left side	263	32.46
Carina	69	8.51

In present study, yield of forcep biopsy & forcep biopsy plus bronchial wash in EEL is 89.25% (723/810) & 93.08 % (754/810) respectively. Yield of EBNA, EBNA plus bronchial wash & EBNA plus forcep biopsy in EEL is 64.56% (523/810), 67.28% (545/810) & 97.65% (791/810) respectively. Total yield of all fiberoptic bronchoscopy guided procedures (EBNA+FB+BW) in EEL is 100%. Additional yield of EBNA in EEL over other CDTs (Conventional Diagnostic Techniques such as forcep biopsy plus bronchial wash) is 6.92% (Table 2) Sensitivity of forcep biopsy & EBNA in diagnosing lung malignancy in EEL is 89.25% & 64.56% respectively. Forcep biopsy is more sensitive technique than EBNA in EEL. (p <0.00001)(Table 3).

Table 2 Diagnostic yield of fiberoptic bronchoscopy guided procedures in exophytic endobronchial lesions

No. of Patients of Exophytic Lesions (n=810)	Positive results (n=810)	Yield (%)
EBNA positive only	523	64.56
FB positive only	723	89.25
Both EBNA and Forcep Biopsy	791	97.65
EBNA+BW	545	67.28
FB+BW	754	93.08
EBNA+FB+BW	810	100

FB: Forcep Biopsy, BW-Bronchial Wash

Table 3 Sensitivity of EBNA and forcep biopsy in exophytic lesions during bronchoscopy

Procedure	Positive yield	Negative yield	Total Diagnosed cases
FB	723	87	810
EBNA	523	287	810

FB: Forcep Biopsy , $p < 0.00001$

Sensitivity of forcep biopsy plus bronchial wash in EEL is 93.08% (754/810). Sensitivity of EBNA plus bronchial wash in EEL is 67.28% (545/810). Sensitivity of EBNA plus forcep biopsy in EEL is 97.65% (791/810) ($p<0.00001$)(Table 4).

Table 4 Sensitivity of EBNA Plus Bronchial Wash and Forcep Biopsy in Exophytic Lesions during Bronchoscopy

Procedure	Positive yield	Negative yield	Total Diagnosed
Forcep Biopsy plus Bronchial wash	754	56	810
EBNA plus Bronchial wash	545	265	810
Both EBNA and Forcep Biopsy	791	19	810

DISCUSSION

Diagnostic yield of EBNA & EBNA plus techniques in endobronchial lesions:

Total yield of EBNA in exophytic endobronchial lesions is 64.56% (523/810). In our previous published studies we have documented 62.60% and 60.66% respectively in small sample size.[11,12] Kacar et al observed yield in 77.9% cases.[13] Overall diagnostic yield of EBNA central lesions suspected to be bronchogenic carcinoma is between 70-96%.[5,14-16]

Yield of EBNA, EBNA plus bronchial wash & EBNA plus forcep biopsy in EEL is 64.56% (523/810), 67.28% (545/810) & 97.65% (791/810) respectively. Thus, EBNA has documented complimentary role to other conventional diagnostic tests bronchial wash and forcep biopsy in increasing significant yield. Study conducted by Salathe et al. reported combination of TBNA with CDT increase yield from 65 to 79 %.[17] Gullon et al. concluded that addition of TBNA to CDT increases diagnostic yield of exophytic endobronchial lesions. [18] Caglayan et al. reported increase in yield from 79 to 91 % after addition of TBNA to CDTs ($p < 0.001$). [19] Gellert et al. and Hapomik et al. concluded that addition of TBNA to routine diagnostic technique improves the diagnostic yield. [10,20] Inadequate tissue sampling due to the presence of necrosis, a blood clot on the lesion or formation of crush artifacts by forcep biopsy makes TBNA an indispensable tool in these lesions.

Dasgupta et al. and guidelines from the American College of Chest Physicians (ACCP) stated that in endobronchial lesions that are either necrotic in appearance or highly vascular, TBNA may be used to obtain a sample by altering the technique in order to directly place the needle into the endobronchial lesion.[5,21] Contradictory to mentioned inference, Karahalli et al. reported no significant improvement in yield by adding TBNA to CDT. [22]

Yield of Forcep biopsy & forcep biopsy plus techniques in exophytic endobronchial lesions:

Total yield of forcep biopsy in exophytic endobronchial lesions is 89.25% (723/810). In our previous published studies we have documented 79.67% and 88.18% respectively in small sample size. [11,12] Kacar et al observed yield in 86.4% cases. [13] Due to the high yield of forceps biopsy for diagnosing endobronchial lesions (67-100%) suspicious for lung cancer, role of TBNA may be limited. [16]

Sensitivity of Forcep biopsy & EBNA in exophytic endobronchial lesions:

Sensitivity of forcep biopsy & EBNA in diagnosing lung malignancy in EEL is 89.25% & 64.56% respectively. Forcep biopsy is more sensitive technique than EBNA in EEL. In our previous published studies we have documented 79.67% & 62.60%, 88.18% & 71.65% respectively in small sample size. [11,12] Kacar et al observed yield in 86.4% & 77.9% respectively. [13] Forcep biopsy is considered as gold standard for diagnosis of malignancy in exophytic endobronchial lesions. Siddiqui et al. reported sensitivity of EBNA and forcep biopsy 69.2 and 88.3 %, respectively. [23] Dasgupta et al. concluded sensitivity of EBNA 85 % and of forcep biopsy 76 % in their studies in exophytic endobronchial lesions. [5] Karahalli et

al. reported 82.7 % sensitivity for forcep biopsy and 68.6 % for EBNA. [22] Other studies by SK Verma et al., Funhasi A et al., Kulpati D et al., Zavala DC et al. and Martin M et al. reported sensitivity of forcep biopsy 81.6%, 83%, 85.7%, 97% and 98 %, respectively in endobronchial lesions. [24] Contradictory to mentioned sensitivity patterns, Caglayan et al. reported higher sensitivity of TBNA over forcep biopsy, i.e., 92 versus 85 %, respectively.[19]

Additional yield of EBN A over other methods:

Additional yield of EBNA in Exophytic lesions over other CDTs (Conventional Diagnostic Techniques such as forcep biopsy plus bronchial wash) is 6.92%. In our previous published studies we have documented 4.19% and 4.87% respectively in small sample size. [11,12] Roth et al.reported that additional yield of EBNA is 8.04 % in their study. [25] Gullon et al. reported 9.5 % additional yield of EBNA in their study. [18] Kaçar et al. reported that additional yield is not satisfactory by EBNA over FB and other CDTs. [13] Karahalli et al. reported that additional yield of EBNA was 1 % in their study. [22] Lundgren et al. did not report an increase in sensitivity of bronchoscopy by adding EBNA to conventional diagnostic methods, but their results were later reversed in other studies. [26] Shure and Fedullo showed that the addition of needle aspiration to FB raised the diagnostic yield from 55 to 87%, and this increase was statistically significant. [27] Moreover, two other trials demonstrated that the combination of EBNA and conventional diagnostic methods increased the sensitivity compared to conventional methods alone. [5,8]

Sole yield of EBNA in exophytic endobronchial lesions & importance of ROSE in increasing yield:

Transbronchial needle aspiration is the only positive test in 52 cases out of 810 diagnosed cases. Although forcep biopsy has diagnosed 723/810 (89.25%) cases & EBNA 523/810 (64.56%) cases, only EBNA is the positive test in 52 cases. In 52 cases diagnosed by cytopathologist in EBNA samples are further processed to immunohistochemistry analysis. All EBNA samples are processed on site as we are having ROSE facility in our center. Govert et al.firstly described the utilization of ROSE-EBNA in sampling central neoplasms; however, this study was not randomized. [6]

Mondoni M et al done RCT and specially documented that addition of needle aspiration to conventional methods will increase the sensitivity of bronchoscopy. [28] They also mentioned that the rate of improvement in sensitivity was significantly higher in the ROSE-EBNA arm, suggesting the importance of ROSE in elevating the sensitivity of EBNA.

Other important observations in present study:

Histopathology type in present study: We have documented adenocarcinoma in 36.79% (298/810) cases, Squamous cell carcinoma in 38.51% (312/810) cases, non-small cell carcinoma in 12.71% (103//810) cases, small cell carcinoma in 8.88% (72/810) cases, and large cell carcinoma in 3.4% (25/810) cases. Adenocarcinoma trends are equally observed histological type as compared to Squamous cell type irrespective of smoking trends in study cases. We have documented that EBNA samples have given satisfactory results with histopathology specimens subjected to immunohistochemistry. In adenocarcinoma, 61% cases are EGFR positive, 18% ALK positive, and 12% ROS positive and 9% are all negative.

Complications during bronchoscopy procedures and techniques: bronchoscopy related hypoxemia documented in thirty-six cases and minor bleeding in forty-two cases. Other complications such as significant bleeding, pneumothorax and death were not seen. Minor bleeding was seen with forcep biopsy mainly in 5.18 % (42/810) cases. Shure et al Bollinger et al. Jin F et al. and ACCP Guidelines on Interventional Pulmonology reported mortality rate of 0.01 % and complication rate 0.7 % in their study. Other potentially life-threatening complications such as respiratory depression, airway obstruction, arrhythmias and infections were also not observed in our study. [21,27,29,30]

In present study predominant gender is male are 59.25% (480/810), smoking addiction in 63.20% (512/810) of which 43.25% cases having smoking

index more than 20 pack years. In spite of higher trends of tobacco exposure, adenocarcinoma histology has been documented in significant number with undifferentiated or non-small cell type.

Rationale for same findings would be processed tobacco or tobacco with added mixtures of nitrous compounds resulting into predisposition to adenocarcinoma.

Commoner radiological presenting features are mass lesion in 42.22% (342/810) cases, Hilar opacity in 34.07% (276/810). Bronchscopically,anatomical location of lesion documented on right side of tracheobronchial in 59.01% (478/810) cases as compared to left side of tracheobronchial wall 32.46% (263/810) & growth at carina documented in 8.51% cases (69/810) cases. Upper lobe bronchi are commoner site on both the sides as compared to other segmental bronchi.

CONCLUSIONS

Endobronchial needle aspiration has documented very crucial role in diagnosing lung cancer in comparison to other conventional diagnostic techniques. Endobronchial needle aspiration was found complimentary to conventional diagnostic techniques in diagnosing lung malignancy in exophytic endobronchial lesions. Importantly, EBNA samples can give rapid results, decrease chance for repeat procedure and guides adequacy of samples before end of bronchoscopy procedure.

Although Forcep biopsy is more sensitive test then EBNA in EEL in diagnosing disease, we have documented EBNA has significant additive yield in proportionate number of cases. Inadequate tissue sampling due to the presence of necrosis, blood clot over the lesion and formation of crush artifacts by forcep biopsy make EBNA a valuable technique in these lesions.

EBNA considered safe, especially when fleshy vascular endobronchial growth is present and risk of bleeding is high with forcep biopsy. EBNA cytology samples can give comparable results to histopathology. EBNA samples are equally processed for immunohistochemistry analysis as histopathology samples. Thus, EBNA is a beneficial, safe and minimally invasive bronchoscopic technique with insignificant side effect in the diagnosis bronchogenic carcinoma.

Disclosures

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Authorship Contributions: Concept-;

Design -; Materials -; Data collection and/or processing - ; Analysis and/or interpretation ; Writing - Critical review - .

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