

RESEARCH ARTICLE

Utility of Various Bronchoscopic Modalities in Lung Cancer Diagnosis

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Abstract

Background: Bronchoscopy and different techniques to obtain tissue sample form the cornerstone of lung cancer diagnostics. The utility, specificity and sensitivity of various techniques are compared against each other and also in relation to the tumour type, location and morphology. **Aim:** To assess and compare the utility of various bronchoscopic procedures in lung malignancies. Study also compares the utility of these techniques on tumour site, morphology and cell type. **Methods:** One hundred and fifty six patients with suspected malignancies in whom bronchoscopy was deemed as the primary diagnostic procedure were selected. These patients underwent bronchoscopic lavage, brushings and biopsy. Samples were assessed by microbiological, cytology and histopathological analysis. **Results:** Bronchoscopic procedures have a high diagnostic accuracy of 81.25% in confirming lung malignancies in central tumours and also in non-accessible peripheral tumours. Bronchial brushings had the highest yield in central tumours (55.9%) and a reasonably good yield even in peripherical tumours (40.8%). When all the modalities were compared against each other, brushings was the single most decisive technique as it alone yielded a diagnosis in a significant 33% of cases, whereas the comparative diagnosis by biopsy alone was in a minority 7.6% of cases.

Keywords: lung cancer- bronchoscopy- brush cytology- lung cancer diagnosis

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Introduction

Lung cancer is one of the leading causes of death from malignant disease in the developed world accounting for about 13% of all new cancer cases worldwide and 19% cancer related deaths 1. The overall 5 year cancer survival rate is dismal 15% in developed world and 5% in developing country 2. This is probably due to late detection of lung cancers. Flexible bronchoscopy (FB) is perhaps the single most important technique in lung cancer diagnosis. Early diagnosis of lung cancer has a critical role from management, prognostication and survival viewpoint. Maximizing the detection rate of FB should therefore be a key objective. The detection rate or diagnostic sensitivity of various FB procedures for malignancy varies widely in published studies. Advanced techniques and innovations like endobronchial ultrasound (EBUS), and Thoracoscopy have vastly improved the yield. Conventional techniques performed by skillful bronchoscopists can still provide a reasonably good yield in lung malignancy diagnosis obviating the need for these expensive and not readily available procedures. So the present study was done to assess the comparative yield of various conventional bronchoscopic procedures done to confirm lung malignancy and also to assess the utility

of these techniques on tumour location, morphology and histological cell type of lung cancers.

Materials and Methods

This study was conducted in the department of pulmonary medicine at Kasturba medical college hospital, Mangalore a tertiary care hospital in Coastal South India. Institutional ethics committee approval was obtained at the outset. From 2010 to 2013 patients with clinical and radiographic findings suggestive of malignancy were included in the study after obtaining written informed consent. Bronchoscopic procedures were the first line of investigations for central lesions which were bronchoscopically accessible. Some of the cases were peripheral lesions in whom image guided percutaneous fine needle aspiration cytology (FNAC) or biopsies were not possible due to narrow window or deemed risky by the radiologists or percutaneous aspiration cytology and or biopsies were negative were also considered for bronchoscopy

Routine frontal chest radiographs was done for all patients. Computerised tomography (CT) was done in all for more accurate localization and also in peripheral tumours in whom percutaneous cytology or biopsy were

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being considered. These cases of suspected malignancies were routinely investigated with two sputum examination for acid fast bacilli by Ziehl neelsen staining (spot and early morning sample) to rule out pulmonary tuberculosis. Induced three sputum samples were sent for cytological examination. Patients posted for bronchoscopy were subjected to fasting for six hours, pre-medicated with injection atropine 0.6 mg intramuscular 30 minutes prior to procedure, given xylocaine 4% mouth gargles and also 4 % xylocaine instilled locally into vocal cords during the procedure as per the standard recommendations. Fiber-optic video bronchoscopy (FB) with visualization and bronchial washings (BW) was done for all cases. Bronchoscopic mass two quadrant biopsies were done in those patients who had mass lesions visible on bronchoscopy or with mucosal irregularity. In those with mucosal abnormality and or in presence of a lesion bronchial brushings (BB) were carried out. A minimum of 2 to 4 brushings were conducted from affected area. If the mass lesions were vascular and bled on brushings, biopsies were aborted. Twenty to fifty ml of saline aliquots was instilled and bronchial lavage aspirates were collected in a mucous extractor. Samples were processed as per standard procedures of cytology and histology. Bronchial lavage samples were also sent for microbiological analysis like acid fast bacilli (AFB) stain, culture and pyogenic culture sensitivity.

Patients in whom bronchoscopic diagnosis could not be obtained, were subjected for CT- guided transthoracic biopsy (TTB) or FNAC. In few cases of malignancy, diagnosis was established by lymph node biopsies or pleural fluid aspiration cytology. During the data analysis patients with an alternate non- malignant diagnosis on sputum or bronchial cytological examination were excluded. Final diagnosis was made based on abnormalities detected by histology (BB/TTB) or cytology (BB/BW/ aspiration cytology/ fluid cytology). If none of the above modalities were conclusive the patient status was deemed as undiagnosed.

For the purpose of analysis, radiographic lesions were grouped as central and peripheral lesions. Bronchoscopic abnormalities were recorded as normal, endobronchial growth (EG), external compression (EC), mural infiltration (MI), stenosis (S) and infiltrative growth (IG). Type of malignancy was recorded based on histology of TBB

Table 1. Comparison of Bronchoscopy Finding Versus Mass Location by Radiography (N=143)

Bronchoscopy findings	Mass location by Radiography						Total	
	Central		Peripheral		Normal			
	No	%	No	%	No	%		
Normal	9	10.2	9	17	0	0.0	18 12.6	
EG	44	50.0	20	37.7	1	50.0	65 45.5	
S	6	6.8	2	3.8	0	0.0	8 5.6	
EC	13	14.8	20	37.7	1	50.0	34 23.8	
MI	9	10.2	1	1.9	0	0.0	10 7.0	
IG	6	6.8	1	1.9	0	0.0	7 4.9	
VC	1	1.1	0	0.0	0	0.0	1 0.7	
Total	88	100	53	100	2	100	143 100	

and TTB or cytology of BB and BW. No major adverse events were observed apart from a few minor ones like minor bleeds, bronchospasm and transient hypoxia. In a few cases biopsies were aborted due to brisk bleed which were controlled however with standard procedures.

Statistical analysis was performed using Statistical package for Social Science (SPSS ver. 11.5) and MS office excel software.

Results

A total of 156 patients were included in the study out of which 135 were male and 21 were female patients. The mean age of patients was 57.7 years. Twelve cases were excluded from statistical analysis as in some cases relevant bronchoscopic investigations could not be carried out while the rest were either occult malignancies or infective causes. One or many of the bronchoscopic techniques yielded a diagnosis in 117 out of 144 eligible patients offering a diagnostic yield of 81.25%. Majority of the lesions (88) were central while a significant proportion of the lesions were still peripheral (53). Squamous cell carcinomas constituted 40.6% of the lesions while 30.1% of lesions were adeno carcinomas (Table1). Sputum cytology confirmed diagnosis in 9 patients (6.29%) of whom 3 were squamous cell carcinoma, 2 adeno carcinoma, 1 small cell carcinoma and 2 reported as atypical cells.

Bronchial brushings had the highest yield in central tumours (55.9%) as is expected. But, surprisingly bronchial brushings had a good yield even in peripheral tumours (40.8%), those which were not amenable to percutaneous biopsy and needle aspiration cytology (Table 2).

Table 2. Comparision of Final Diagnosis Versus Mass Location by Radiography

Final Diagnosis	Mass location by Radiography						Total	
	Central		Peripheral		Normal			
	No	%	No	%	No	%		
Squamous cell Ca	40	45.5	17	32.1	1	50	58 40.6	
Small Cell Ca	9	10.2	0	0	0	0	9 6.3	
Adeno Ca	24	27.3	19	35.8	0	0	43 30.1	
Poorly differentiated Ca	2	2.3	1	1.9	1	50	4 2.8	
Suspicious	4	4.5	2	3.8	0	0	6 4.2	
Small/Large cell Ca	0	0	1	1.9	0	0	1 0.7	
Others	2	2.3	0	0	0	0	2 1.4	
Undiagnosed	7	8	13	24.5	0	0	20 14	
Total	88	100	53	100	2	100	143 100	

Table 3. Yield in Central Tumours

Yield from various techniques	Total no of central tumours n=93	Percentage
Lavage	10	10.00%
Brushings	52	55.90%
Biopsy	30	32.20%

Table 4. Yield in Peripheral Tumours

Yield from various techniques	Total no of peripheral tumours n= 54	Percentage
Lavage	5	9.20%
Brushings	22	40.70%
Biopsy	8	14.81%
CT-FNAC	14	25.90%
CT-Biopsy	7	12.90%

Table 5. Yield in Central and Peripheral Tumours

Yield from various techniques	Total no of central tumours N=93	Total no of peripheral tumours N=54 N (%)
Lavage	10 (10)	5 (9.2)
Brushings	52 (55.9)	22 (40.7)
Biopsy	30 (32.2)	8 (14.81)
CT-FNAC	0	14 (25.9)
CT-Biopsy	0	7 (12.9)

Table 6. Bronchoscopic Morphological Appearance of Various Tumour Cell Types

Type of tumour	Endoluminal growth n= 65	Infiltrative growth n=7	external compression n=34	Mucosal Infiltration N=10	Normal N=17
Squamous cell ca	41	5	5	3	4
Adeno carcinoma	10	1	14	3	9
Small cell carcinoma	5	1	1	1	0
suspicious	5	0	2	0	4
undiagnosed	4	0	8	2	0
Large cell carcinoma	0	0	1	0	0
Poorly differentiated	0	0	3	1	0

Table 7. Yield of Bronchoscopic Procedural Techniques Versus Tumour Morphology on Bronchoscopy

Type of lesion	Lavage	Brushings	Biopsy
Endoluminal growth (65)	3	42	28
External compression (34)	3	14	3
Infiltrative growth (7)	1	5	2
Mucosal irregularity (10)	2	5	2
Normal study (17)	0	2	0

Tumour appearance on bronchoscopy as visualized was classical endoluminal lesion in most squamous cell carcinomas (70%), whereas amongst adeno carcinoma the lesions were more equivocal in findings, with external compression (37%) followed by endoluminal lesion (27%) and normal appearance in 24.3% of cases. Small cell carcinomas again were often endoluminal lesions (62.5%) (Table 3).

Bronchoscopic biopsies had an average yield for squamous cell carcinomas (33.89%) but a poor yield in adeno carcinomas (11.1%). Bronchial brushings had a significantly high yield rates for both squamous (54.2%) and adeno carcinomas (55.5%). Interestingly for small cell carcinomas both brushings (66.6%) and biopsies (77.7%) had somewhat similar yields.

The yield of various bronchoscopic techniques also depended on the morphological appearance of the lesion visualized on bronchoscopy. Surprisingly brushings (64.6%) scored better than biopsy (43%) even for endoluminal lesions. For other lesions like external compression, mucosal irregularity and infiltrative lesions also brushings had a fairly good yield. Biopsy to the contrary did yield a diagnosis in few of the non-endoluminal lesions vindicating its usefulness even in such lesions Overall biopsy had a better yield in terms of percentages (58%) as against brushings (55%). But this needs to be viewed in the context of biopsy being

Table 8. Yield from Bronchoscopic Techniques

Technique	Number of patients In whom attempted	Positive yield Number of patients	Suspicious or atypical cells seen	Percentage
Bronchial lavage	141	11	5	7%
Bronchial brushings	138	76	5	55%
Bronchial biopsies	67	39	3	58%*

*Chi square test p value < 0.001

attempted in fewer patients (67) as against brushings (138) (Table5).

When the three modalities of brushings, biopsy and lavage were compared against each other, brushings was the single most decisive technique as it alone yielded a diagnosis in a significant 33% of cases, whereas the comparative diagnosis by biopsy alone was in a minority 7.6% of cases and in just one case was lavage positive with negative brush and biopsy and only in 3 cases where all brush, biopsy and lavage positive for malignancy. The combined yield of brush and biopsy was 13.1% while a significant 18% of cases were negative by all the three modalities. When brushings and biopsy were compared, its sensitivity was 55.88%, specificity 55.56% with a diagnostic accuracy of 55.74% (Table6). However, the yield of biopsy was comparatively higher than bronchial brushing which was found to be statistically significant with Chi square test showing p value < 0.001.

There were 27 cases in which all bronchoscopic techniques like brushings, lavage and biopsy failed to give a diagnosis and in 14 of these cases diagnosis was possible by other modalities like per-cutaneous aspiration cytology, biopsy, lymph node fine needle aspiration cytology and biopsy. About 4 cases were reported as suspicious for malignancy or as atypical cells but definitive

Table 9. Evaluation of Bronchial Lavage, Bronchial Brushings and Bronchoscopic Biopsies in Diagnosis of Bronchogenic Carcinoma (n=144)

Lavage, brushings and biopsy	Number of cases	Percentage
Negative by all modalities	27*	18%
Positive by all modalities	4	2.70%
Positive by biopsy, negative by lavage and brushings	11	7.60%
Positive by brushings, negative by lavage and biopsy	48	33.30%
Positive by lavage, negative by brush and biopsy	1	0.69%
Positive by lavage and brush, negative by biopsy	7	4.86%
Positive by lavage and biopsy, negative by brush	1	0.69%
Positive by brush and biopsy, negative by lavage	19	13.10%

*Out of 27 cases negative by all bronchoscopic modalities, 14 were diagnosed by CT guided FNAC/ Biopsies, 9 cases remained undiagnosed and 4 cases were reported as suspicious showing atypical cells but were not confirmed of malignancy.

tumour sub-type could not be confirmed. Around 9 cases of suspected malignancies eluded diagnosis and were labelled as undiagnosed and offered the option of other procedures.

Discussion

It is well recognized that the fiberoptic bronchoscope has greatly extended the range over which tissue may be obtained from pulmonary lesions. Fiberoptic bronchoscopy has been accepted by the clinician as a relatively safe technique which has significantly extended the range over which clinician can visualize and diagnose bronchogenic carcinoma. But there is lot of conflicting data on the diagnostic yield of various bronchoscopic procedures like bronchial lavage, bronchial brush cytology, bronchoscopic biopsies. Not many studies have compared the yield of each of these procedures against the other.

The yield of these various techniques vary depending on factors ranging from operators skill, size of the lesion, site of the lesion (whether central or peripheral), morphologic nature of the lesion as visualized on bronchoscopy. Apart from this, technical considerations like smearing, staining techniques and expertise of the pathologist may also affect the yield of these procedures.

The overall diagnostic yield of bronchoscopy in diagnosing lung cancers in our study was 81.25%. This is quite high in comparison to other similar studies 3. This could be because even in quite a few peripheral tumours, bronchoscopic brushings were attempted with good yield. Squamous cell carcinoma (40.6%) was the most common sub-type diagnosed in our study followed by adeno carcinoma (30.1%). There was a higher incidence of adenocarcinomas diagnosed in our study as reported widely in the literature4. This could be due to a general rise in prevalence of adeno carcinomas as reported lately, higher female population in our study and also due inclusion of quite a few peripheral tumours not amenable

to percutaneous biopsy being included in our study.

The diagnostic yield from various techniques of tissue sampling has been discussed by several authors and the general conclusion is that those methods which obtain tissue directly from the tumor (biopsy and brushings) are superior to indirect techniques (washings and post-bronchoscopic collections of sputum). Our data would support this conclusion for both peripheral and central carcinomas. In our study there were only 11 cases in which diagnosis was established by bronchial washings and sensitivity was quite low at 7%. There was only one case in which lavage was positive and both biopsy and brush were negative. The overall sensitivity of bronchial lavage as compared to biopsies were low at 16.13%, a higher specificity of 85.71% was however seen with a diagnostic accuracy of 49.15%. Bronchial washing is a safer technique and the malignant cells can be readily recognized and typed. However tumour cell exfoliation may not be significant for the lavage to stain positive for malignant cells unless it is a florid tumour. Though the yield from lavage is not high but it is a safe, simple and a quick procedure it should be included in the protocol. Also lavage may yield alternative or associated diagnosis like tuberculosis. The overall accuracy of bronchial washing was 75% and 75.4% by two other studies by Truong5 et al and Chaudhary6 et al respectively, whereas in present study it was higher (87.3%).

In our study when the yields of bronchial brush cytology was compared to bronchoscopic biopsy, it yielded a sensitivity 55.88% and specificity 55.56%. These values would suggest that it is probably better to combine both these procedures wherever feasible to maximize the yield as almost in about half the cases, the diagnosis would have been missed if a single procedure was attempted. Brush cytology was generally done for all patients as the procedure is relatively safe. In contrast biopsy was not attempted or aborted in patients with bleed and in superficial lesions not amenable for bronchoscopy. In our study biopsy was done in only 67 patients as against 141 patients in whom brushings were attempted however the yield of biopsy was statistically significant in comparison to brushings. One other reason why brush cytology was more frequently attempted and often positive as compared to biopsy was due procedural difficulties as superficial lesion, ulcerative lesions, those located more remotely or in difficult to access segments as in collapsed left upper lobe sub-segment. Also, often in a biopsy the superficial necrosed fragile non representative tissue obtained is histopathologically inconclusive. On the other hand, bronchial brushings is a relatively simpler procedure and flexible brush can reach angulated difficult to access segments. Also, brush cytology has superior yield for lesions with mucosal irregularity (50%) and infiltrative lesion (70%). Due to lesser incidence of brisk bleeding more passes with brushings are attempted leading to a better diagnosis. There were also a few cases in our study where the tumour was not visible but brush was advanced into the offending segment as localized on a CT pre-procedure and brush cytology often yielded positive diagnosis.

In our study brushings had the best decisive yield

(33%) as a significant number of cases (48) were positive only by brushings and were inconclusive by lavage and biopsy. As compared to brushings biopsy had a better yield statistically in terms of cases attempted. But, brushings had an overall superior yield with positive predictive value of 61.29% and a diagnostic accuracy of 55.74% as it was attempted in 138 cases as compared to 67 biopsy attempted cases. The wide variation could be attributed to varying inclusion criterions, study methodology, sample retrieval and processing. Various studies have shown the sensitivity of bronchial brushings to range from 48-85%⁷⁻¹⁰. Brushings had a good yield in both central tumors (55.9%) and peripheral tumors (40.7%). A recent study that examined the comparative yield of various cytological specimens demonstrated that most sensitive technique was CT FNAC - 87.25% followed by brushings 77.78% and BAL 72.69%. Since our study was primarily a study done for bronchoscopically accessible tumour, comparative FNAC data is not available but brushings had a somewhat similar yield of 76%¹¹.

Bronchoscopic biopsy is a gold standard for bronchoscopic procedures. It has the advantage of yielding more information like differentiation, accurate diagnosis of tumour sub-type, and scope for cell block for immunohistochemistry studies. Biopsy could be attempted in only 67 (58%) of cases as compared to brushings 138 (76%), however the yield in those attempted cases were 58% with yield statistically more significant than brushings. But, there were only 11 cases (7%) in which biopsy offered a decisive positive yield with negative lavage and brushings. This again supports our observation that biopsy as a stand-alone procedure might not clinch the diagnosis and also has lower sensitivity compared to brushings. But is invaluable as it offers a higher specificity and scope for immunohistochemistry studies, which in the present day scenario is essential from therapeutics and prognostication view point.

As anticipated the most common lesion diagnosed by bronchoscopic techniques was squamous cell carcinoma in 40.6% of the cases, however these were also accessible by bronchoscopy in 32% of the cases in spite of their peripheral location. This is possibly due to larger size of the lesions of squamous cell carcinomas that could be diagnosed by bronchoscopy in spite of their peripheral location. This finding has diagnostic implications as in peripheral mass lesions with normal serum carcinoembryonic antigen levels (S. CEA) in whom squamous cell carcinomas are a likely possibility, bronchoscopy can be considered the first line of diagnostic procedure, more so if patient has underlying emphysematous lung with blebs, to minimize complications and maximize yield. Adeno carcinoma was the next most commonly diagnosed lesion in 30% of the cases. An interesting finding was that a significant 24 cases of adeno carcinoma diagnosed where centrally located which were bronchoscopically diagnosed. In era of thinner fibreoptic scopes the accessibility has improved diagnosis of even a traditionally peripheral tumor like adeno carcinoma.

As expected the yield of bronchoscopy was high in central tumours with brushings fetching a higher yield (55.9%) versus biopsy (32.2%), whereas in peripheral

tumors, brushings still fetched a better yield (40.7%) as against biopsy (14.81%). This finding has special relevance as the bronchoscopic appearance in most adeno carcinomas was external compression followed by endoluminal growth and in this context too brushings had a decisively good diagnostic value (41%).

Limitations

There was perhaps an element of operator variability as bronchoscopes were performed by 5 independent but fully trained and experienced operators. Also, the possibility of inter-observer variability in reporting the cytology and histopathology exists. Other bronchoscopic procedures like transbronchial needle aspiration (TBNA) and transbronchial lung biopsy (TBLB) though attempted in some cases were not included as these were not standardized in the study protocol. Cell block of the lavage sample was done in a few cases and it has a promising role as it provides for immunohistochemistry studies and thereby obviating need for biopsy in some cases where biopsy sample cannot be obtained. Since cell block analysis for tumour cells could not be done for all cases these were not included in the study procedures.

In conclusion, timely bronchoscopy is perhaps the most vital intervention in early and accurate diagnosis of lung malignancies. Various bronchoscopic techniques have variable yield depending on site, type of tumour, accessibility, operator skill and tumour morphology. Our study suggests that bronchoscopic brush cytology is probably the single most technique with a decisive diagnostic yield irrespective of the site and type of tumour. In fact it scores over biopsy as it could be performed in almost all patients unlike a biopsy and unlike biopsy yielded diagnosis even in conditions like mucosal irregularity, infiltration and external compression wherein an obvious growth was not visible. Biopsy is the gold standard still in histopathological diagnosis of lung cancers and should be attempted in all cases wherever feasible without undue complications. However it is not possible to perform biopsy in all cases due to factors like bleeding, inaccessibility of lesion and expertise involved. When performed together, a combination of brushings and biopsy offers a significant yield with potential advantages in terms of offering immunohistochemistry studies.

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