



Research Article

LIQUID BASED CYTOLOGY VERSUS CONVENTIONAL BRONCHIAL WASH AND BRONCHIAL BRUSH CYTOLOGY FOR THE DIAGNOSIS OF LUNG CANCER

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ABSTRACT

Background: Liquid based cytology is a method of retrieving and processing of cytological material for assessment of both gynecological and non-gynecological cases introduced in 1996. Lung cancer is broadly classified into two categories are Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC), with the latter being more common.

Aims: To study the diagnostic accuracy obtained for the bronchial wash and bronchial brush cytology with Conventional Smears (CS) and Liquid Based Cytology (LBC).

Material & Methods: All patients who were clinically and radiologically suspected of lung cancer were included in this study. Bronchoscopy was performed in all cases. Bronchial brushing and washing were collected and processed as conventional smear cytology and liquid based cytology smear was processed using the SurePath system. Bronchial biopsies were received, processed and stained with haematoxylin & eosin stain.

Results: A total of 104 cases, 24 benign cases 5 of which reactive, out of 19 inflammatory, 11 of which shows chronic granulomatous inflammation. Out of 65 malignant cases, squamous cell carcinoma was the most common malignancy accounting for 35 cases, followed by 17 cases of adenocarcinoma, 7 of adenosquamous carcinoma, 4 of small cell carcinoma and 2 cases of carcinoid tumor. The remaining 15 cases were unremarkable on bronchial biopsy. Bronchial brushing and washing in liquid based cytology method showed higher sensitivity, a higher specificity and increased diagnostic accuracy when compared to conventional cytology and the difference were found to be statistically significant.

Conclusions: The liquid based cytology was better than conventional cytology and should be performed in all suspected cases of lung cancer where biopsy is not possible.

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INTRODUCTION

Liquid based cytology (LBC) is an automated method of slide preparatory technique for both gynaecological and non-gynaecological specimens. LBC was introduced in the year 1996.^[1] It has replaced conventional cytology in most big centres. ThinPrep and Sure Path two systems are currently approved by the US food and Drug Administration for cervical cytology. The cells are dispersed in fluid and separated by centrifugation or filtration and deposited on the slide as a thin layer by centrifugation (SurePath system) or application of pressure (ThinPrep). ThinPrep uses the filtration method with CytoLyt as preservative, while SurePath uses the centrifugation method and CytoRich as preservative.^[2] Lung cancer is the most common lethal cancer worldwide and it contributes to 30% of male and 26% of female cancer-related deaths and approximately 1.38 million people die of lung

cancer each year.^[3,4] The lung cancer is broadly classified into two histological subtypes namely Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC), latter being more common.

Aims & objectives: The diagnostic accuracy obtained for bronchial wash and bronchial brush cytology processed with Conventional Smears (CS) and Liquid Based Cytology (LBC) was studied.

MATERIAL & METHODS

The present study was conducted prospectively within one year's duration in the Department of pathology in collaboration with Department of respiratory medicine. Inclusion criteria: Patients presenting with visible endobronchial and submucosal masses during bronchoscopy. Exclusion criteria: Patients, those who were not willing to give consent for bronchoscopy.

Flexible fibre-optic bronchoscopy was performed after obtaining informed consent. Patient found on clinical examination and radiology to have suspicious for lung cancer

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patients were included in this study and bronchoscopy was than performed. Bronchoscopy based bronchial brush and bronchial wash specimen were obtained and bronchial biopsies were taken.

After bronchial brushing conventional smears were made and bronchial brush was rinsed in in LBC preservative (CytoRich-RED BDTM-Atlanta, USA) for LBC. Sample from bronchial washing were collected in 95% ethyl alcohol for conventional smears as well as in LBC preservative (CytoRich-RED BDTM-Atlanta, USA) for LBC. All samples were processed of conventional cytology and liquid based cytology was processed using the SurePath system. Bronchial biopsies were processed and stained with Haematoxylin & Eosin stains. The conventional and LBC smears of both bronchial wash and brush were examined independently by two cytopathologists. The cyto-histological correlation was made. All unsatisfactory cases on cytology and histologically was not included in the study. Histopathology was considered as gold standard technique for final diagnosis in all cases. Our study was approved by the Ethical Committee of King George’s Medical University, Lucknow.

Statistical analysis

The statistical analysis of data was done using SPSS (Statistical Package for Social Sciences) Version 15.0 Statistical Analysis Software. The value represented in number (%), kappa value, Chi Square test and p Value.Diagnostic interpretations were done by two cytopathologists.

RESULTS

The study group consisted of 104 cases selected on the basis of clinical, radiological and bronchoscopy findings. The age of patients varied from 30 to 84years, maximum number of cases was found in 5th decades followed by 6th decades. Peak age of occurrence was 55years for lung cancer in this study. Male: Female ratio was 2.1:1. Smokers accounted for 70.2% of all the cases and non-smokers were 29.8%. The cough was present among majority of the patients (93.3%), chest pain was observed in 54.8% of the patients, hemoptysis in 18.3% of the patients. Out of the 104 cases, 24 were benign, 5 of them reactive, 19 inflammatory, 11 of which are cases of chronic granulomatous inflammation. Out of 65 cases (62.5%) positive for malignancy on biopsy, squamous cell carcinoma was the most common malignancy accounting for 35cases(53.85%), followed by adenocarcinoma 17cases (26.15%), adenosquamous carcinoma 7cases (10.77%), small cell carcinoma 4 cases(6.15%) and carcinoid tumor 2 cases (3.08%). The 15 remaining cases (14.4%) show unsatisfactory pathology on bronchial biopsy [Table 1][Fig1&2].

Table 1 Distribution of cases on the basis of histopathological diagnosis

| Histopathology | No. (n=104) | % |
|-------------------------|-------------|-------|
| Benign | 24 | 23.1 |
| Reactive | 5 | 20.8 |
| Inflammatory | 8 | 33.4 |
| Granulomatous | 11 | 45.8 |
| Malignant | 65 | 62.5 |
| Squamous cell carcinoma | 35 | 53.85 |
| Adenocarcinoma | 17 | 26.15 |
| Adenosquamous carcinoma | 7 | 10.77 |
| Small cell carcinoma | 4 | 6.15 |
| Carcinoid | 2 | 3.08 |
| Unsatisfied | 15 | 14.4 |

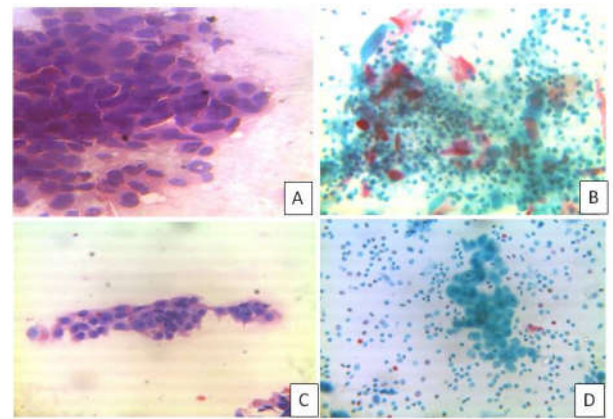


Fig1

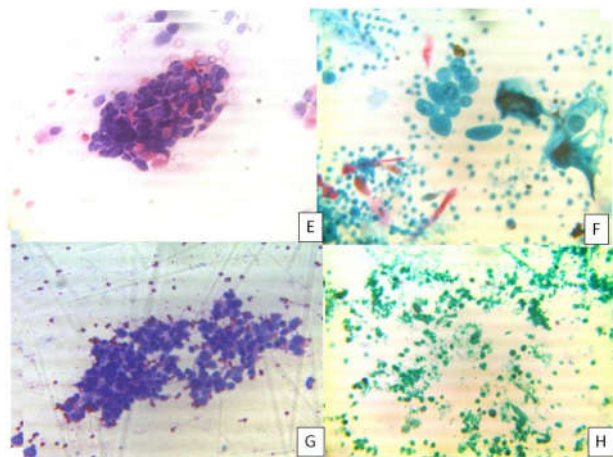


Fig 2

Out of 89 cases, on the basis of cytomorphological features, the level of agreement of conventional cytology with histopathology, was found in 30 (34.48%). Level of agreement was slight and which was statistically not significant [Table2]. (2 cases reported as inadequate in the conventional smear but in the LBC and histopathology reported as carcinoid cases.

Table 2 Level of Agreement of Conventional cytology and Histopathology (n=87)

| Conventional Cytology | Histopathology | | | | | |
|-----------------------|----------------|-----|----|-----|-----|---|
| | B | SCC | AD | ADS | SCA | |
| B | 58 | 13 | 24 | 12 | 6 | 3 |
| SCC | 21 | 9 | 11 | 1 | 0 | 0 |
| AD | 6 | 2 | 0 | 4 | 0 | 0 |
| ADS | 1 | 0 | 0 | 0 | 1 | 0 |
| SCA | 1 | 0 | 0 | 0 | 0 | 1 |
| | 87 | 24 | 35 | 17 | 7 | 4 |

κ=0.069(Slight agreement); p=0.230 [κ=kappa value] & p =level of significance]

Out of 89 cases, on the basis of cytomorphological features, the level of agreement of Liquid based cytology with histopathology agreement was found in 52 (58.43%).

Table 3 Level of Agreement of Liquid Based Cytology and Histopathology (n=89)

| LBC | Histopathology | | | | | | |
|-----|----------------|-----|----|-----|-----|---|---|
| | B | SCC | AD | ADS | SCA | C | |
| B | 39 | 13 | 12 | 7 | 4 | 2 | 1 |
| SCC | 30 | 7 | 23 | 0 | 0 | 0 | 0 |
| AD | 14 | 4 | 0 | 10 | 0 | 0 | 0 |
| ADS | 3 | 0 | 0 | 0 | 3 | 0 | 0 |
| SCA | 2 | 0 | 0 | 0 | 0 | 2 | 0 |
| C | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| | 89 | 24 | 35 | 17 | 7 | 4 | 2 |

κ=0.419(Moderate agreement); p<0.001 [κ=kappa value] & p =level of significance]

Level of agreement was moderate and was statistically significant [Table3]. Among 89 cases included in the present study, 67 cases were positive and 22 cases were negative in LBC. Both bronchial brush and wash cases were positive and negative shown in the table 4.[Table 4]

Table 4 Distribution of cases among Bronchial Brush, Bronchial Wash, LBC and histopathology

| | Brush Cytology | Bronchial Wash Cytology | LBC | Histopathologic Examination |
|----------|----------------|-------------------------|-----|-----------------------------|
| Positive | 57 | 32 | 67 | 89 |
| Negative | 32 | 57 | 22 | 0 |
| Total | 89 | 89 | 89 | 89 |

Comparison of the cytomorphological features like cellularity, pleomorphism and adequacy of LBC & conventional smears were also evaluated in the present study. The cytomorphological details of 89 cases were predominantly found in LBC as compare to conventional smears. However better cellularity, pleomorphism and adequacy was found in LBC as comparison to conventional smears. Statistical analysis of these variables were not significant [Table5].

Table 5 Comparison of Cytomorphological details and Adequacy between BB and BW by Conventional Cytology &LBC

| Conventional cytology | Total (N=89) | BB (n=57) | | BW (n=32) | | Statistical significance | |
|-----------------------|--------------|-----------|------|-----------|------|--------------------------|-------|
| | | No. | % | No. | % | χ^2 | P |
| Cellularity | 56 | 30 | 52.6 | 26 | 81.3 | 7.195 | 0.007 |
| Pleomorphism | 30 | 20 | 35.1 | 10 | 31.3 | 0.135 | 0.713 |
| Adequate | 58 | 35 | 61.4 | 23 | 71.9 | 0.990 | 0.320 |
| LBC | | | | | | | |
| Cellularity | 76 | 49 | 86.0 | 27 | 84.4 | 0.042 | 0.839 |
| Pleomorphism | 62 | 41 | 71.9 | 21 | 65.6 | 0.385 | 0.535 |
| Adequate | 67 | 42 | 73.7 | 25 | 78.1 | 0.217 | 0.641 |

The sensitivity of bronchial brush and wash in conventional method was found to be 27.7% with specificity 54.2%. PPV and NPV were 62.1% and 21.7% respectively with diagnostic accuracy of 34.8%. The overall sensitivity of LBC was found to be 60.0% with specificity 54.2%. PPV and NPV were 78.0% and 33.3% respectively with diagnostic accuracy of 58.4%. Bronchial brushing and washing in LBC method showed good sensitivity, specificity and diagnostic accuracy compared to conventional methods in our study which was statistically significant (chi-square value (χ^2 test) is 30.7;p value is <0.001)[Table6].

Table 6 Diagnostic accuracy (sensitivity, specificity, PPV, NPV, Accuracy) of Conventional and LBC against Histopathology

| | Sens | Spec | PPV | NPV | Diagnostic accuracy |
|------------------------|------|------|------|------|---------------------|
| Conventional (Overall) | 27.7 | 54.2 | 62.1 | 21.7 | 34.8 |
| Conventional (BB) | 28.6 | 60.0 | 66.7 | 23.1 | 36.8 |
| Conventional (BW) | 26.1 | 44.4 | 54.5 | 19.0 | 31.3 |
| LBC(Overall) | 60.0 | 54.2 | 78.0 | 33.3 | 58.4 |
| LBC(BB) | 61.9 | 53.3 | 78.8 | 33.3 | 59.6 |
| LBC(BW) | 56.5 | 55.6 | 76.5 | 33.3 | 56.3 |

For diagnostic accuracy, the chi-square value (χ^2 test) is 30.7;p value is <0.001(statistically highly significant)

DISCUSSION

Respiratory cytology is increasingly being used in the initial evaluation, especially in suspected lung cancer. Bronchial

wash and lavage cytology is a widely accepted, safe, simple, and minimally invasive technique. Moreover, bronchial wash technique samples out peripheral areas of lung those are beyond the reach of bronchial brush. [5]

Bronchial brushing has the advantage that the surface of the suspicious lesion is scraped by the help of a brush passed through the bronchoscope.[6] Thus this technique manages to dislodge the cells from the surface of those well differentiated malignant lesion, which do not shed readily. Thus the chances of getting adequate cytological material by bronchial brush in comparison to the cells which was found in bronchial washing. These factors contribute in the increased diagnostic yield of bronchial brushing. Thus this technique manages to 'dislodge' the cells from the surface of those well-differentiated malignant lesions too, which do not exfoliate cells readily. Moreover, since the surface of the malignant lesion is scraped by the brush, the cells retrieved show better preserved morphological details in comparison to the cells which have already exfoliated into the bronchial cavity.

Cytologists favor LBC smears because of clean background, even cell distribution and better cell preservation. Time needed to screen Liquid Based Cytology slide is less than that of conventional cytology. [7] With the advent of flexible fiberoptic bronchoscope, the respiratory cytology took new turn as sample like bronchial washings, bronchial brushings, broncho-alveolar and trans-bronchial needle aspirations could be collected from the respiratory tract, yielding significant amount of cytological material. [6]

Elsheikh *et al*, [8] 2006 studied the comparison of ThinPrep (TP) with conventional cytopins (CS) in evaluation of 88 non gynaecologic specimen specimens for a variety of parameters including cellularity, cytologic morphology, specimen preparation, screening time, laboratory cost effectiveness, cytologist preference, and impact on final diagnosis. TP demonstrated better nuclear chromatin morphology and more uniform distribution of cells. The study indicated that TP was 3 times more helpful than CS in rendering a definitive diagnosis of malignancy. Thin Prep, however, was associated with certain artifacts that cytologists must become familiar with when examining such preparations. SurePath cytology test should be applied to the cytological diagnosis of pulmonary malignant tumors. The combination of conventional bronchial brushing smears and SurePath liquid-based cytology can improve the diagnosis value of fiberoptic bronchoscopy for pulmonary primary and secondary malignant tumors.[9]

Thin Prep produced high quality specimens suitable for diagnostic purposes in regard to overall accuracy and lower non diagnostic rates.[10] Bronchial brushing and washing in LBC method showed good sensitivity, specificity and accuracy compared to conventional methods in this study. Out of 65 malignant cases, squamous cell carcinoma was the most common malignancy constituting of 35 cases (53.85%), followed by adenocarcinoma 17cases (26.15%), adenosquamous carcinoma 7cases (10.77%), small cell carcinoma 4 cases(6.15%) and carcinoid with 2cases(3.08%) confirmed by bronchial biopsy in this study. The above observation quite close to the study by Rawat *et al*. On 107 cases, squamous cell carcinoma accounted for 55 cases(51.4%). adenocarcinoma 12 cases(11.21%), large cell

carcinoma 4cases(3.73%), unclassified 17cases(15.88%) and small cell carcinoma 19 cases(17.75%).^[11]

Bronchial brushing showed better cellular preservation, nuclear characteristic compared to washing specimen. The sensitivity of conventional method was found to be 28.6% with specificity 60.0% in bronchial brush smears. PPV and NPV were 66.7% and 23.1% respectively with diagnostic accuracy of 36.8%. The sensitivity of conventional was found to be 26.1%with specificity 44.4% in bronchial wash smears. PPV and NPV were 54.5% and 19.0% respectively with accuracy of 31.3% in Bronchial Wash. The sensitivity of LBC method was found to be 61.9% with specificity 53.6% in bronchial brush smears.PPV and NPV were 78.8% and 33.3% respectively with diagnostic accuracy of 59.6%. The sensitivity of LBC was found to be 56.5% with specificity 55.6% in bronchial wash smears. PPV and NPV were 76.5% and 33.3% respectively with accuracy of 56.3% in Bronchial Wash [Table 6]. LBC method showed good sensitivity, specificity and diagnostic accuracy compared to conventional methods in our study which was statistically significant (chi-square value (χ^2 test) is 30.7; p value is <0.001)[Table6]. Rawat *et al* reported sensitivity of brushing to be 69.15% and that of washing to be 47.66% which was similar to our study.^[14] Bronchial brushing and washing in LBC method showed good sensitivity, specificity and accuracy compared to conventional methods indicating that there were more chances of bronchial brush cytological diagnosis to be correct than that of washing. Comparison of cytological characteristic of bronchial brushing and washing showed that cellularity and pleomorphism of the smear was greater in brush specimen with numerous malignant cells noted against the clear background where bronchial washing specimen showed mostly single cells with few very small cell clusters which were larger in brush specimen. Very few studies are available in the literature where results using Liquid Based Cytology have been compared with conventional cytology. No differences were found in diagnostic accuracy between LBC and conventional cytology of bronchial wash specimen.^[12, 13] The limitation of CS such as suboptimal smears with insufficient squamous cells, presence of obscuring blood, dense inflammation, mucin, and thick smears with overlapping epithelial cells reduce its sensitivity to as low as 50% with a rise in false negativity rate ranging between 14% and 33%.^[14-16] Liquid-based cytology which is widely practiced in the western setup, was developed to improve the diagnostic reliability of Pap smears by reducing the number of inadequate smears and false negativity rate, and also allow important ancillary tests such as human papillomavirus (HPV) testing.^[14,17] Although there is sufficient western literature on LBC, the studies from India comparing CPS and LBC techniques are sparse.^[14,15] Moreover, there have been conflicting results with regard to the quality of LBC results.^[18,19] Some studies done using bronchial brushing for cytodiagnosis of lung cancer have emphasized its high accuracy rate in the evaluation of neoplastic and non-neoplastic pulmonary lesions.^[20]

As far as cyto-morphological parameters were concerned among adequate samples both the smear preparation techniques were equally good for evaluation of preserved cells. This perhaps was because of immediate delivery of material in the preservative fluid and the smears prepared by automate techniques leading to better visualization of nuclear details. These were concordant with studies of various authors where

they found almost equal sensitivity and specificity of both techniques in interpretation of aspiration samples of TTFNA from peripheral nodular lesions of lung.^[21]

Most of the authors have found LBC preparations better to CS in assessment of the above samples from lung masses. However, few with varying results have evaluated TBNA and TTFNA. Various authors observed better sensitivity and specificity of TBNA samples by using LBC.^[22] They found that sensitivity of LBC was 82.1% while in CS it was 56%. The specificity of LBC was 87.5%, and for CS it was 82.5%. These finding were more are less concordant with our study.

Limitation of the study: Sampling error & loss of material during decanting was also a major pitfall in Sure Path LBC. Majority of background material, arrangement and pattern of cells are lost during processing, also has some disadvantages in Liquid Based Cytology.

CONCLUSION

We conclude that Liquid Based Cytology gave a higher yield of cells and positive pathological features than conventional smear cytology in our study. It is used as a definitive diagnostic tool in those cases where biopsy is not possible.

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