Lung malignancy: Diagnostic accuracies of bronchoalveolar lavage, bronchial brushing, and fine needle aspiration cytology

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ABSTRACT

Background: Early diagnosis of lung cancer plays a pivotal role in reducing lung cancer death rate. Cytological techniques are safer, economical and provide quick results. Bronchoscopic washing, brushing and fine needle aspirations not only complement tissue biopsies in the diagnosis of lung cancer but also comparable. Objectives: (1) To find out diagnostic yields of bronchoalveolar lavage, bronchial brushings, FNAC in diagnosis of lung malignancy. (2) To compare relative accuracy of these three cytological techniques. (3) To correlate the cytologic diagnosis with clinical, bronchoscopic and CT findings. (4) Cytological and histopathological correlation of lung lesions. Methods: All the patients who came with clinical or radiological suspicion of lung malignancy in two and a half year period were included in study. Bronchoalveolar lavage was the most common type of cytological specimen (82.36%), followed by CT guided FNAC (9.45%) and bronchial brushings (8.19%). Sensitivity, specificity, positive and negative predictive value for all techniques and correlation with histopathology was done using standard formulas. Results: The most sensitive technique was CT FNAC – (87.25%) followed by brushings (77.78%) and BAL (72.69%). CT FNAC had highest diagnostic yield (90.38%), followed by brushings (86.67%) and BAL (83.67%). Specificity and positive predictive value were 100 % each of all techniques. Lowest false negatives were obtained in CT FNAC (12.5%) and highest in BAL (27.3%). Highest negative predictive value was of BAL 76.95 % followed by BB 75.59% and CT FNAC 70.59%. Conclusion: Before administering antitubercular treatment every effort should be made to rule out malignancy. CT FNAC had highest diagnostic yield among three cytological techniques. BAL is an important tool in screening central as well as in accessible lesions. It can be used at places where CT guided FNAC is not available or could not be done due to technical or financial limitations.

KEY WORDS: Correlation, cytology, lung cancer

INTRODUCTION

Lung cancer is one of the most prevalent and lethal cancers, accounting for 17.8% of all cancer deaths.[1] Since 1970s, the 5-year survival rate of lung cancer has remained unchanged at <15%.[1] It has been recognized that the prognosis of lung cancer is strongly related with the stage of cancer at the time of diagnosis, and 5-year survival rates range from 5% for stage IV cancers to 80% for stage I cancers.[1] Therefore, improving the detection rate of early stage lung cancer is essential for improving the prognosis of lung cancer. In India initially thought to be infrequent, lung cancer is the fifth common cancer.[1] Squamous cell type is the most common cell type in smokers and adenocarcinoma in nonsmokers.[1] Small cell carcinoma

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has a weaker association with smoking.\textsuperscript{[3]} Symptoms such as fever, cough, expectoration, hemoptysis, weight loss, and anorexia are common to both tuberculosis (TB) and lung cancer. A significant number of lung cancer cases are initially misdiagnosed and treated as TB.\textsuperscript{[4]} More so in our country where TB is still the most common disease and is the main culprit for delay in diagnosis and treatment of lung cancer.

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. A long-standing goal of cancer researchers has been to develop techniques that would facilitate earlier diagnosis and treatment of lung cancer and thereby decrease its mortality. Although histopathology remains the gold standard, but it is not possible to perform bronchial biopsies in all patients with suspicion of cancer. In cases where lesions are peripheral, and there is risk of hemorrhage taking bronchial biopsy becomes more difficult and requires expertise. Biopsies are time-consuming and there is increased pressure on pathologist to report cases as early as possible. Cytologic techniques are safer, economical, and provide quick results. Bronchoscopic washing, brushing, and fine needle aspirations not only complement tissue biopsies in the diagnosis of lung cancer but are also comparable.

The availability of good reliable investigation will enable us to diagnose lung cancer at an early stage, making it amenable to current treatment regimes.\textsuperscript{[5]} This will ultimately affect patient's survival.

**MATERIALS AND METHODS**

The study was carried out at the Department of Pathology, Bhagwan Mahaveer Cancer Hospital and Research Center, Jaipur receiving patients not only from Rajasthan but also nearby states. All the patients who came with clinical or radiological suspicion of lung malignancy in our institute in 2½ year period were included in the study.

Out of 1004 patients visiting our institute, with clinical, radiological suspicion of lung malignancy, 504 patients comprise the sample for the study who had both cytology and histopathology examination done at our institute or brought specimens from outside hospitals.

All the study subjects were identified and were explained about the nature and purpose of the study. After obtaining their informed consent, they were inquired about their clinical history and other sociodemographic information. These were recorded on a predesigned schedule.

Bronchoscopy specimens include:
1. Bronchoalveolar lavage (BAL)
2. Bronchial washing (BW)
3. Bronchial brushing (BB)
4. Transbronchial needle aspiration (under computed tomography [CT] guidance)
5. Transbronchial lung biopsy/endobronchial lung biopsy.

**Procedure**

In general, both washings and brushings were taken from any clinically suspicious area, by repetitive instillation of 3–5 ml of sterile balanced saline solution. Brushings were obtained by small circular stiff-bristle brush. Brushings were obtained before taking “bite” biopsies so that the blood did not obscure smears for washings and brushings.

In the absence of cells or agents, diagnostic of pathological process, large number of well preserved, optimally stained ciliated bronchial cells, and macrophages were required for specimen adequacy. Those specimens with few cells or cell details obscured by blood or air dried were deemed unsatisfactory for analysis. Excessive numbers of ciliated or squamous epithelial cells (>5%) were indicative of contamination by bronchial or oral material, indicating that the BAL specimen was not representative of the distal portion of the respiratory tract. Criterion for rejection was (1) Paucity of alveolar macrophages, (<10 alveolar macrophages per 10 high-power fields (HPF) or <25 alveolar macrophages per HPF in combination with criterion two and three), (2) excessive number of epithelial cells either showing degenerative changes or exceeding the number of alveolar macrophages, (3) a mucopurulent exudates of polymorphonuclear cells, (4) numerous red blood cells with anyone inadequacy criterion, (5) degenerative changes or artifacts.

With regard to CT-guided fine needle aspiration cytology (FNAC), there was no specific specimen adequacy criterion. In general, 2–3 passes optimize the relationship between sample adequacy rates and patient comfort.

BAL and BW after receiving in the laboratory were stirred with the help of applicator stick, poured into centrifuged tubes, and subsequently centrifuged at 2000 rpm for 10 min. The supernatant was decanted, and three smears were made from sediment on previously albuminized slides, two smears fixed in 95% of ethyl alcohol fixative, and one slide kept dry for Giemsa staining. Staining was done by Harris's hematoxylin (regressive staining).

**RESULTS**

The study group consisted of 550 cytological specimens from 504 patients over a study period of 2½ years. Bronchioalveolar lavage was the most common type of cytological specimen 82.36%, followed by CT guided FNAC 9.45%, and BBs 8.19% [Table 1].

The mean age in our study group was 57.60 [Table 2] with male to female ratio of 8.4:1 [Table 3]. In our study, cough was the most common presenting complaint (62%) followed by dyspnea (55.3%), chest pain (45%), and...
weight loss (31.67%) [Table 4]. 8.53% patients in our study had a history of antitubercular therapy before being diagnosed with lung cancer [Table 5]. The prevalence of smoking was 35.9% in the study population. Fifty-eight percent of smokers were diagnosed with lung cancer. Squamous cell carcinoma was the most common primary bronchogenic tumor (47.67%) in smokers, followed by small cell carcinoma (34.29%) [Table 6]. Only one patient in our study group had a positive family history of lung cancer.

Mass lesion (26.67%) with or without collapse was the most common radiological finding in our study [Table 7]. Other findings included pleural effusion (20%), opacity (12.67%), consolidation/cavities/nodules/fibrosis suggestive of TB (5.33%). A normal chest X-ray was found in 26% of cases [Table 8].

Out of 300 lung cancer patients, bronchoscopically visible tumors were found in 122 (40.67%) patients. Squamous cell carcinoma and small cell carcinoma were more commonly associated with bronchoscopically visible tumors compared to other cell types. The right main bronchus was most commonly involved by visible tumors 23.77%, followed by left main bronchus 18.85%, and right upper lobe 13.11% [Tables 9 and 10].

The most sensitive technique was CT FNAC - 87.25% followed by brushings 77.78% and BAL 72.69%. The positive predictive value of the three cytological techniques was 100%. Lowest false negatives were obtained in CT FNAC 12.50% and highest in BAL 27.30%. The highest negative predictive value was of BAL 76.95%. CT FNAC had highest diagnostic yield 90.38%, followed by brushings 86.67%, and BAL 83.67% [Table 11].

The highest typing accuracy was observed for squamous cell carcinoma in 72.13% of central lesions and 69.51% of peripheral lesions. 53.33% of central small cell carcinomas were correctly typed and 24.44% of peripheral small cell carcinoma. Adenocarcinoma was predominantly

### Table 1: Type of cytological specimens under study group

| Nature of specimen | Total number | Percentage |
|--------------------|--------------|------------|
| Bronchioalveolar lavage/washing | 453 | 82.36 |
| Bronchial brushings | 45 | 8.19 |
| CT-guided FNAC | 52 | 9.45 |
| Total cytological samples | 550 | |

Table: Computed tomography, FNAC: Fine needle aspiration cytology

### Table 2: Age-wise distribution of cases

| Age in years | Total no of cases | Percentage |
|--------------|------------------|------------|
| 10-25 | 4 | 0.79 |
| 26-40 | 17 | 3.37 |
| 41-55 | 143 | 28.38 |
| 56-70 | 272 | 53.97 |
| 71-85 | 68 | 13.49 |
| Total | 504 | |

### Table 3: Sex wise distribution of patients

| Sex | Number of patients | Percentage |
|-----|-------------------|------------|
| Male | 444 | 88.10 |
| Female | 60 | 11.90 |
| Total | 504 | |

### Table 4: Presenting complaint

| Complaint | Number of patients with malignancy | Percentage of malignant cases |
|-----------|-----------------------------------|-----------------------------|
| Cough | 186 | 62 |
| Dyspnea | 166 | 55.33 |
| Chest pain | 135 | 45 |
| Hemothysis | 60 | 20 |
| Hoarseness | 23 | 7.67 |
| Weight loss | 95 | 31.67 |
| Fever | 37 | 12.33 |
| Lymphadenopathy | 5 | 1.67 |

### Table 5: Tuberculosis and antitubercular treatment

| Cases | Tuberculosis | Percentage | Antitubercular therapy | Percentage |
|-------|--------------|------------|------------------------|------------|
| Malignant | 23 | 4.56 | 43 | 8.53 |
| Nonmalignant | 30 | 5.95 | 74 | 14.68 |
| Total | 53 | 9.51 | 117 | 23.21 |

### Table 6: Smoking and type of malignancy

| Histopathology type | Smokers | Percentage |
|---------------------|---------|------------|
| Squamous cell carcinoma | 49 | 46.67 |
| Small cell carcinoma | 36 | 34.29 |
| Nonsmall cell carcinoma | 6 | 5.71 |
| Adenocarcinoma | 2 | 1.90 |
| Others | 12 | 11.43 |
| Grand total | 105 | |

### Table 7: X-ray findings in malignant cases

| Number of patients | Percentage |
|--------------------|------------|
| Mass lesion | 80 | 26.67 |
| Pleural effusion | 60 | 20.00 |
| Opacity | 38 | 12.67 |
| Koch’s chest | 16 | 5.33 |
| Collapse | 8 | 2.67 |
| Bone metastasis | 1 | 0.33 |
| No abnormality | 78 | 26.00 |
| Not available | 19 | 6.33 |

### Table 8: Side of involvement

| Side | Total |
|------|-------|
| Right | 125 |
| Left | 73 |
| Both | 14 |
| Lower end trachea | 1 |

### Table 9: Computed tomography findings

| Type of lesion | Number of patients | Percentage |
|----------------|--------------------|------------|
| Mass | 42 | 84 |
| Calcification | 1 | 2 |
| Coin lesion | 1 | 2 |
| Nodal involvement | 1 | 2 |
| No abnormality | 5 | 10 |
peripherally located; typing accuracy was 80% and 50% for central lesions. A clear distinction between small and nonsmall cell carcinoma was made in 62.5% of peripheral lesions and 78.57% of central lesions, typed as nonsmall cell carcinomas.

**DISCUSSION**

The study group consisted of 550 cytological specimens from 504 patients over a study period of 2½ years. Bronchoalveolar lavage was the most common type of cytological specimen 82.36%, followed by CT-guided FNAC 9.45%, and BBs 8.19% [Table 1].

All three techniques were not used simultaneously in all patients under study. In 47 patients (15.67%), two types of specimens were received: BAL and BBs in 20 (6.67%) patients, BAL and CT-guided FNAC in 22 (7.33%) patients, and BBs and CT-guided FNAC in 5 (1.67%) patients. In two patients, all three types of specimens were received.

In patients with malignancy, the mean age for males was 58.00 (standard deviation [SD] ± 10.175) and for females 55.06 (SD ± 11.28) [Table 2]. A male dominance was seen in the study group, 8.4:1. Our findings are consistent with other Indian studies as shown in Table 3. Cough and dyspnea were the most common complaints followed by chest pain and weight loss [Table 4]. While taking clinical history, every attempt was made to get detailed history regarding TB or the use of antitubercular drugs. TB still is a stigma in our country where patients were reluctant in providing clear history of TB treatment. This fact is clearly depicted in our data, Table 5 where 53 (9.51%) patients gave a positive history of TB while 117 (23.21%) patients admitted the use of antitubercular therapy. Of the 117 who took antitubercular therapy, 43 patients were positive for malignancy, and 74 patients had no malignancy. Among the 43 patients who received ATT more than half of them took drugs for more than 3 months indicating that a significant time had elapsed before a definite diagnosis of lung, malignancy could be made.

CT-guided FNAC had highest sensitivity among the three techniques. There were no false positive cases reported on cytology; therefore, the positive predictive value was 100% for all techniques [Table 11].

The sensitivity of BAL in various other studies from literature varies from 21% to 78%. Our results fall within this range [Table 12]. This reported a wide range of sensitivity may be due to difference in case selection. Some investigators discard the first aliquot which is relatively enriched in the bronchial material. For malignancies originating in the bronchial tree, this may represent material with the highest diagnostic yield. Some clinicians filter the BAL specimen through loose weave gauze to remove mucous. Malignant cells often present in clumps may get inadvertently removed by this procedure.

Although the sensitivity of BAL was low 72.69% compared to other techniques, but it is still very useful technique as it is least invasive and with multiple sampling the yield can be improved [Figures 1-3]. Like BAL, there is a wide range of sensitivity of BBs-varying from 21% to 93% [Table 13]. The causes for varying sensitivity in other studies include the use of different techniques for the retrieval and processing of brushing specimens such as the type of brush used capped or uncapped and the inclusion of “suspicious” cases as positive for calculation of sensitivity. It is better than BAL due to less degeneration in brushing specimens in comparison to BAL [Figures 4 and 5].

The sensitivity and specificity of CT-guided FNAC were found to be 87.25% and 100%, respectively [Table 14]. The sensitivity of CT FNAC in this study is low in comparison to other studies. The major limitation while performing CT-guided FNAC was financial constraints. It was therefore not possible to perform CT-guided FNAC in all patients due to which the absolute number of patients undergoing procedure were less. In such situation, it was not always possible to obtain sufficient material for cytological assessment. Further with the presence of high-grade cancers, there was more necrosis which reduced the yield of viable tissue as there was more of necrotic material which resulted in false negative cases. Increased inflammation also contributed to low yield of CT FNAC.

False positives in cytology can be reported due to misinterpretation of smears due to cellular changes in

### Table 10: Proportion of lung cancer cell type with bronchoscopically visible and nonvisible tumors

| Characteristics | Bronchoscopically visible tumor | Squamous carcinoma | Small cell carcinoma | NSCLC | Adenocarcinoma | Others |
|-----------------|--------------------------------|-------------------|---------------------|-------|---------------|--------|
| Yes (n=122)     | 63                             | 33                | 16                  | 5     | 5             | 5      |
| No (n=178)      | 91                             | 48                | 8                   | 9     | 22            | 22     |
| Total (n=300)   | 154                            | 81                | 24                  | 14    | 27            | 27     |

NSCLC: Nonsmall cell lung cancer

### Table 11: Comparison of various cytological techniques

| Characteristics        | BAL/BW (%) | BB (%) | CT FNAC (%) |
|------------------------|------------|--------|-------------|
| Sensitivity            | 72.69      | 77.78  | 87.25       |
| Specificity            | 100        | 100    | 100         |
| False positive         | 0          | 0      | 0           |
| False negative         | 27.31      | 22.22  | 12.50       |
| Positive predictive value | 100       | 100    | 100         |
| Negative predictive value | 76.95     | 75.00  | 70.59       |
| Diagnostic efficacy    | 83.67      | 86.67  | 90.38       |

CT: Computed tomography, FNAC: Fine needle aspiration cytology, BAL: Bronchoalveolar lavage, BW: Bronchial washing, BB: Bronchial brushing
chronic inflammatory disorders such as pneumonia (atypical histiocytes), TB, bronchiectasis, (misinterpretation of cuboidal epithelial cells as small cell carcinoma), squamous metaplasia, and alveolar cell polymorphism in lung fibrosis. False positive have very unfortunate consequences for patients; therefore, some advice “underreporting” instead of “over reporting” of suspicious cases.\(^9\) If cytology is suspicious for malignant cells, a repeat biopsy with a clinical correlation with radiological/bronchoscopic findings is necessary before ruling out malignancy. Our results are in concordance with those of Lachman\(^9\) Rennard\(^10\) who also did not encounter any false positives. As our center is a referral hospital, the cases we received had work up before coming to our hospital. This resulted in low false positives as there was increased effort for ruling out malignancy.

27.31% of cases were false negatives on BAL, compared with 22.22% on brushing, and 12.50% on CT FNAC. The reasons of false negatives could have been superadded inflammation, nonrepresentative material, or hypocellular aspirate. False negatives imply that the cytologic specimen does not contain malignant cells. The absence of malignant cells could be attributed to the inability of malignant cells to dislodge from epithelial surface causing lavage fluid to be low in malignant cells. Therefore, it is not uncommon to get false negatives on cytology due to the paucity of cells in cytological smears.
Table 12: Cytology-bronchoalveolar lavage

| Diagnosis                | Number of patients | Percentage |
|--------------------------|--------------------|------------|
| Squamous cell carcinoma  | 94                 | 20.97      |
| Nonsmall cell carcinoma  | 45                 | 9.93       |
| Small cell carcinoma     | 30                 | 6.62       |
| Poorly differentiated carcinoma | 06         | 1.32       |
| Adenocarcinoma           | 01                 | 0.22       |
| Metastatic carcinoma     | 01                 | 0.22       |
| Malignant epithelial neoplasm | 20        | 4.42       |
| Dysplasia                | 04                 | 0.88       |
| Negative                 | 250                | 55.19      |
| No opinion               | 02                 | 0.44       |
| Total                    | 453                |            |

Table 13: Cytology-bronchial brushings

| Diagnosis                | Number of patients | Percentage |
|--------------------------|--------------------|------------|
| NSCLC                    | 7                  | 15.55      |
| Squamous cell carcinoma  | 09                 | 20.00      |
| Small cell carcinoma     | 03                 | 6.67       |
| Malignant epithelial neoplasm | 2          | 4.44       |
| Negative                 | 24                 | 53.33      |
| Total                    | 45                 |            |

NSCLC: Nonsmall cell lung cancer

Table 14: Computed tomography guided fine needle aspiration cytology diagnosis

| Diagnosis                | Number of patients | Percentage |
|--------------------------|--------------------|------------|
| NSCLC                    | 08                 | 15.38      |
| Metastatic carcinoma     | 01                 | 1.92       |
| Small cell carcinoma     | 04                 | 7.69       |
| Round cell tumor         | 01                 | 1.92       |
| Poorly differentiated carcinoma | 02    | 3.85       |
| Squamous cell carcinoma  | 13                 | 25.00      |
| Adenocarcinoma           | 06                 | 11.53      |
| Negative                 | 17                 | 32.69      |
| Total                    | 52                 |            |

NSCLC: Nonsmall cell lung cancer

Final histopathology diagnosis of 300 malignant cases taken as the gold standard in our study yield, 154 cases (51.33%) of squamous cell carcinoma which form the most common malignancy in our study [Table 15]. The second malignancy to follow was small cell carcinoma 81 cases (27%). Adenocarcinoma was next 17 cases (5.67%). Although in west, there is increased the incidence of adenocarcinoma[11] to the extent that in some countries adenocarcinoma has surpassed squamous cell carcinoma but in our country, squamous cell carcinoma is still the most common primary lung malignancy.[1,3] In 22 cases (7.33%), a diagnosis of NSCLC could only be given despite efforts as repeated samples could not be taken due to the poor general condition of the patient. Similarly, in two cases, only a diagnosis of malignancy could be assigned with no further classification in small or nonsmall cell type, due to necrosed, poorly differentiated lesions. Eight cases (2.67%) of poorly differentiated carcinoma were finally diagnosed. The other less common malignancies include, three undifferentiated large cell carcinoma, two spindle cell carcinoma, two mixed small-nonsmall cell carcinoma, one bronchoalveolar carcinoma, one carcinoid tumor, and one hematolymphoid malignancy. We diagnosed six cases of metastatic carcinoma in the lung: Two cases of mesothelioma, one case each of adenoid cystic carcinomas, squamous cell carcinoma from head and neck region,
adenocarcinoma from prostate and malignant fibrous histiocytoma from thigh region. Of the two spindle cell carcinoma, we got immunohistochemistry confirmation for one as synovial sarcoma.

Thus, although histopathology remains the gold standard for diagnosis one can rely on cytology techniques for quick reporting of lung lesions, especially CT FNAC where typing of tumors could be done efficiently [Figures 6-8].

CONCLUSION

In a developing country like India where there is an enormous burden of TB in the general population, there is a great risk of missing the diagnosis of cancer; therefore, it is prudent to use lung cytology techniques which are affordable, quick, and reliable for the screening of suspected cases.

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Conflicts of interest

There are no conflicts of interest.

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