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# Study of cytomorphology and immunohistochemistry on cell block for categorisation of primary lung tumours

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**Abstract**
**Introduction:** Lung cancer is the most common cancer and is the leading cause of mortality worldwide. It accounts for 1-5 million deaths in the world and 2.5 million deaths in developing countries.[1]
**Objectives**
1. To study the morphology of primary lung tumours on fine needle aspiration samples. 2. Categorisation of lung tumours by cytomorphology and with immunohistochemistry on cell block wherever available.
2. To assess the diagnostic accuracy of FNAC of lung tumours

**Methodology:** This study was a prospective study conducted on fine needle aspiration samples of 245 cases presenting as lung masses over a period of one year from march 2015 to February 2016.
**Results:** The following observations were made on the sample size of 245 cases of lung tumours. The age of occurrence was between 32-88 years. Most common clinical presentation is cough with expectoration and haemoptysis. Most commonly the lesions were located in the right lung (61.2%). Adenocarcinoma was the most common tumour in our study, followed by squamous cell carcinoma, and neuroendocrine carcinoma. 2 cases of adenosquamous carcinoma, 2 cases of primary plasmacytoma and 1 case of Non-Hodgkin's lymphoma were also noted. Out 245 cases,30 cases were unsatisfactory aspirate. Out of 215 satisfactory aspirate, IHC was available for 54 cases. IHC confirmed the diagnosis of adenocarcinoma in 30 cases, squamous cell carcinoma in 10 cases, neuroendocrine carcinoma in 11 cases and adenosquamous carcinoma in 2 cases, and 1 case of plasmacytoma lung. We had 2 cases with discordance between cytomorphology and IHC (2 cases which were diagnosed as neuroendocrine carcinoma on cytolomorphology, the IHC findings showed positivity for adenocarcinoma). Immunohistochemistry is helpful in subtyping non- small cell carcinoma, NOS and poorly differentiated carcinoma into adeno, squamous and neuroendocrine carcinomas. 2 cases of adenosquamous cell carcinoma were also confirmed by IHC.
**Conclusion:** The diagnostic accuracy of Fine needle aspiration cytology for primary lung tumours in our study is 87.75%. The sensitivity is 96.4% and specificity 100% in the study. The high accuracy rate was obtained due to correlation with clinical, radiological and cytopathological findings.

**Keywords:** Fine needle aspiration cytology, adenocarcinoma, squamous cell carcinoma, immunohistochemistry

## Introduction
Lung cancer is the most common cancer and is the leading cause of mortality worldwide. It accounts for 1-5 million deaths in the world and 2.5 million deaths in developing countries [1]. Fine needle aspiration cytology (FNAC) is relatively safe, rapid, reliable technique for the diagnosis of pulmonary mass lesions with the aid of CT and ultrasound [2]. FNAC not only distinguishes between benign and malignant lesions but also helps in detection of infectious diseases like tuberculosis. Lung cancer is broadly categorized into non-small cell lung carcinoma (NSCLC) and small-cell carcinoma. Approximately 85% lung cancers are of NSCLC type.
It is necessary to subtype non small cell lung carcinoma into squamous, adenocarcinoma, neuroendocrine carcinoma which is required for therapeutic management of the patients.
Cytology is highly accurate and a well-recognized method to distinguish small cell lung carcinoma from non small cell lung carcinoma and immunohistochemistry studies aid in further subtyping of lung carcinoma [3].

The emergence of molecular tests for diagnosis and prediction of response to specific treatment emphasize the importance of the fine needle aspiration as a means of getting representative material from lung neoplasms [8].

**Objectives**

1. To study the morphology of primary lung tumours on fine needle aspiration samples.
2. Categorisation of lung tumours by cytomorphology with immunohistochemistry on cell block wherever available.
3. To assess the diagnostic accuracy of FNAC of lung tumours

**Materials and methods**

Patients with lung lesions were assessed by obtaining a brief history. The clinical and radiological findings were obtained. Consent was taken. Under aseptic precautions, the fine needle aspiration was done under the guidance of CT scan and ultrasound. Air dried were stained by May-Grunewald-Geimsa (MGG) while wet fixed smears were stained by Papanicolaou (Pap) staining while remaining material was processed for cell block and paraffin embedding. Immunohistochemistry was performed on cell block specimen using a panel of antibodies like CK7, TTF1, napsin A, CK 20, P63, P40, synaptophysin, chromogranin etc depending on case wherever available.

Data was used to classify tumours based on WHO classification of lung tumours. The cytomorphological findings were correlated with the immunohistochemistry performed on cell block specimen wherever available and possible, to find out the accuracy, sensitivity and specificity of FNAC of lung tumours in our institution. All the cases were analyzed with reference to the age, sex, clinical findings, type of lesions, cell block and IHC findings.

**Inclusion criteria**

1. Only fine needle aspiration specimen of primary lung tumours obtained from the Kidwai memorial institute of oncology are included in the study
2. Lung masses diagnosed on CT/ ultrasound are included in the study
3. Informed consent for procedure is taken from all the patients are included in the study.

**Exclusion criteria**

1. Patients with infectious lesions of lung, benign tumours and metastatic tumours to lung are excluded from the study.

**Statistical analysis**

Statistical significance for the comparison between cytology diagnosis and IHC was made using chi-square test. Statistical significance was set at P value <0.05.

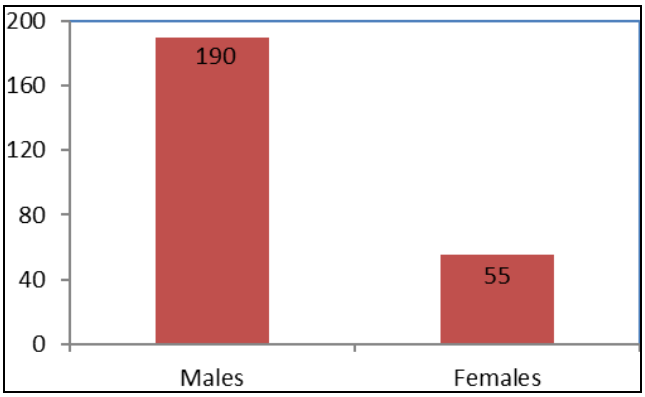
**Results**

FNAC has gained vast clinical recognition for early diagnosis and proper management of patients with benign and malignant lesions in various organs including lung lesions. This is a prospective study with study period of one year (March 2015 to February 2016) in Kidwai Memorial Institute of Oncology. A total of 245 cases of lung FNA were done. Both CT guided (102) and USG (143) guided FNA were performed.

Out of 245 cases, 215 were satisfactory aspirates and 30 were unsatisfactory which showed only components of blood. Out of 245 cases 190 were male patients and 55 were female patients. In our study most commonly patients were in age group of 51 to 60 years.

**Table 1:** Showing number of cases with satisfactory and unsatisfactory aspirates.

| Aspiration | No of cases | Percentage |
|---|---|---|
| Satisfactory | 215 | 87.8% |
| Unsatisfactory | 30 | 12.2% |
| Total | 245 | 100% |




**Graph 1:** Showing sex distribution- Male: female ratio=190:55=3.4:1

**Table 2:** Showing age distribution of lung carcinoma in our study

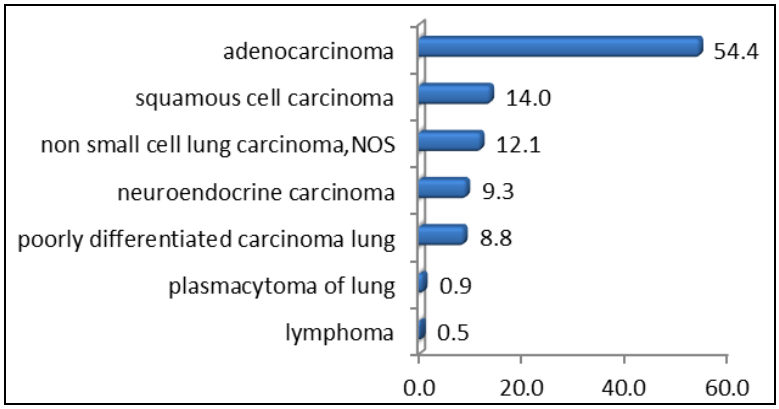
| Age Group | No of patients | Percentage (%) |
|---|---|---|
| 31-40 | 17 | 6.9% |
| 41-50 | 37 | 15.1% |
| 51-60 | 76 | 31.0% |
| 61-70 | 72 | 29.3% |
| 71-80 | 39 | 15.9% |
| 81-90 | 04 | 1.6% |
| Total | 245 | 100% |

**Incidence of lung tumours on fine needle aspiration cytomorphology.**

The following table (table 3) depicts the incidence of lung lesions in our study. Adenocarcinoma formed the largest group followed by Squamous cell carcinoma.

**Table 3:** Incidence of lung lesions on fine needle aspiration cytology

| Cytomorphological diagnosis (FNAC) | No of cases | Percentage (%) |
|---|---|---|
| Adenocarcinoma | 117 | 54.4% |
| Squamous cell carcinoma | 30 | 14% |
| Non-small cell lung carcinoma, NOS | 26 | 12.1% |
| Neuroendocrine carcinoma | 20 | 9.3% |
| Poorly differentiated carcinoma | 19 | 8.8% |
| Plasmacytoma | 2 | 0.9% |
| Lymphoma | 1 | 0.5% |
| Total | 215 | 100% |




**Graph 2:** Showing incidence of lung tumours on cytomorphology

**Adenocarcinoma (ADC)**

Adenocarcinoma is the most common primary lung tumour in our study (Fig1). Out of total 215 cases, 117(54.4%) cases were diagnosed as adenocarcinoma on FNAC. Immunohistochemistry tests were available for 30 cases. Out of these 30 cases, 4 cases were diagnosed as poorly differentiated carcinoma, 4 cases as Non-small cell carcinoma NOS and 2 cases as neuroendocrine carcinoma on cytomorphology. Other 20 cases had direct diagnosis of adenocarcinoma of cytology. All these cases showed positivity for CK7, TTF1, napsin A. Age at presentation varied from 31 years to 90 years. Most of the cases were in the age group of 51 to 60 years (25.6%). On cytology smears showed tumour cells arranged in glandular pattern and nests displaying prominent nucleoli with eosinophilic to mucinous cytoplasm. Few cases showed extracellular pools of mucin.

**Squamous cell carcinoma (SQCC)**

The next most common primary lung tumour in our study is squamous cell carcinoma (Fig 2). On cytology 30 cases (14%) were diagnosed as squamous cell carcinoma out of 215 cases. Immunohistochemistry test was available for 10 cases. Out of these 10 cases 4 showed poorly differentiated carcinoma and 6 cases had direct diagnosis of squamous cell carcinoma on cytology. They showed positivity for CK7, CK5/6, P63 and P40 and negative for CK20. Most of the cases presented in the age group of 61 to 70 years (50%).

On cytology smears showed tumour cells arranged in clusters and singles. Cells showed hyperchromatic nucleus, moderate cytoplasm with keratinisation and few of the cells were scattered singly showing dense orangophilic cytoplasm on Pap stain. Few of the cells also showed spindle shaped nucleus. Large areas of necrosis and inflammation were noted in few cases.

**Neuroendocrine tumours (NET)**

Neuroendocrine tumours are the 3rd most common primary lung tumour identified in our study (fig 3). There are total of 20 cases diagnosed on cytology. Most of the cases were in the age group of 61 to 70 years (20%). Immunohistochemistry test was available for 11 cases. 10 cases of neuroendocrine carcinoma on cytomorphology were confirmed by IHC and one case poorly differentiated carcinoma on cytology had IHC positivity for neuroendocrine markers. All the cases showed bright positivity for CK7 which showed membranous staining, and cytoplasmic strong positivity for synaptophysin and chromogranin and 3 out 11 cases showed nuclear positivity for TTF1. Most of the cases had KI- 67 index of 80%. There were no Carcinoid tumours in our study. There were 2 cases which were discordant between cytomorphology and IHC (2 cases of large cell neuroendocrine carcinoma on cytomorphology showed IHC markers positivity for adenocarcinoma).

Cytology – Small cell carcinoma is the most commonly recognised category in our study which accounted for 8 cases, followed by large cell neuroendocrine carcinoma of 4 cases, and 4 cases of neuroendocrine carcinoma not classified.

Small cell neuroendocrine carcinoma on cytology showed sheets and clusters of small sized cells with round to oval nuclei with fine granular chromatin and scant cytoplasm. Nuclear moulding is noted. Areas of necrosis were seen in few of the cases.

Large cell neuroendocrine carcinoma showed sheets of large cells with hyperchromatic nucleus, prominent nucleoli and moderate cytoplasm. Few cases also showed necrosis.

**Non small cell carcinoma, NOS**

Non small cell carcinoma is designated for the lesions with the solid histology which is difficult to categorise as either squamous cell carcinoma or adenocarcinoma on cytomorphology. In our study 26 cases were diagnosed with non small cell carcinoma, NOS on cytology.

Cytology- Smears showed a solid histology with tumour cells arranged in cohesive clusters, nucleus is hyperchromatic to vesicular with prominent nucleoli. Cytoplasmic keratinisation was not seen and few of the cases also showed areas of necrosis.

Cell block was available for only 4 cases. All 4 cases of non small cell lung carcinoma NOS on cytology showed IHC positivity for adenocarcinoma. They were positive for CK7, TTF1, Napsin A, and negative for CK20.

**Poorly differentiated carcinoma**

This is next common category diagnosed on cytology. This is a non specific category showing highly pleomorphic cells arranged in sheets which could not be categorised as adenocarcinoma or squamous cell carcinoma or as neuroendocrine carcinoma. This category included 19 cases in our study. Cytology smears showed highly pleomorphic tumour cells arranged in sheets and scattered singly. Cells showed hyperchromatic to vesicular nucleus with or without

prominent nucleoli and scant cytoplasm. No obvious keratinisation noted. Areas of necrosis were also seen in few cases. Immunohistochemistry was available for 10 cases. IHC of these cases showed positivity for adenocarcinoma in 3 cases, squamous cell carcinoma in 4 cases, adenosquamous carcinoma in 2 cases and small cell neuroendocrine carcinoma in one case.

**Adenosquamous cell carcinoma**

2 cases presented with poorly differentiated morphology on cytology and cell block in our study. They were diagnosed as adenosquamous carcinoma on IHC. They showed positivity for CK7, TTF1, napsin A, p40 and P63.One case was female and the other is male patient in the age of 62 years and 70 years respectively.

**Extramedullary primary plasmacytoma of lung**

There were 2 cases of primary plasmacytoma of lung in our study (fig 4). Cytology smears showed sheets of atypical plasma cells. Cells showed round to oval nucleus with cart wheel chromatin situated at periphery of the cell and abundant basophilic cytoplasm. Few binucleate cells were also noted. Cell block and IHC was available for one case which showed positivity for CD138, lambda and negative for CK 7 and kappa.

**Primary lymphoma of lung**

A single case of primary lymphoma of lung was seen in our study. Cytology smears showed a sheets of monomorphic atypical lymphoid cells which are medium sized showing coarse chromatin with few cells showing prominent nucleoli and scant cytoplasm suggestive of non- Hodgkin lymphoma. Cell block and IHC was not available for this case. Further biopsy was performed for confirmation on histopathology and IHC of which showed diffuse large B cell lymphoma.

Inadequate or unsatisfactory aspirates There were 30 cases who presented with large lung masses on CT scan suggestive of malignancy. Cytology showed only hemorrhagic aspirates after the procedure was repeated for twice.

**Diagnostic accuracy**

In our study out of 245 cases who presented with lung masses underwent fine needle aspiration under the guidance of USG or CT scan. Adequate material was obtained in 215 cases (87.8%). Totally 93 cases had cell block diagnosis. Out of 93 cases having cell block, IHC test was performed in 54 cases. IHC was taken as gold standard for the final diagnosis. Correlation of cytomorphology with IHC was performed. Two cases out of 54 were false negative (i.e., 2 cases were given as large cell neuroendocrine carcinoma on cytomorphology but IHC showed diagnosis of adenocarcinoma). Treatment was started for all the cases who had follow up based on cytology diagnoses. Two cases which were confirmed as adenocarcinoma on IHC had mutation testing for EGFR and ALK which were negative.

Sensitivity and specificity of cytology diagnosis was calculated by using immunochemistry as gold standard for final diagnoses.

**Table 4:** showing correlation between cytomorphology and IHC

| S. No. | Cytomorphology diagnosis | IHC diagnosis | Concordant (True positive cases) | Discordant (False negative cases) |
|---|---|---|---|---|
| 1 | Adenocarcinoma, Non-small cell carcinoma, NOS and poorly differentiated carcinoma | adenocarcinoma | 28 | |
| 2 | Squamous cell carcinoma and poorly differentiated carcinoma | Squamous cell CA | 10 | |
| 3 | Neuroendocrine carcinoma and poorly differentiated carcinoma | Neuroendocrine carcinoma | 11 | |
| 4 | Poorly differentiated carcinoma | Adenosquamous carcinoma | 2 | |
| 5 | Neuroendocrine carcinoma | adenocarcinoma | | 2 |
| 6 | Plasmacytoma | | 1 | |
| | Total | | 52 | 2 |

**Table 5:** Statistical values for malignant tumours with IHC correlation in our study

| S. No. | Sensitivity | Specificity |
|---|---|---|
| 1 | True positive | 52 |
| 2 | False positive | - |
| 3 | True negative | - |
| 4 | False negative | 2 |
| 5 | Sensitivity | 96.4% |
| 6 | Specificity | 100% |
| 7 | Accuracy | 87.75% |

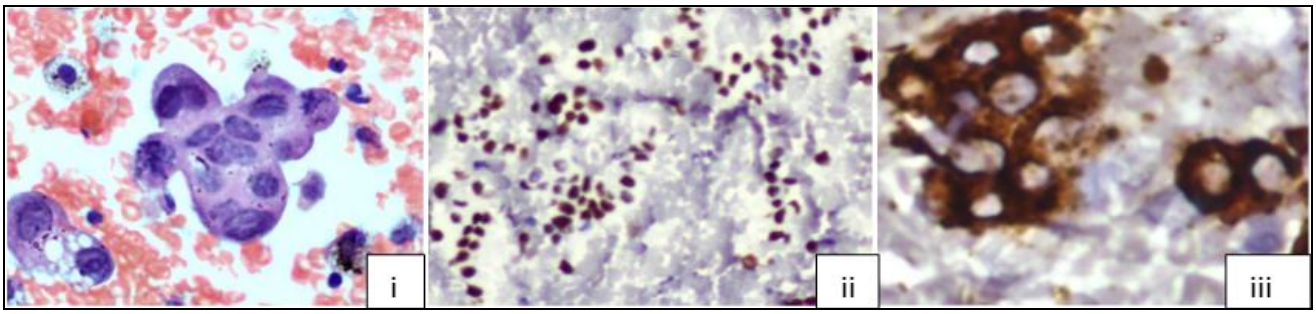



**Fig 1:** Showing adenocarcinoma of lung i. FNA showing tumour clusters with vague glandular pattern and eosinophilic to mucinous cytoplasm, ii. Nuclear TTF 1 positivity in tumour cells, iii. Cytoplasmic napsin A positivity in tumour cells.

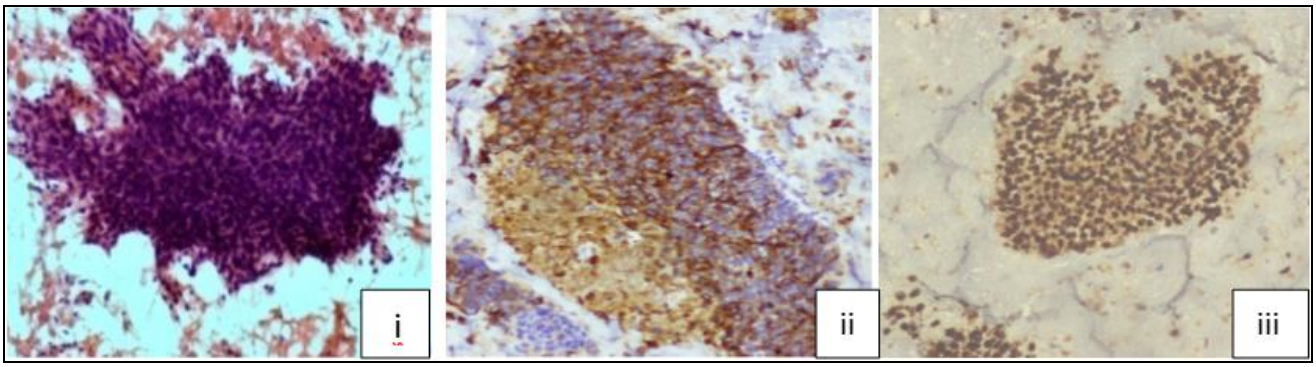



**Fig 2:** Squamous cell carcinoma of lung i. FNA showing neoplastic cells arranged in clusters with spindle shaped hyperchromatic nuclei and eosinophilic cytoplasm, ii. CK 7 positivity in tumour cells iii. p40 positivity in tumour cells

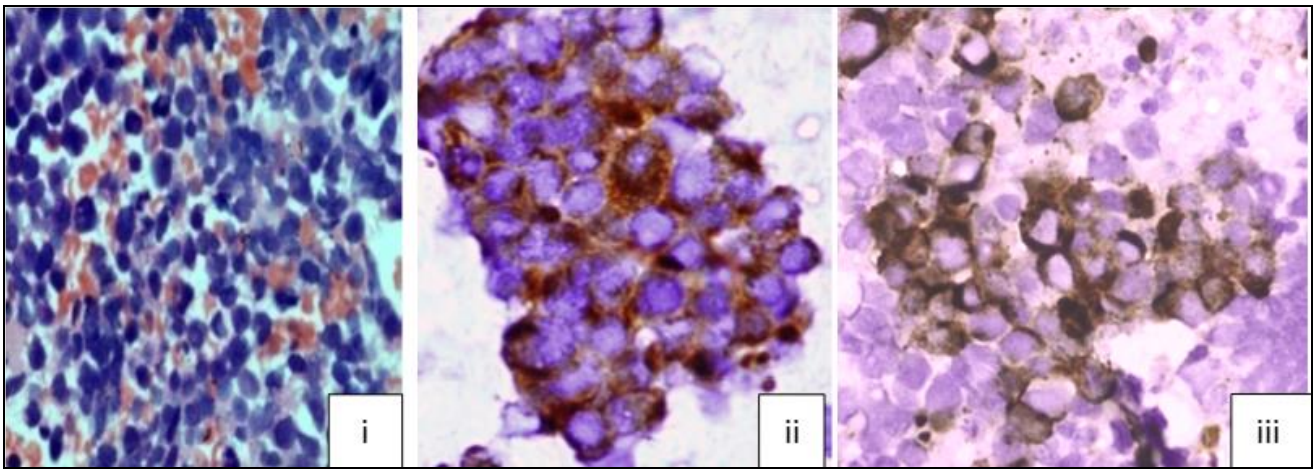



**Fig 3:** Neuroendocrine carcinoma of lung i. FNA of small cell neuroendocrine carcinoma displaying hyperchromatic nuclei, nuclear moulding and scant cytoplasm, ii. Synaptophysin positivity in tumour cells iii. Chromogranin positivity in tumour cells.

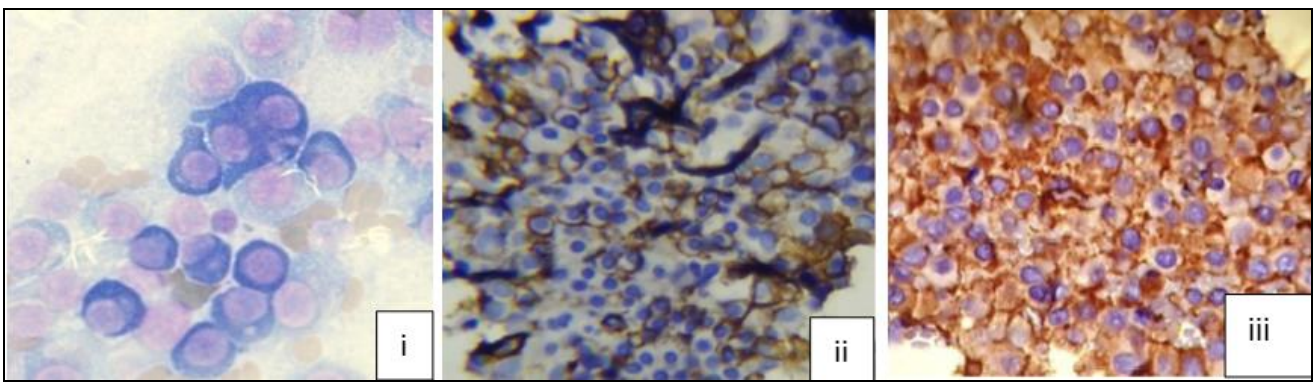



**Fig 4:** Primary plasmacytoma of lung. i. FNA showing tumour cells arranged in sheets with eccentric nuclei and abundant cytoplasm, ii. tumour cells are positive for CD138, iii. Positivity for cytoplasmic lambda staining in tumour cells.

## Discussion

Lung cancer is a major cause of morbidity and mortality throughout the world with variation among nations and ethnicities. The pathological classification of lung cancer was recently updated (WHO 2015). Accurate pathologic diagnosis is crucial for selecting appropriate treatment.

The ability to reach a conclusive diagnosis with FNA depends on optimal performance of all stages of the procedure. The FNA is performed by pathologists under imaging guidance, usually USG or CT scan. The sampling equipment and technique, location of the lesion, its size, texture, necrosis and amount of aspirated material are important factors.

Cytopathology techniques have the potential to provide useful diagnostic information from specimens of pulmonary lesions obtained through minimally invasive procedures including expectorated sputum, washings, lavages, brushings and aspiration procedures [33].

The utilization of the entire sample for preparation of cytological smears, cell block, and optimal staining are important factors. Specific antibodies for immunohistochemistry help increase the diagnostic accuracy. Cell block can provide enough tissue sections for immunohistochemical stains.

Emergence of molecular tests for diagnosis and prediction of response to specific treatment emphasize the importance of the FNA, as a means of getting representative material from lung neoplasm. The new treatment modalities, including targeted biological therapies and specific chemotherapeutic agents dictate the need for unquestionably accurate diagnoses, with optimal use of immunohistochemical stains and maximal preservation of representative tissue. FNA, side by side with other diagnostic and prognostic assays help in achieving these goals [8].

In a study, of more than 13,000 pulmonary fine needle aspiration (FNA) specimens from 436 institutions, by Zarbo RJ *et al.* The diagnostic sensitivity was 89% for the procedure itself and 99% for the pathologist's interpretation which correlated with our study having diagnostic accuracy of 87.75% and sensitivity of 96.4% [52].

A review of thoracic FNA by a study conducted by C. J. R. Stewart and I. S. Stewart revealed a specificity of 100% in cases of malignancies which was also noted in our study. FNA has also been shown to have a high degree of positive predictive value (99%) in a large study. A negative result, generally, is less reliable and most reports document a false negative rate of 10–20% for lung aspiration cytology [17].

Our institution being a tertiary cancer centre, USG /CT guided FNAC of lung lesions is done as a routine diagnostic work up in all suspected malignant lung lesions. FNAC is done by the experienced cytopathologists. The procedure was repeated after 4 days if the material is inadequate during the first pass. Continuous interactions and case discussions between the pathologist, radiologist and clinician in our institution resulted in a high accuracy rate (87.75%) in our study.

### Adenocarcinoma

Adenocarcinoma is the most common primary lung tumour. In our study, out of 215 cases of satisfactory aspirate, 126(58.6%) cases were in the adenocarcinoma category on cytolomorphology.

**Table 6:** Comparison of adenocarcinoma with other studies

| Study | No of cases on cytology | Histopathology/ cell block/IHC | True positive | Correct diagnosis |
|---|---|---|---|---|
| Kravotsav *et al.* [12] | 82 | 42 | 42 | 100% |
| Sumana Mukherjee, *et al.* [30] | 40 | 40 | 40 | 100% |
| Present study | 118 | 28 | 28 | 100% |

### Squamous cell carcinoma

Squamous cell carcinoma is the next most common primary tumour noted in our study constituting to 41cases (19%).

**Table 7:** Comparison of squamous cell carcinoma with other studies

| Study | No of cases on cytology | Histopathology/ cell block/IHC | True positive | Accuracy |
|---|---|---|---|---|
| Dr.Sumita Das *et al.*[32] | 58 | 58 | 56 | 96.5% |
| Li Liang *et al.*[44] | 28 | 28 | 28 | 100% |
| Present study | 30 | 10 | 10 | 100% |

### Neuroendocrine tumours.

Neuroendocrine tumours are next most common tumour noted in our study. Out of 215 cases, 20 cases (9.3%) were of neuroendocrine tumours. 2 cases showed false negative results (2 cases of large cell neuroendocrine carcinoma on cytomorphology showed IHC positivity for adenocarcinoma).

On cytology 8 cases had diagnosis of small cell carcinoma and 3 cases had large cell carcinoma based on morphological features. Ki- 67 index is more than 20% in all the cases. None of the cases had diagnosis of Carcinoid in our study.

**Table 7:** Comparison of neuroendocrine tumours with other studies

| Study | No of cases on cytology | Histopathology/ IHC | True positive | Correct diagnosis |
|---|---|---|---|---|
| Patricia I. Delgado *et al.*[45] | 18 | 18 | 18 | 100% |
| Moumita Sengupta *et al.*[33] | 6 | 6 | 6 | 100% |
| Present study | 20 | 13 | 11 | 84.6% |

**Non-small cell carcinoma, NOS**

Non-small cell carcinoma, NOS constituted to 22(10.2%) cases in our study. The diagnosis of Non small cell carcinoma, NOS was made on cytomorphology in 26 cases. Cell block and IHC was available for 4 cases, all of which showed positivity for adenocarcinoma.

**Poorly differentiated carcinoma**

There were 19 cases of poorly differentiated carcinoma diagnosed on cytology. 11 cases had cell block and IHC confirmation. These cases were further categorised on IHC, out of which 4 cases were adenocarcinoma, 2 were adenosquamous carcinoma, 4 cases were squamous cell carcinoma and 1 case was neuroendocrine carcinoma.

Poorly differentiated carcinoma on cytology presents with large pleomorphic cells, with nucleoli, with or without necrosis and no evidence of keratinisation or glandular morphology or neuroendocrine features. IHC is helpful in such cases for confirmation of diagnosis.

**Adenosquamous cell carcinoma**

Adenosquamous cell carcinoma included 2(0.9%) cases in our study. Both the cases presented as poorly differentiated carcinoma on cytology and cell block. IHC stains showed positivity for both adeno and squamous cell markers like TTF1, Napsin A, p40, p63 and CK7.

In a study of Patricia I. Delgado *et al*. Out of 210 malignant lung cases 10 cases were diagnosed as non small cell lung carcinoma on cytology and histology showed IHC showed diagnoses of adenosquamous cell carcinoma

**Primary Plasmacytoma lung**

We also had 2(0.9%) cases of primary plasmacytoma of lung who presented in a elderly age group with multiple lung nodules and pleural effusion in one case. Cytology they showed sheets of atypical plasma cells. One case also had IHC confirmation showing positivity for CD138 and lambda. Soft tissue extramedullary plasmacytoma (SEP) represents approximately 3% of all plasma cell neoplasm.

**Primary lymphoma of lung**

We had a single case of primary non – Hodgkin's lymphoma in a 32 year old female patient. Cytology showed monotonous sheets of lymphoid cells. Cell block and IHC confirmation was not available for this case. Needle core biopsy and IHC was performed at a later date showed diagnosis of diffuse large B-cell lymphoma.

In study of 24 cases by Jung Han Kim *et al*, there were 13 patients with MALT lymphoma and two with MALT lymphoma accompanied by large B-cell lymphoma, seven with diffuse large B-cell lymphoma and two with anaplastic large cell lymphoma.

**Conclusion**

Fine needle aspiration cytology under the guidance of ultrasound or CT scan can be applied in the diagnosis of lung tumours. Clinical and radiological findings are a must in giving an accurate diagnosis on cytology. FNAC also reduces the time for diagnosis, less complications and also helps in initiating the line of treatment. It is rapid, safe diagnostic modality in lung space occupying lesions. FNAC sample in addition can also be used for cell block study and other ancillary studies like immunohistochemistry and molecular tests. FNAC has a vital role in early diagnosis of lung tumours which helps the clinician in planning the proper line of treatment like chemotherapy or targeted therapy in cases of adenocarcinoma.

Combined cytomorphology, cell block diagnosis and Immunohistochemistry diagnosis helps in subtyping of primary lung carcinoma which is necessary for therapeutic management of patients.

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