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Research Article

# A Detailed Study of Seventy Cases of Non-Small Cell Carcinoma of Lung, Immunohistochemical Study and its Histo-Cytological Correlation

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## Abstract

**Background:** Lung cancer is most common cancer and one of the leading causes of death due to cancer. With newer 2015 WHO Classification, immunohistochemistry (IHC) is now recommended, when possible, not only for small biopsies/cytology, but also for resected specimens.

**Aims and Objectives:** The main aims of this study is, to subtype non-small cell lung carcinoma (NSCLC) on fine needle aspiration (FNA) and small biopsy specimen, using a minimal antibody panel, to evaluate the role of immune histochemical markers for accurate diagnosis of NSCLC & to correlate sensitivity of FNA and small biopsy specimen to sub classify NSCLC.

**Materials and Methods:** It is a prospective study of total number of seventy cases of non-small cell lung carcinoma (NSCLC), diagnosed on immunohistochemistry (IHC) for the duration of January 2013 to February 2015.

Patients' clinical details, fine needle aspiration cytology reports, biopsy reports and IHC reports were used for the data.

**Results:** The study results showed that, by using limited panel of IHC (TTF-1, P63, and Desmoglein 3), differentiation between adenocarcinoma and squamous cell carcinoma is possible.

Sensitivity of sub typing adenocarcinoma and squamous cell carcinoma are 88% and 73% respectively.

Sensitivity of sub typing adenocarcinoma and squamous cell carcinoma on biopsy are 85% and 70%.

**Conclusion:** Sensitivity of sub typing adenocarcinoma and squamous cell carcinoma on biopsy are 82% and 100%, when only cytology and histopathological examination were taken into account.

Sensitivity and accuracy of sub typing NSCLC are high with both guided aspiration and biopsy specimens.

With the use of IHC, rare tumour like sarcomatoid carcinoma was also diagnosed. Hence, immunohistochemistry represents a complementary tool for the routine diagnosis of lung cancer and for the identification of the different histological types and prognostic factors.

***Keywords:*** *Non-Small Cell Lung Carcinoma; Immunohistochemistry; Histo-Cyto Correlation; Statistics*

## Introduction

Lung cancer is most common cancer in the world and one of the leading causes of death due to cancer in both men and women [1,2]. According to recent data the most common subtype of lung carcinoma is adenocarcinoma (ADC) [2,3].

One of the great advances in the past decade in lung cancer diagnosis and treatment, is the concept of personalized medicine, in which therapeutic decisions are based on the specific histological and genetic characteristics of the patient's tumor.

This has given a new importance for pathologists to classify non-small cell lung carcinoma (NSCLC) further into specific pathologic subtypes (e.g., ADC versus squamous cell carcinoma (SSC) as this determines eligibility for certain types of molecular testing and therapeutic strategies.

Discovery that, epidermal growth factor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements are effective targets for EGFR tyrosine kinase inhibitors or ALK inhibitors in patients with advanced lung adenocarcinoma has not only revolutionized therapeutic strategies, but transformed clinical practice for pathologists.

With newer 2015 WHO classification, immunohistochemistry (IHC) is now recommended, whenever possible, not only for small biopsies/cytology, but also for resected specimens. Various IHC panels have been used to maximize the proportion of accurately sub typed non-small cell lung carcinoma (NSCLC).

## Materials and Methods

A prospective study of total number of seventy cases of NSCLC were diagnosed on IHC during this period, for the duration of January 2013 to February 2015. Only cases with fine needle aspiration cytology (FNAC), percutaneous biopsy and IHC were done were included in the study.

Patients' clinical details, FNAC, Biopsy reports and IHC reports were used for the data.

Following set of antibodies were used wherever required:

TTF-1, AE1, CEA, CK7, CK20, Chromogranin, Synaptophysin, p63, Vimentin, Desmoglein 3.

The IHC diagnosis was considered as the final diagnosis and the results of FNAC and biopsy were compared with the IHC diagnosis.

"Compliance with Ethical Standards": we have taken an institutional committee approval for the publication of this manuscript.

## Results

After evaluating total seventy cases of NSCLC, following are the results obtained, The mean age of the sample was 57.4 years with the range of 30 - 84 years. A gender wise examination of the patients' age revealed that the mean age was 58.2 years for the males and 53.8 years for the females.

The peak incidence of lung carcinoma with twenty-seven cases (38.5% of all cases) were seen in age group of 50 - 59 years, followed by 60 - 69 years age group, with twenty two cases (31.5% of all cases).

Majority of the cases (i.e. 81.4%) in the present study were males, with male: female ratio of 4.4:1.

Around seventy percentage of patients in this study were current or ex-smokers. Majority of smoker were men than women. (84.2% versus 15.8%).

Of the total thirty-eight cases of adenocarcinoma, 58% were found to be smokers and of the twenty-three cases of SCC, 91% were smokers.

Of total registered seventy cases, adenocarcinoma was the most common malignancy among all comprising of thirty-eight cases, followed by SCC constituting twenty-three cases. The diagnosis of NSCLC was offered on IHC in four cases and other cases were poorly differentiated carcinoma (03 cases) and sarcomatoid carcinoma (02 cases).

**Cyto-IHC correlation**

| Final diagnosis (n = 70) | Cyto-concordance | Cyto-inconclusive | Cyto-NSCLC | Cyto-Discordance |
|---|---|---|---|---|
| Adenocarcinoma (n = 38) | 29 | 04 | 03 | 02 |
| SCC (n = 23) | 08 | 03 | 04 | 08 |
| NSCLC NOS (n = 04) | 03 | 00 | 00 | 01 |
| Poorly differentiated ca (n = 03) | 00 | 01 | 01 | 01 |
| Sarcomatoid ca (n = 02) | 00 | 01 | 01 | 00 |

***Table 1:*** *Cyto-IHC correlation.*

The cases, in which the diagnosis on cytology correlated with IHC were considered as cyto-concordant and those with a difference in diagnosis were cyto-discordant.

Cyto-concordance was seen in 40 cases. Out of the 38 adenocarcinoma cases, 29 cases were rightly diagnosed on cytology, 03 cases were broadly put under the category of NSCLC on cytology, 04 cases had inadequate material and 02 cases were diagnosed as SCC.

Out of the 23 cases of SCC, 08 cases were rightly diagnosed on cytology, 04 cases were broadly put under the category of NSCLC on cytology, 03 cases had inadequate material, 07 cases were diagnosed as adenocarcinoma and 1 case was diagnosed as poorly differentiated carcinoma.

Out of the four cases of NSCLC in the study, 03 cases were rightly diagnosed on cytology and 01 case was diagnosed as adenocarcinoma. (Out of total 26 cases).

Out of the three cases of poorly differentiated carcinoma, one case was broadly put under the category of NSCLC on cytology, one case had inadequate material and one case was diagnosed as adenocarcinoma.

Out of the two cases of sarcomatoid carcinoma in the study, one case was broadly put under the category of NSCLC on cytology and one case had inadequate material.

Sensitivity of sub typing adenocarcinoma and SCC are 88% and 73% respectively.

**Histo-IHC correlation**

| Final diagnosis (n = 70) | Histo- concordance | Histo-Inconclusive | Histo-NSCLC | Histo- Discordance |
|---|---|---|---|---|
| Adenocarcinoma (n = 38) | 22 | 04 | 09 | 03 |
| SCC (n = 23) | 07 | 03 | 12 | 01 |
| NSCLC NOS (n = 04) | 00 | 01 | 03 | 00 |
| Poorly differentiated ca (n = 03) | 02 | 00 | 00 | 01 |
| Sarcomatoid ca (n = 02) | 00 | 01 | 00 | 01 |

***Table 2:*** *Histo-IHC correlation.*

Those cases in which the diagnosis on biopsy correlated with IHC, were considered as histo-concordant and those with a difference in the diagnosis were histo-discordant.

Histo-concordance was seen in 31 cases. Out of the 38 cases of adenocarcinoma in the study, 22 cases were rightly diagnosed on biopsy, nine cases were broadly put under the category of NSCLC on cytology, four cases which were given two possibilities as diagnosis, two cases were diagnosed as SCC and one case was diagnosed as poorly differentiated carcinoma.

Out of the 23 cases of SCC, 07 cases were rightly diagnosed on biopsy, 12 cases were broadly put under the category of NSCLC on cytology, 03 cases which were given two possibilities as diagnosis and one case was diagnosed as adenocarcinoma.

Out of the four cases of NSCLC, 03 cases were rightly diagnosed on biopsy and one case was given two possibilities.

Out of the 03 cases of poorly differentiated carcinoma, two cases were rightly diagnosed on biopsy and one case was diagnosed as Adenocarcinoma.

Out of the 02 cases of sarcomatoid carcinoma, one case was given two possibilities as diagnosis and one case was given as adenocarcinoma.

Sensitivity of sub typing Adenocarcinoma and SCC on biopsy are 85% and 70%.

**Histo-cyto correlation**

Those cases in which the diagnosis on cytology correlated with biopsy were considered as cyto-concordant and those with a difference in the diagnosis were cyto-discordant.

Cyto-concordance was seen in 34 cases. Out of the 24 cases diagnosed as adenocarcinoma on biopsy, 18 cases were diagnosed similarly on cytology, one case was broadly put under the category of NSCLC on cytology, four cases had inadequate material and one case was diagnosed as SCC.

Out of the 10 cases of SCC diagnosed on biopsy, seven cases were diagnosed similarly on cytology, one case was broadly put under the category of NSCLC on cytology and two cases were diagnosed as adenocarcinoma.

Out of the 25 cases of NSCLC diagnosed on biopsy, 07 cases were diagnosed similarly on biopsy, 02 cases had inadequate material & 16 cases were diagnosed either as adenocarcinoma or SCC.

Out of the 08 cases of poorly differentiated carcinoma diagnosed on biopsy, 02 cases were diagnosed similarly on cytology, 02 cases had inadequate material, 02 cases were diagnosed as NSCLC and 02 cases were diagnosed as adenocarcinoma on cytology.

Sensitivity of sub typing of adenocarcinoma and SCC on biopsy are 82% and 100% respectively, when only cytology and Histopathological examination were taken into account (Table 3).

| Histological type | TTF-1 (%) | CEA (%) | CK7 (%) | DESMOGLEI 3 (%) | P63 (%) | AE1 (%) |
|---|---|---|---|---|---|---|
| Adenocarcinoma | 74 | 74 | 84 | - | - | - |
| Squamous cell carcinoma | - | 22 | 57 | 61 | 61 | - |
| NSCLC NOS type | - | 25 | 100 | - | - | - |
| Poorly differentiated ca | - | - | - | - | - | 100 |
| Sarcomatoid carcinoma | - | - | - | - | - | 100 |

***Table 3:*** *Immunohistochemical profile of the various types of NSCLC.*

In our study, out of the 38 cases of Adenocarcinoma, 28 cases showed Thyroid Transcription Factor-1 (TTF-1) positivity, 25 cases showed TTF-1, Cytokeratin 7 (CK7)/ Carcinoembryonic Antigen (CEA) positivity and 10 cases showed TTF-1 negativity, but CK7/CEA

positivity. Only one case showed Tumour Protein 63 (P63) positivity in adenocarcinoma. We found only one case of metastatic carcinoma, where primary site was prostate. Another one case showed positivity of TTF-1, CK7, CEA, AE1 (Cytokeratin), Chromogranin and synaptophysin in two different cell population, which was given diagnosis as adenocarcinoma with neuroendocrine carcinoma composite.

Out of 23 cases of SCC, 14 cases showed P63 positivity, among which 05 cases showed both P63 and Desmoglein 3 positivity and 09 cases showed P63 negativity, but Desmoglein 3 positivity. The CK7 marker showed positivity in 13 cases, whereas CEA showed positivity in 05 cases.

Out of 04 cases of NSCLC NOS (Not Other Specified) type, all showed positivity of CK7, AE1 (1 case) and CEA (1 case).

Three cases showed only AE1 positivity and hence were categorised as poorly differentiated carcinoma, and further typing was not possible.

Both cases of sarcomatoid carcinoma showed positivity of Vimentin and AE1, however negative for TTF-1 and CK7.

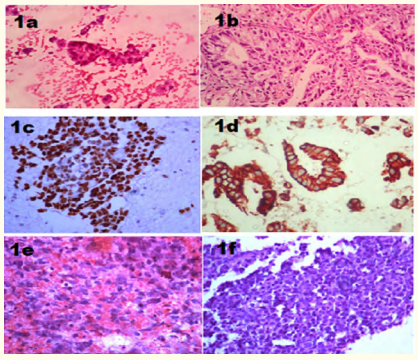


***Figure 1:*** *Adenocarcinoma FNAC: (1a) Cluster of malignant cells with pale eosinophilic cytoplasm & vesicular chromatin with eccentric nuclei (pap x400), Biopsy: (1b) malignant cells in glandular pattern, with vesicular chromatin and prominent nucleoli and few showing vacuolated cytoplasm. (H&E, x100, x400) IHC: (1c) TTF- 1 positive, (1d) CK7 positive; Poorly differentiated carcinoma, FNAC: (1e) malignant cells scattered with haemorrhagic background. Biopsy: (1f) malignant cells in clusters with poor differentiation.*

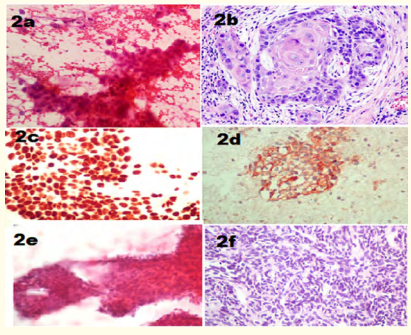


***Figure 2:*** *SCC FNAC: (2a) malignant tumour cells in cluster non keratinising, Biopsy: (2b) malignant squamous cells showing keratinisation and intercellular bridging. IHC: (2c) P63 positive, (2d) Desmoglein 3 positive. Sarcomatoid carcinoma, FNAC: (2e) malignant cells in sheets, spindle in shape showing nuclear atypia, Biopsy: (2f) malignant spindle cells in sheet.*

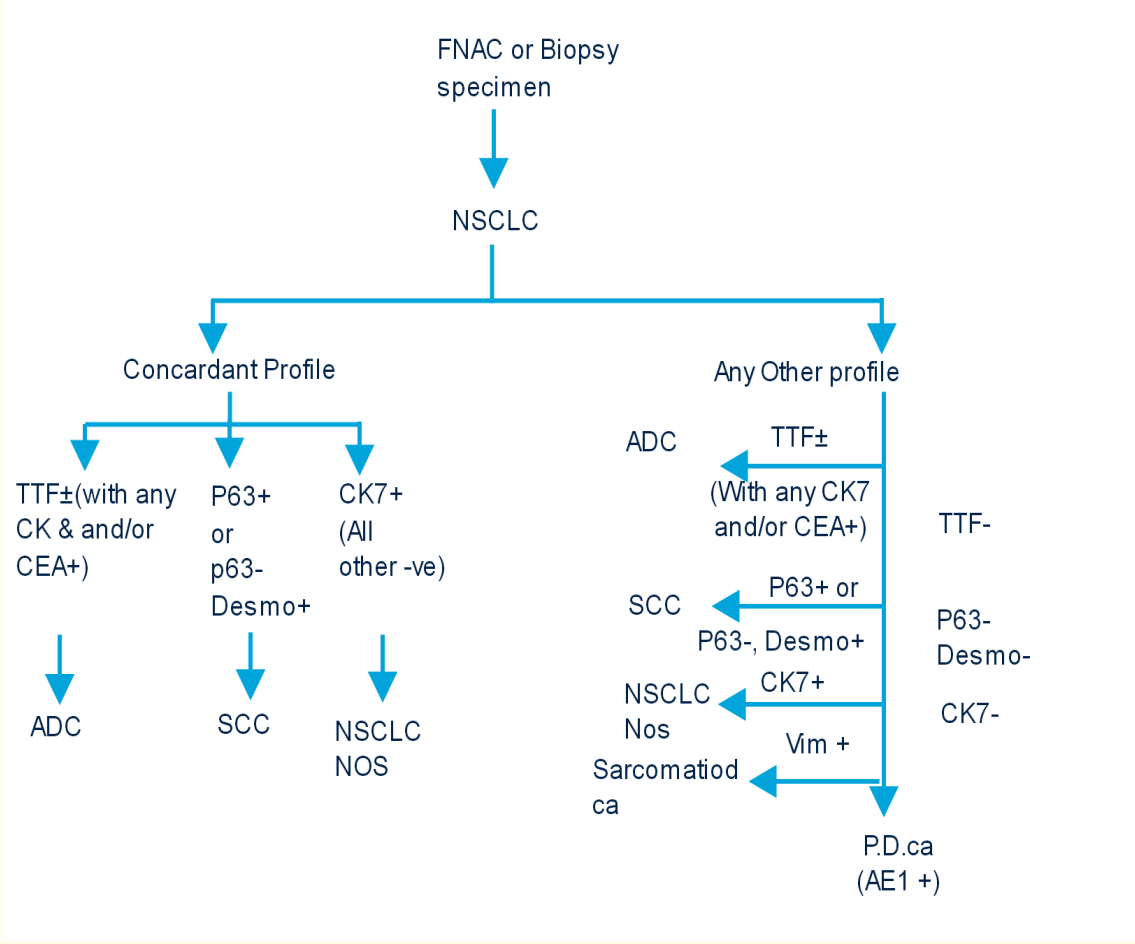


***Figure 4:*** *Diagnostic algorithm based on the different immunoprofile combinations in 70 cases originally diagnosed as NSCLC is shown in the figure above.*

## Discussion

The study was undertaken at our institute, a tertiary care hospital and referral centre for patients suspected lung malignancy for further evaluation and treatment.

The overall mean age in our patients was 57.4 years. (58.21 years in males and 53.84 years in females). Most of our study belongs to the patients of age group 50 - 59 years. Koul., *et al*. study [7] reported mean age for men as 58.28 years and for females as 53.26 years, whereas in most of the other reported studies from India, the average age lung cancer is approximately 55 years. This is comparable with other studies like Sheikh., *et al* [8].

There was a clear male predominance with a male-female ratio of 4.4:1. This finding is comparable to other studies, as reported by other authors like Koul., *et al.* [7] & Sheikh., *et al*. [8] Majority of NSCLC cases were males in our study. Out of all, 38 cases were adenocarci-

noma & 23 cases of SCC. Out of all the remaining cases, four cases were NSCLC NOS type, three cases were poorly differentiated carcinoma and two cases were sarcomatoid carcinoma.

Women were more of younger age group than men in all lung carcinoma cases. This observation was seen for women and men both, when histological type was taken into account. In particular, adenocarcinoma was diagnosed in younger age group in both women and in men. This relationship has been reported previously by Radzikowska., *et al* [9].

The smoker to nonsmoker ratio in the present study was 2.2: 1. The Ratio of smoker to non smoker observed in our study correlates well with that of Sheikh., *et al* [8].

Out of all the cases of NSCLC, the most common subtype was adenocarcinoma (54.3%), followed by SCC (32.8%). The incidence of adenocarcinoma was reported to be significantly higher than that of SCC in studies conducted by Mondal., *et al*. [5], where as in certain other national and international studies, prevalence of SCC was more than adenocarcinoma [8]. Though SCC was used to be considered the commonest lung tumour, studies indicate that adenocarcinoma may have overtaken it in incidence [4].

This study demonstrated that a limited panel of IHC markers may reliably refine NSCLC histotyping or, at least, provide the most likely differentiation lineage of poorly differentiated lung cancers.

The proposed antibody panel includes IHC markers that are well-known, commercially available, inexpensive, commonly used, standardized in any pathology laboratory and easily applicable to either bronchial biopsies (Table 4).

| Marker | Sensitivity (%) | Specificity (%) | PPV *(%) | NPV** (%) |
|---|---|---|---|---|
| TTF-1 | 74 | 100 | 100 | 70 |
| P63 | 61 | 92 | 88 | 73 |
| CK7 | 82 | 100 | 100 | 27 |
| CEA | 67 | 67 | 97 | 11 |
| Deamoglein3 | 82 | 100 | 100 | 75 |
| Vimentin | 100 | 100 | 100 | 0 |

**PPV – Positive predictive value **NPV – Negative predictive value*

***Table 4:*** *Statistical analysis of various markers of IHC.*

A panel of immunophenotypic markers were able to address the correct tumor histotype in the majority of the investigated cases. We observed that a similar panel of markers, which included TTF1, p63, CEA, and CK7, were helpful to reduce the percentage of unclassified cases, suggesting the most probable histotype of tumors.

Sensitivity of cytology of sub typing, adenocarcinoma and SCC are 88% and 73% which are same as observed in Nizzoli., *et al.* study [10].

Out of two cases of adenocarcinoma, one case was misdiagnosed as SCC due to paucicellularity and one case was misdiagnosed as SCC due to lack of differentiation.

Eight cases of SCC were misdiagnosed as Adenocarcinoma or poorly differentiated carcinoma, due to the poor differentiation of neoplastic cells and presence of necrosis. In particular, nonkeratinizing poorly differentiated squamous cell carcinoma is subject to misclassification by FNAC [6].

One case of NSCLC was over diagnosed as adenocarcinoma on FNA, but then after final study of IHC, it showed only CK7 positivity, hence it was given diagnosis as NSCLC NOS type. One case of poorly differentiated carcinoma was diagnosed as adenocarcinoma on FNA, but it showed only AE1 positivity, hence final diagnosis was given as poorly differentiated carcinoma.

Sensitivity of biopsy, in sub typing adenocarcinoma and SCC are 85% and 70% respectively, which are same as observed in various study like Burnett., *et al* [12].

We found some of the limiting factors for the interpretation and accurate classification in Biopsy specimens. Out of the three cases of adenocarcinoma, the strongest predictors for difficulty in sub typing were, poor differentiation of the tumour, where distinguishing morphologic features were not apparent [6].

One case of SCC was diagnosed as poorly differentiated carcinoma due to non keratinisation and poor differentiation. Despite these limitations, with the help of morphology and immunohistochemistry, we observed high concordance, while sub classifying the NSCLC.

One case of sarcomatoid carcinoma was misdiagnosed as adenocarcinoma on biopsy, but after IHC it showed AE1 and Vimentin positivity, hence it was given diagnosis as sarcomatoid carcinoma and one case of poorly differentiated carcinoma, which was misdiagnosed as adenocarcinoma, but after when it showed only AE1 positivity, it was given final diagnosis as poorly differentiated carcinoma.

Sensitivity of sub typing adenocarcinoma and SCC on biopsy are 82% and 100% respectively, when only cytology and histopathological examination were taken into account. These results are similar to observation seen in the study like A. Hasanovic., *et al* [13].

In the present study, TTF1 was the most specific marker of adenocarcinoma, although its sensitivity is only 74%, well comparable to the results reported in the study like Jagirdar., *et al.* [14] This marker has been largely used in biopsy or cytological series, because the nuclear reactivity is readily apparent even in poorly cellular samples and its specificity is high, similar to observation seen in Loo *et al.* study [11].

In agreement with previously published reports like Pelosi., *et al.* [15], the majority of SCC had a diffuse and strong P63 nuclear expression, but one case of adenocarcinoma also displayed some P63 reactivity. In the absence of TTF1, CK7 co expression confirmed adenocarcinoma with high specificity (100%), supporting its role as an additional adenocarcinoma marker [16].

Co expression of Desmoglein-3 and P63 supported a diagnosis of SCC, and proved them highly specific for SCC (SP = 100). Desmoglein 3 was never seen in association with TTF1.

So, overall our data shows that, appropriate panels of IHC markers allow the correct classification of cases, which were originally diagnosed as NSCCL on the basis of morphology alone. When the immunoprofile fulfilled the expected criteria for glandular and squamous cell differentiation, the final tumor classification on biopsy was anticipated with a high rate of sensitivity and specificity. In the case of a heterogeneous immunoprofile, it was demonstrated that TTF1 is the most robust predictor of adenocarcinoma and truncated p63 is the most robust predictor of SCC when TTF1 was negative. CK7 and CEA markers are preferentially (but not exclusively) expressed in adenocarcinoma.

Desmoglein-3 is useful specifically for new candidates, favoring a diagnosis of SCC. These findings, combined with other recent data on biopsy and cytology samples like Kim DH et al.[17] indicate that, correct lung cancer histotype assessment can be obtained in a large fraction of cases, even in those cases with limited amount of neoplastic cells.

Sensitivity and accuracy of sub typing NSCLC are high, with both guided aspiration and biopsy specimens.

In addition, the current study indicates that the percentage of indeterminate diagnoses (NSCLC-NOS) can be reduced to 10%-15%, even in analysis of poorly differentiated carcinoma case series. Thus it is confirmed to say that immunoprofiling plays a definitive role in NSCLC to support histology-driven selection of systemic therapy [18].

Now, lung cancer therapy is becoming personalized for individual patients, based on the histological cell type and subtypes of lung cancer (adenocarcinoma versus SCC). So, the pathologist's role and approach to lung cancer diagnosis in small biopsies and cytology has been affected dramatically. Differentiation between Adenocarcinoma and SCC is possible using limited panel of IHC (TTF-1, P63, and Desmoglein 3). Rare tumour like sarcomatoid carcinoma was diagnosed on IHC.

Hence, immunohistochemistry represents an important complementary tool for the routine diagnosis of lung cancer, for the identification of the different histological types and prognostic factors.

**Disclosure of potential conflicts of interest:** Nil

**Informed consent:** we have taken an informed consent from the all participants of the study.

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