Original Article

Fine-needle aspiration cytology in the diagnosis and typing of lung carcinomas

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ABSTRACT

Background: New developments in thoracic oncology have challenged the way pathologists approach pulmonary carcinoma. Categorization as small cell or nonsmall cell is no longer adequate, and a distinction between adenocarcinoma (ADC) and squamous cell carcinoma (SqCC) is necessary for specific therapy. **Aim:** To determine the diagnostic accuracy of fine-needle aspiration cytology (FNAC) in the diagnosis and subtyping of primary lung carcinoma and reliability of the cytological parameters. **Settings, Design, and Subjects and Methods:** Histologically confirmed lung carcinomas diagnosed on FNAC were evaluated for various cytological parameters by three pathologists, and data were statistically analyzed. **Results:** A total of 39 cases (22 ADCs, 9 SqCCs, 6 small cell carcinomas and 2 poorly differentiated carcinomas) were studied. The features frequently observed in small cell carcinoma included small cell size (83%), scant cytoplasm (83%), nuclear molding (100%), and granular chromatin with nuclear streaks (67%) in the background. SqCCs showed single cells (66%), distinct cell borders (44%), abundant homogenous cytoplasm (78%), hyperchromatic nuclei (56%), and keratinous debris (22%) whereas ADCs showed glands (45%), three-dimensional (68%) and papillary (23%) clusters, indistinct cell borders (77%), cytoplasmic vacuolation (55%), vesicular chromatin (45%), and mucinous (23%) background. There was a statistically significant agreement between cytologic and histologic diagnosis ($P < 0.001$) with a very good level of agreement ($\kappa = 0.9$). The overall percentage of agreement was 97%, with substantial agreement between the observers ($\kappa = 0.73$). Cell size, cohesion, cell borders, molding, chromatin texture, and cytoplasmic characteristics were significantly associated with the diagnosis. **Conclusion:** Cytologic subtyping of lung carcinoma is feasible and reasonably accurate.

Key words: Adenocarcinoma, cytology, fine-needle aspiration, lung carcinoma, small cell carcinoma

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in men and women.[1] Cytology is a major, and sometimes, the only diagnostic modality used in the initial evaluation of patients with lung cancer. An early, accurate diagnosis is of paramount importance for initiating specific therapy. Most patients with lung cancer present with clinically advanced disease and therefore are not candidates for surgery with curative intent but are rather treated with systemic therapy.

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In the age of personalized medicine, cytological material from fine-needle aspiration cytology (FNAC) may be the only available diagnostic specimen, and the only material available for molecular studies, necessary for current therapeutic decision making.[2] New recommendations for screening of high-risk population coupled with the ongoing development of minimally invasive techniques and procedures for sampling lung lesions will most likely further increase the need for accurate diagnosis and molecular characterization of malignant tumors on small biopsy/FNAC specimens. These advances in the understanding of molecular mechanisms underlying lung cancer and the development of new targeted therapies challenge the traditional diagnostic dichotomization between small cell

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lung carcinomas (SCLC) and non-SCLC (NSCLC) and prompt a more specific characterization of NSCLC into squamous or adenocarcinoma (ADC) category.[3]

Traditionally, NSCLC sub-classification has been based on morphologic assessment of routine hematoxylin and eosin (H and E)-stained histological specimens. Because cytology specimens, such as FNAC, differ in the preparation and technique from traditional histology, and the accuracy of subtyping these specimens has been challenged, there is considerable evidence supporting the utility of cytology in both subtyping NSCLC and providing material for predictive and prognostic studies so far.[4] The present study aimed at determining the diagnostic accuracy of FNAC in the diagnosis, subtyping of primary lung carcinoma, checking the reliability of certain cytological parameters and also to recognize the source of discrepancy.

SUBJECTS AND METHODS

By retrospective review, FNAC (imaging-guided transthoracic/transbronchial) slides of those patients who were diagnosed as having primary carcinoma of lung on histopathology were retrieved from the files of the cytology laboratory between January 2006 and June 2011. All the FNAC slides (including H and E, Pap, and Modified Giemsa stained slides) belonging to each of these cases were independently reviewed by three pathologists for the presence or absence of cytomorphologic features mentioned below. The 2004 WHO classification of lung tumors was considered for classification of the cases. Because the focus of this study was to determine the accuracy of FNAC in tumor diagnosis and subtyping, only those cases with unequivocal malignant features were considered and hypocellular/"suspicious" or "atypical" cases were excluded. Metastatic tumors were also excluded based on both clinical workup and immunohistochemistry. A final diagnosis was offered based on the predominant features favoring a particular entity. The discrepant cases were reviewed, and a final consensus diagnosis was reached. Also, the reason for such a discrepancy was checked. The various cytomorphological features that were analyzed include: (a) Cell type: Oval, round, cylindrical, spindle, small, large, pleomorphic, multinucleated, and presence of ghost cells; (b) cytoplasmic features: Scanty, abundant, microvacuolated or macrovacuolated, clear, eosinophilic granular, glassy or keratinized, and laminated (due to cytoplasmic tonofilaments), well demarcated; (c) nuclear characteristics: Size and shape as for cell type; hyperchromatic with coarse or finely granular chromatin, pale or vesicular, and pyknotic nuclei. The nucleoli, when present, were recorded as single or multiple, and small prominent. Special attention was paid to the presence of nuclear cytoplasmic inclusions and grooving that were only regarded as a feature in neoplastic cells showing little or no pleomorphism. Cellular arrangement was recorded as: Single; clusters; sheets; glands; balls; branching or papillary structures; overlapping; monolayered; tight or loose. The presence of background keratin and mucus was also recorded. Univariate analysis was performed for each of the criteria with calculation of sensitivity, specificity, and the Fisher exact two-sided test *P* value. Statistical analyses of categorical data were performed using a two-tailed Fisher exact test or χ^2 test as appropriate. A $P = 0.05$ was considered as statistically significant. Fleiss kappa statistic was computed to examine agreement between the consensus fine-needle aspiration (FNA) diagnosis and the final histopathological diagnosis and also the agreement between the three reviewing pathologists (observer variation).

RESULTS

A total of 39 cases were included in the study that included 25 (64.1%) men and 14 women (35.9%) with their age ranging from 26 to 90 years (median - 55 years). On FNAC, 22 cases were classified as ADC, seven cases as squamous cell carcinoma (SqCC) and nine cases as small cell carcinoma [Table 1]. On histopathology, a total of 22 ADCs, nine SqCCs, six small cell carcinomas, and two poorly differentiated carcinomas were diagnosed [Table 1]. The architectural parameters, cellular and nuclear details, and background and additional features studied are indicated in Tables 2-5; the microscopy is depicted in Figures 1–8. The significant features observed in small cell carcinoma included small cell size (71%) (wherein the cells were predominantly small), scant cytoplasm (86%), nuclear molding (100%) and granular/stippled chromatin (86%), inconspicuous nucleoli (86%) with nuclear streaks (71%) in the background. Among SqCCs, the significant features included distinct cell borders (70%), abundant homogenous cytoplasm (80%), hyperchromatic nuclei (60%), and keratinous debris (20%). The statistically significant findings among ADCs included glands/acinar arrangement, three-dimensional and papillary clusters, indistinct cell borders, cytoplasmic vacuolation, vesicular chromatin, and mucinous background.

The exact correlation is depicted in Table 6. Two cases of ADCs were wrongly typed, one as small cell carcinoma and other as SqCC on FNAC. Overall accuracy of FNAC in diagnosing these three malignancies (that is adeno, squamous, and small cell carcinomas) was about 97% with accuracy of recognizing squamous cell and small cell carcinoma reaching up to 100%. The accuracy of properly typing ADC was comparatively low (91%). There was a statistically significant agreement between cytologic and histologic diagnosis ($P < 0.001$) with a very good level of agreement, $\kappa = 0.9$ with overall percentage of agreement

Table 1: The distribution of cases on FNAC and the final histopathological diagnosis

Diagnosis HPE	FNAC			
	ADC	SqCC	Small cell carcinoma	Total
ADC	18	1	3	22
SqCC	2	6	1	9
Small cell carcinoma	1	-	5	6
Poorly differentiated carcinoma	2	-	-	2
Total	23	7	9	

FNAC: Fine-needle aspiration cytology, HPE: Histopathological examination, SqCC: Squamous cell carcinoma, ADC: Adenocarcinoma

Table 2: The cytoarchitectural features

Architectural parameters	ADC (*n*=22) (%)	SqCC (*n*=10) (%)	Small cell carcinoma (*n*=7) (%)	*P*
Cellularity				
Low	3 (14)	1 (10)	1 (14)	0.6
Moderate	10 (45)	8 (80)	3 (43)	
High	9 (41)	1 (10)	3 (43)	
Arrangement				
Clusters	20 (91)	10 (100)	5 (71)	0.5
Singles	11 (50)	2 (20)	5 (71)	0.2
Acini	10 (45)	0	1 (14)	0.03
Papillary cluster	5 (23)	0	1 (14)	0.04
Cell layers				
Three-dimensional	13 (59)	3 (30)	1 (14)	0.2
Monolayered	10 (45)	6 (60)	6 (86)	
Outline				
Smooth	12 (55)	5 (50)	2 (29)	0.4
Irregular	10 (45)	5 (50)	5 (71)	0.2
Cohesion				
Discohesive	5 (23)	2 (20)	4 (57)	0.005
Tight	17 (77)	8 (80)	3 (43)	

SqCC: Squamous cell carcinoma, ADC: Adenocarcinoma

Table 3: The cytological characters of cells in malignancies

	ADC (*n*=22) (%)	SqCC (*n*=10) (%)	Small cell carcinoma (*n*=7) (%)	*P*
Pleomorphism				
Mild	1 (5)	0	1 (14)	0.4
Moderate	14 (64)	7 (70)	5 (71)	
Marked	7 (32)	3 (30)	1 (14)	
Cell size				
Small	0	0	5 (71)	0.045
Medium	16 (73)	9 (90)	2 (29)	
Large	6 (27)	1 (10)	0	
Cell shape				
Round/oval	12 (55)	3 (30)	3 (43)	0.4
Polygonal	12 (55)	9 (90)	4 (57)	0.09
Spindle	2 (9)	3 (30)	3 (43)	0.02
Cell margins				
Distinct	5 (23)	7 (70)	0	0.04
Indistinct	17 (77)	3 (30)	7 (100)	
Cytoplasm				
Scant	3 (14)	1 (10)	6 (86)	0.004
Abundant	15 (68)	8 (80)	1 (14)	
Vacuolated	11 (50)	1 (10)	0	
Homogenous	8 (36)	8 (80)	1 (14)	

SqCC: Squamous cell carcinoma, ADC: Adenocarcinoma

of 97%. Fleiss kappa statistic was computed to examine agreement between three raters. There was substantial

Table 4: The nuclear characteristics of cells in malignancies

	ADC (*n*=22) (%)	SqCC (*n*=10) (%)	Small cell carcinoma (*n*=7) (%)	*P*
Nuclear borders				
Regular	13 (59)	5 (50)	5 (71)	0.12
Irregular	9 (41)	5 (50)	2 (29)	
Nuclear molding	3 (14)	1 (10)	7 (100)	0.01
Chromatin				
Coarse	9 (41)	4 (40)	1 (14)	0.02
Stippled	1 (5)	0	6 (86)	
Vesicular	10 (45)	3 (30)	0	
Hyperchromatic	2 (9)	6 (60)	0	
Nucleoli				
Inconspicuous	7 (32)	4 (40)	6 (86)	0.2
Conspicuous	11 (50)	5 (50)	1 (14)	
Macronucleoli	4 (18)	1 (10)	0	

SqCC: Squamous cell carcinoma, ADC: Adenocarcinoma

Table 5: The other features of these malignant cells

	ADC (%)	SqCC (%)	Small cell carcinoma (%)	*P*
Background				
Necrosis	10 (45)	6 (60)	6 (86)	0.1
Nuclear streaks	1 (5)	0	5 (71)	0.001
Mucin	6 (27)	0	0	0.002
Clean	6 (27)	4 (40)	1 (14)	0.06
Add findings				
Nuclear grooves	5 (22.7)	0	0	
Keratin debris	0	2 (20)	0	
Cell wrapping	1 (4.5)	0	0	
Bare nuclei	0	0	1 (14)	

SqCC: Squamous cell carcinoma, ADC: Adenocarcinoma

Table 6: Accuracy of FNAC diagnosis in comparison with the histopathology

Histopathology	FNAC			
	ADC (%)	SqCC (%)	Small cell carcinoma (%)	Total
ADC	21 (91)	1	1	23
SqCC	-	9 (100)	-	9
Small cell carcinoma	-	-	6 (100)	6
Poorly differentiated carcinoma	1	-	-	1
Total	22	10	7	39

SqCC: Squamous cell carcinoma, ADC: Adenocarcinoma, FNAC: Fine-needle aspiration cytology

agreement between the raters $\kappa = 0.73$. The agreement was better between two of the pathologists (senior pathologists). Cell size, cohesion, cell borders, molding, chromatin texture, and cytoplasmic characteristics were significantly associated with the diagnosis.

DISCUSSION

Bronchopulmonary cancer is one of the most widespread malignant diseases, which has a continuous increase of incidence in most of the countries and has been the main cause of death in men. Establishing the type of pulmonary

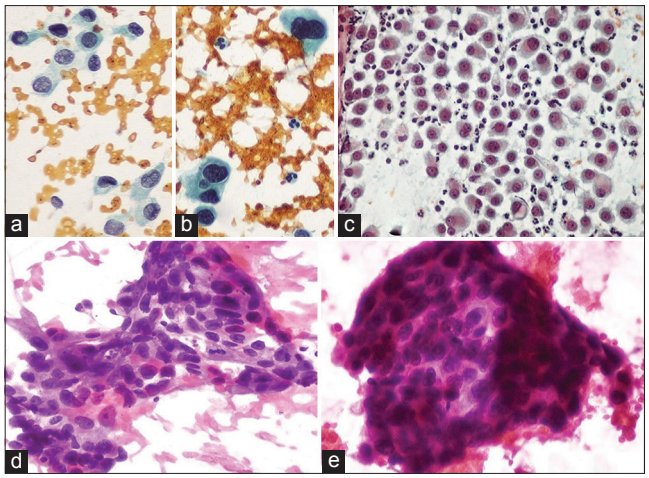

Figure 1: Microphotographs showing the cytoarchitectural details of adenocarcinoma. (a-c) Cells in singles Pap stain, (d and e) Cells in cohesive clusters H and E stain

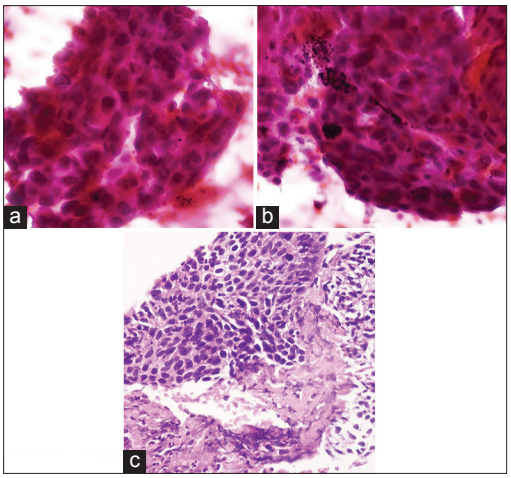

Figure 2: Microphotographs showing the architectural details of squamous cell carcinoma. (a and b) H and E stain of cytological smears showing relatively cohesive clusters. (c) Histopathological section of the corresponding squamous cell carcinoma (H and E, ×100)

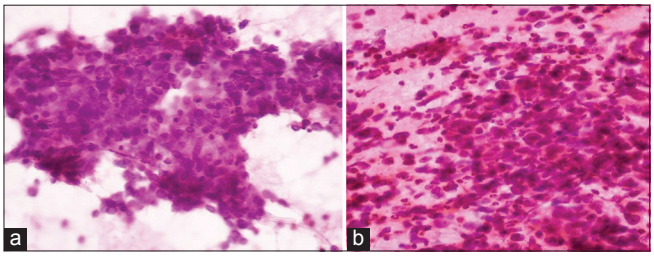

Figure 3: Microphotographs showing the cytoarchitectural details of Small cell carcinoma. (a) Relatively cohesive clusters (H and E). (b) Discohesive clusters and single cells with bare nuclei

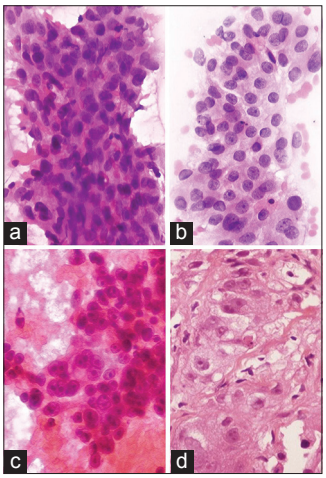

Figure 5: Microphotograph showing the nuclear characters of the cells in adenocarcinoma. Note the relatively finer nature of the chromatin with inconspicuous (a) to small (b) to large/macronucleoli (c). (d) The histopathological section of the lesion with macronucleoli

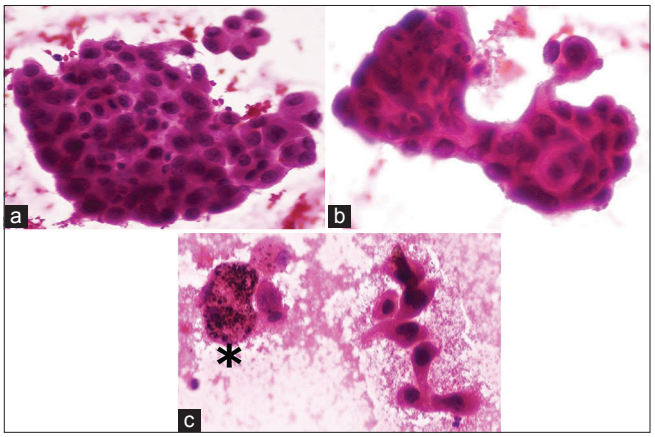

Figure 4: Microphotographs (a to c) showing the cytoplasmic nature and cell membrane characters of the cells in squamous cell carcinoma. Note the distinct cell borders and homogenous cytoplasm with coarse chromatin of the nucleus. Figure c also shows an alveolar macrophage (asterix) and elongated/curved squamoid cells

carcinoma is very important especially for the therapy and the prognosis of the disease, which also depends on the grade of cellular differentiation.[5] The current classification of lung cancer recognizes four major histological subtypes, namely, SqCC, ADC, large-cell carcinoma, and SCLC. The two essential requirements for pathologic specimens in the era of personalized therapies for NSCLC are accurate subtyping as ADC versus SqCC. Approximately, 60% of patients with NSCLC present with unresectable stage IIIB or IV disease, where the only pathologic material guiding systemic therapy may be small biopsy or cytology specimens.[6,7] FNAC has become recognized as a safe and effective diagnostic tool, as a result of improved aspiration tools and techniques, better control of complications, and increased experience of cytopathologists in interpreting aspirate specimens. In recent years, FNAC has been increasingly used for establishing the diagnosis of lung cancer and classifying the specific tumor type. Also, ultrasound-assisted FNA is becoming the method of choice in all patients with a high clinical probability of lung carcinoma.[8] Thus, FNAC in many cases is the only diagnostic specimen available for guiding therapeutic decisions. Also, on many occasions, the morphology

may be distorted on a small biopsy specimen because of extensive crush artifact. In this setting, cytology has an edge over histology because of better preservation and fewer artifacts. Also, due to immediate fixation, cytology provides greater nuclear and cytoplasmic resolution than histology. FNAC is increasingly used for establishing the diagnosis and classification of lung cancer. Also, FNAC can provide significant prognostic information to clinicians managing patients with pulmonary carcinoma. Correct cytological typing of lung cancer is important in clinical management, and it is generally accepted that the cell type diagnosed from cytology material will be an accurate reflection of the main tumor.[9] However, the performance characteristics of cytology in lung cancer diagnosis and subtyping are not well-established. This has made us to take the study interestingly. In our study, FNAC diagnosis agreed with the final diagnosis in 97% of cases overall; this accuracy figure reached 100% for squamous cell and small cell carcinomas, but only 91% for ADC as indicated in Table 6. Published reports reveal that the sensitivity of FNAC for the diagnosis of lung cancer ranged from 56% to 90%.[10] In previous studies, there was a wide-range of cytohistological agreement in nonsmall cell carcinomas of the lung, from 72% to 100% for SqCC, 29% to 100% for ADC.[11-18] Table 7 depicts the comparison of the accuracy of cytological typing in some of the studies.[5,7-10,15,19-21]

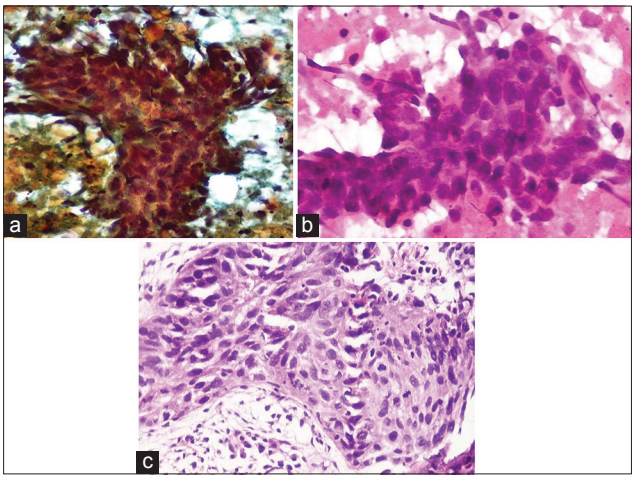

Figure 6: Microphotograph showing the nuclear characters of the cells in Squamous cell carcinoma. Figure a and b: Note the coarse hyperchromatic nature of chromatin with inconspicuous to small nucleoli. Figure c shows the histopathology of the squamous cell carcinoma

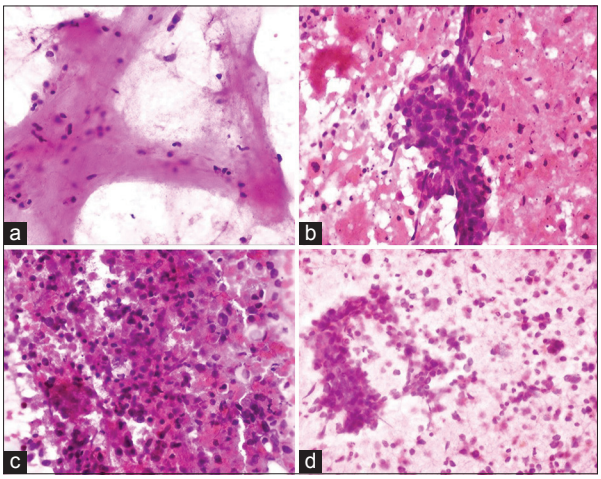

Figure 8: Microphotograph showing the background characters. (a) The mucinous background observed in adenocarcinoma. (b) The keratinous background of squamous cell carcinoma. (c) A necrotic background and (d) The bare nuclei and nuclear streaking in small cell carcinoma

In general, the important cytological characters of ADC on FNAC are cohesive clusters of cells with round, polygonal cells arranged in the form of glandular/papillaroid and three-dimensional structures. They generally showed an indistinct cell borders with abundant vacuolar/foamy cytoplasm. The nuclei are either vesicular or hyperchromatic (depending on the degree, usually vesicular) with irregular nuclear membrane prominent nucleoli. Many nuclei in addition showed nuclear grooves. The background can vary from clean to necrosis; however, extracellular mucin may be seen.[22] SqCCs showed cohesive

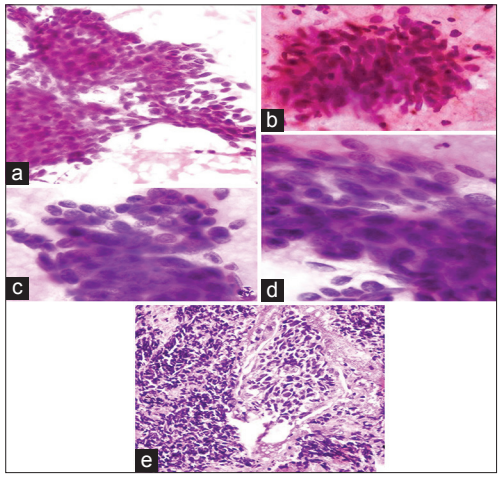

Figure 7: Microphotograph showing the nuclear characters of the cells in Small cell carcinoma. (a-c) Note the high nuclear/cytoplasmic ratio, scant delicate basophilic cytoplasm (H and E). (d and e) Also shows a regular nuclear border with a stippled chromatin and inconspicuous nucleoli. Nuclear molding can be easily made out. (d) The corresponding histopathology (H and E, ×100)

Table 7: The comparison of findings (in percentage) across various studies

Authors	SqCC (%)	Small cell carcinoma (%)	ADC (%)
Payne *et al.*[15]	93	100	50
Rudd *et al.*[5]	88	100	98
Matsuda *et al.*[9]	93.9	91.3	77.3
Colquhoun *et al.*[19]	80		85
Cataluña *et al.*[10]	89.5	77.8	86.4
Diacon *et al.*[8]	95	88	95
Rekhtman *et al.*[7]	74		93
Nizzoli *et al.*[20]	100		82
Das *et al.*[21]	96.5	100	100
Present study	100	100	91

SqCC: Squamous cell carcinoma, ADC: Adenocarcinoma

and discohesive clusters with polygonal cells with distinct cell borders having homogenous/orangeophilic cytoplasm. Spindle cells can also be observed. The nuclei are irregular to smooth with coarse chromatin. The background is generally necrotic, and keratin may be observed in well-differentiated forms.[23] Small cell carcinoma exhibits clusters and monolayered sheets having a smooth outline. The cells are small to medium with a high nuclear/cytoplasmic ratio, scant delicate basophilic cytoplasm. The oval nuclei commonly have a regular nuclear border with a stippled chromatin and inconspicuous nucleoli. Nuclear molding is commonly observed. The background shows nuclear breakdown or apoptotic bodies with/without necrosis.[24,25] In the present study, the cytological characters that included cohesion, cell size, cell border, cytoplasm, molding, nature of chromatin, and background were statistically significant. The diagnosis of ADC poses several diagnostic difficulties apart from specific problems associated with needle biopsy. Not all malignant cells with large cytoplasmic vacuoles are ADCs. Degenerate squamous cells may also show this feature. A study of the nucleus may help because a large nucleolus in a vesicular nucleus is characteristic of ADC, whereas an irregular hyperchromatic nucleus is characteristic of SqCC. Where the nucleus and cytoplasm are indeterminate, there is a tendency if squamous metaplasia is also present, to call these indeterminate malignant cells as squamous carcinoma, even though it is known that one may see squamous metaplasia of the bronchial superficial epithelium when it is stretched or distorted by a deeper mucosal carcinoma of any cell type.[26] Two cases of ADCs were wrongly typed, one as small cell carcinoma and another one as SqCC on FNAC. The discrepancy in these two cases was mainly an interpretive error that can be explained by the variable morphology and differentiation exhibited by ADC. Also, the diagnosis was attempted on relatively less cellular aspirates that also showed crush artifacts. The first discrepant case was wrongly diagnosed as small cell carcinoma because vague streaking and cytoplasmic stripping was observed [Figure 9]. The second case was mistaken for a SqCC as the cytoplasm appeared to be relatively dense, opaque, and homogenous with a vague cell wrapping [Figure 10]. So, one should be extremely cautious while reporting on a relatively hypocellular smear with badly preserved cells/smears with artifacts. So, a single cytological parameter/variable is less reliable on its own as a specific feature of ADC. When two or more of these variables are present in combination, the diagnostic accuracy would be high. These characteristics, combined, seem to be useful as a complementary criterion for detecting or typing these lung tumors. These observations need to be tested in a prospective survey to establish their true utility. One of the cases was very poorly differentiated on histology and was difficult to further subcategorize. However, this case showed certain cytomorphological features of ADC. This can be explained by an observation (unpublished experience) that cell morphology is most often preserved on cytology as compared to much of the crush/handling/processing artifacts of small Tru-cut/core biopsies. Even though histologic diagnosis is considered a gold standard in cytologic/histologic correlation studies, in this instance, rather than representing an "incorrect" diagnosis, discordance was due to cytology allowing a more specific diagnosis because cytologic preparations preserved more identifiable features of differentiation than histology. In general, highly differentiated tumors are easily recognized.[27] It has to be noted that many pulmonary tumors contain tumor cell subpopulations with varying morphology and differentiation with their presence complicating the diagnosis.[28] One reason has been the lack of rigid cytological and histological criteria used for the various tumor types. But we will still be left with

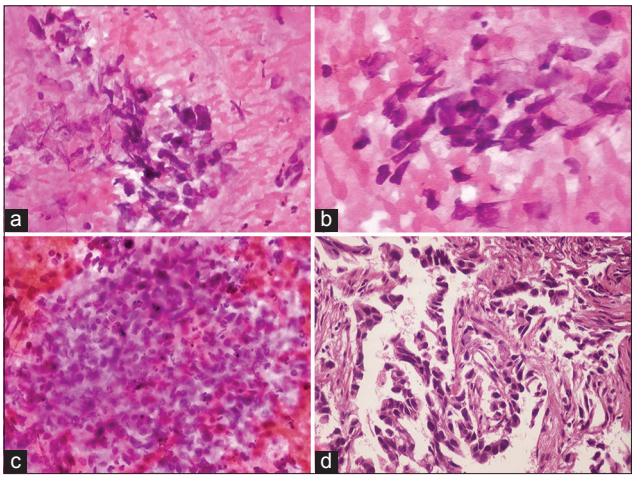

Figure 9: Microphotograph showing the cytological features (Figures a to c) of a case wrongly diagnosed as small cell carcinoma which was an adenocarcinoma on histopathology (Figure d)

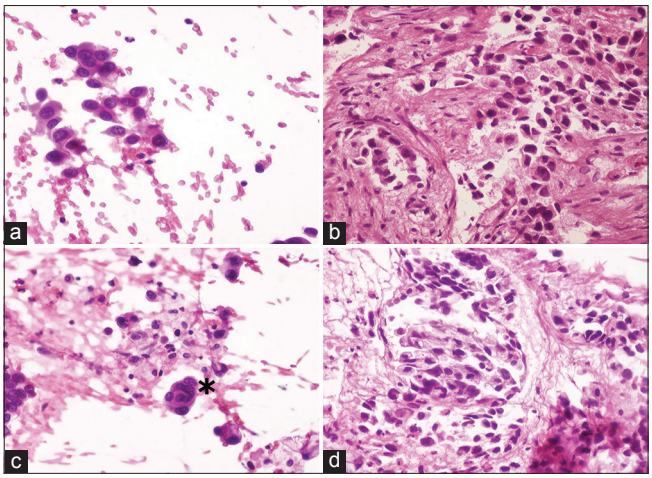

Figure 10: Microphotograph showing the cytological features (Figures a and c) of a case wrongly diagnosed as squamous cell carcinoma which was an adenocarcinoma on histopathology (Figure b and d).Note the cell wrapping (asterix) in Figure c

a small proportion of poorly differentiated tumors, where a precise diagnosis cannot be made on light microscopy. Only 3% of NSCLC were poorly differentiated in this study, whereas a wide-range of frequency of poorly differentiated/NSCLC-Not otherwise specified (NOS) (3– 37%) has been previously reported.[22,28-30] The poorly differentiated carcinomas can take many more different morphological shapes together with differentiated tumor cell groups. In a review of the California Cancer Registry, it was reported that NSCLC-NOS represents 22% of pathologic (32% of cytologic and 19% of histologic) diagnoses of NSCLC and that there has been a substantial increase in this diagnosis between 1989 and 2006.[31] Furthermore, the degree of differentiation of the tumor may vary from place to place, and Chuang *et al*. affirmed that if clear-cut morphological criteria cannot be satisfied a diagnosis of "lung cancer, nonsmall cell type" should be made.[32] While in the majority of cases a line of differentiation can be clearly identified by morphology, difficulties arise in a subset of cases. Perhaps IHC studies might have an important role and would act as a powerful tool for revealing a line of differentiation as ADC versus SqCC in morphologically unclassifiable cases.[33] One limitation of the present study is the limited sample size, and we feel that this has to be tested in a prospective survey to establish their true utility.

CONCLUSION

FNAC has proven to be an invaluable tool not only for diagnostic accuracy of pulmonary carcinomas classification but also as a reliable and adequate source of material suitable for subtyping, additional test like molecular analysis. But pulmonary cytology is more accurate in the diagnosis of well to moderately differentiated carcinomas, than in poorly differentiated. The present study has attempted to evaluate certain cytological features to subtype the common primary lung carcinomas, and better recognition of these patterns should provide improved overall accuracy and better reproducibility. These characteristics in combination are more useful as a complementary criterion for detecting or typing the lung tumors. These data would help in better typing of nonsmall cell carcinoma and help in reducing the rate of NSCLC-NOS diagnosis.

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Conflicts of interest
There are no conflict of interest.

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