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Original Research Article

Rising Incidence of Pulmonary Adenocarcinoma: Our Experience Using Computed Tomography Guided Transthoracic Fine Needle Aspiration Cytology (CT Guided TT FNAC) at a Tertiary Care Centre, Jaipur

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ABSTRACT

Objectives: Pulmonary malignancies continue to represent a serious health problem and a major consideration in the delivery of health care. Accounts approx.12% of all new cancers. Their frequencies have been changing from SCC to adenocarcinoma in recent years. Study was conducted to identify the changing trend in cytomorphological pattern, to assess the relevance of demographic factors with various pulmonary malignancies & to evaluate the need of precise subtypification and multidisciplinary approach.

Materials & Methods: Present prospective descriptive study conducted on n-522 patients of suspected pulmonary mass lesions for a period of $2^{1/2}$ years. CT guided TT FNAC was done and smears were processed by routine cytochemical techniques. Special stains were used wherever needed.

Results: Adequacy of smears found in n-471(90.23%). Age ranged 16 - 90 years (peak 6-7th decades). Primary pulmonary malignancy found in n-398 (76.24%). According to WHO Classification of Lung Tumors 2015 and IASLC/ATS/ERS for cytology, most common type was adenocarcinoma (n-194) 48.75% followed by SCC (n-134) 33.67%.

Conclusion: CT guided TTFNAC is safe, simple, fast and reliable technique for the diagnosis of pulmonary mass lesions with > 94 % accuracy and may reach up to 100% if aided with ICC. It should be used as first line investigation. Study suggests the rising incidence of lung adenocarcinomas. Hence more population based studies with multi-disciplinary approaches are needed to establish this rising trend & to channelize the resources for development of molecular and genetic lab setups.

Key Words: CT guided Transthoracic FNAC (TT FNAC), Pulmonary mass lesion, Adeno-carcinoma, NSCLC (Non-Small Cell Lung Carcinoma).

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INTRODUCTION

Pulmonary malignancies are one of the most frequent malignancies in the industrialized nations.[1] They continue to represent a serious health problem and a major consideration in the delivery of health care.[2] Accounts approx.12% of all new cancers[3] and are the number one cause of cancer morbidity & mortality worldwide. These are the commonest cause of death from cancer in males. According to recent studies the incidence is on the rise in women[1]. Metastatic pulmonary lesions are also common. The relative frequency and clinic-pathological profile of different morphological subtypes of pulmonary malignancies have been changing in recent years.[4] Mentrier in 1886 used the FNAC technique for the first time to diagnose lung cancer.[5] Fear of neoplastic implantation in the needle tract have initially inhibited its use but have proven groundless.[6]

Now a days percutaneous or transthoracic FNAC is a rapidly emerging diagnostic modality to assess the nature of radiologically demonstrated lung lesions.[7-9] Recognition of accuracy of FNAC and simpler methods of treating pneumothorax have brought this method within the reach of most hospitals, radiologists and pathologists.[10,11]

In patient with lung cancer which is inoperable owing to local factors or the patient's general condition, CT guided FNAC confirms the diagnosis and reveals the tumor type.[12] Our study focuses on the demographic factors (gender, age, smoking) clinical and radiological correlation with various cyto-morphological spectrum of pulmonary malignancies, importance of multi-disciplinary approach and need of more precise sub typification due to advent of new targeted therapies.

MATERIAL AND METHODS

The present cross sectional prospective descriptive hospital based study was conducted in the department of pathology, SMS medical college, Jaipur for two & half year period i.e. January 2014 to June 2016, on n-522 patients who had pulmonary SOL by imaging studies.

Informed consent was taken from all the patients included in our study. The study complied with the guidelines of the local ethical committee. Patients with severe respiratory distress, massive pleural effusion, hydropneumothorax, unconscious and uncooperative were excluded from the study. Detailed personal & occupational history was taken and the procedure was carried out with proper aseptic care under CT guidance by 20G, 88mm long spinal needle. Following correct placement of the needle, aspirate was obtained and smears were prepared immediately on clean glass slides. Wet fixed smears were stained by Hematoxyline & Eosine (H&E) and air dried smears by May-Grunwald Giemsa (MGG) stain. Special stains like mucicarmine, Periodic Acid Schiff (PAS) and Gomori's methenamine silver (GMS) were done wherever needed.

A follow-up CT was done on every patient immediately after the procedure to rule out pneumothorax. Smears were screened and broadly categorized into unsatisfactory, benign, suspicious for malignancy and malignant lesions depending on cytomorphological features. The radiological impression of each lesion was recorded. Both cytological and radiological diagnosis were tabulated and compared statistically.

Table 1: Demographic Details

SUBJECT	SUBHEADINGS	TOTAL NUMBER	PERCENTAGE (%)
Age	**<20 years**	5	0.95
	21-30	7	1.34
	31-40	40	7.66
	41-50	105	20.11
	51-60	136	26.05
	61-70	181	34.70
	71-80	38	7.28
	>80 years	10	1.91
Sex	**Male**	426	81.60
	Female	96	18.40
History of smoking	**Smoker**	308	59.01
	Non smoker	214	40.99
Radiological diagnosis	**Malignant**	504	96.55
	Benign	18	3.45
Sampling	**Adequate**	471	90.23
	Inadequate	51	9.77
Cytological findings	**Malignant**	398	76.24
	Suspicious for malignancy	25	4.79
	Benign	48	9.20
	Inadequate	51	9.77

Table 2: Male To Female Distribution Of Smoking Habits

CATEGORY	TOTAL NUMBER	PERCENTAGE (%)
Smoker male	299	57.29
Non-smoker male	127	24.33
Smoker female	9	1.72
Non-smoker female	87	16.66

Table 3: Clinical Presentation

SYMPTOME	NUMBER OF CASES	PERCENTAGE (%)
Irritable cough	407	77.97
Anorexia	88	16.85
Loss of weight	92	17.62
Dyspnoea	160	30.65
Chaist pain	477	91.38
Hemoptysis	175	33.52
Pyrexia	70	13.41
Change in voice	55	10.53

Table 4: HRCT / CECT Findings

APPEARANCE	NUMBER OF CASES	PERCENTAGE (%)
Atelectasis with SPML*	97	18.58
Atelectasis with emphysema & SPML	105	20.11
Emphysema with SPML	180	34.48
Pneumonia with SPML	169	32.37
ILD with SPML	29	5.55
Pleural effusion with SPML	358	68.58
Solitary pulmonary nodule	25	4.79
Multiple nodules/masses	16	3.06
Lymphangitiscarcinomatosa	4	0.76
Rib destruction	8	1.53

*SPML=Solitary Pulmonary Mass Lesion

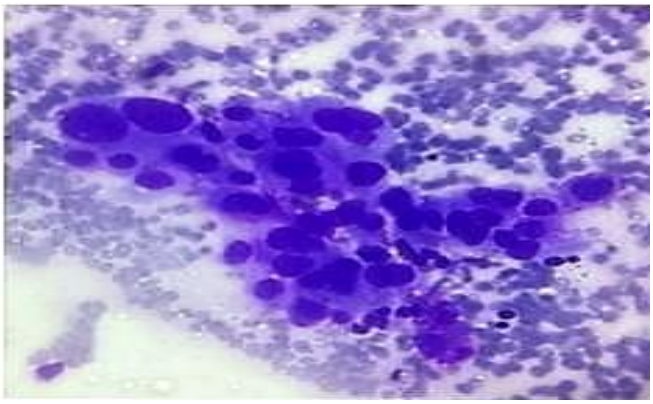

Fig 1-A. MGG (400X) Adenocarcinoma: Cohesive monolayered sheet of cells showing papillary, glandular and ball like arrangement, delicate cytoplasm, nuclear pleomorphism and atypia.

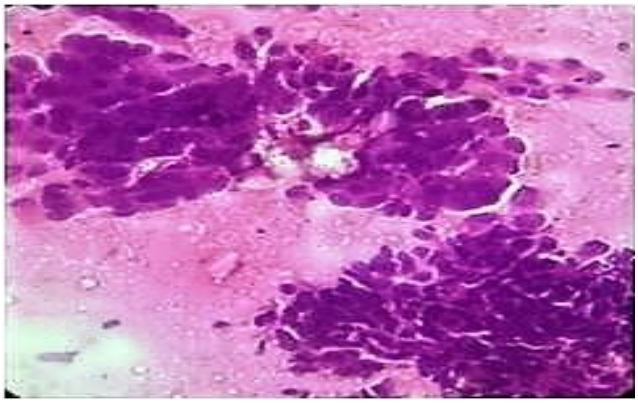

Fig.1-B. H&E (400X). Adenocarcinoma: showing papillary & glandular arrangement of cells having delicate eosinophilic cytoplasm with high N/C ratio.

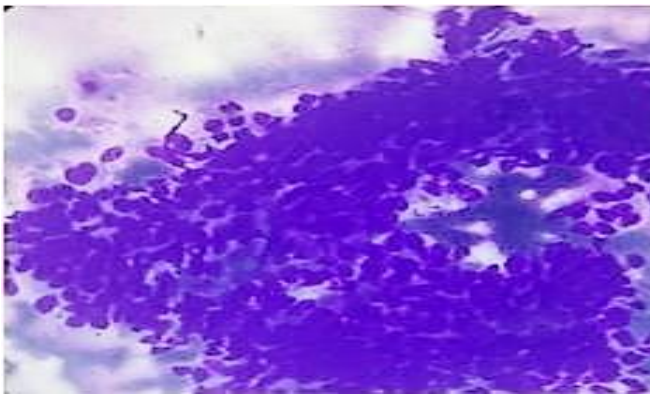

Fig.2-A. MGG (400X) Non-Keratinizing SCC: Irregular clumps of relatively cohesive malignant epithelial cells, with features of nuclear pleomorphism and variation in chromatin density.

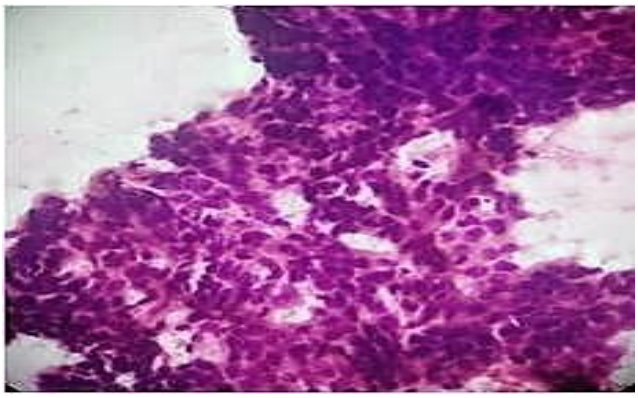

Fig.2-B. H&E (400X). Non-Keratinizing SCC: Sheets & clumps of loosely cohesive malignant epithelial cells, high N/C ratio, nuclear pleomorphism & variable chromatin density with prominent nucleoli.

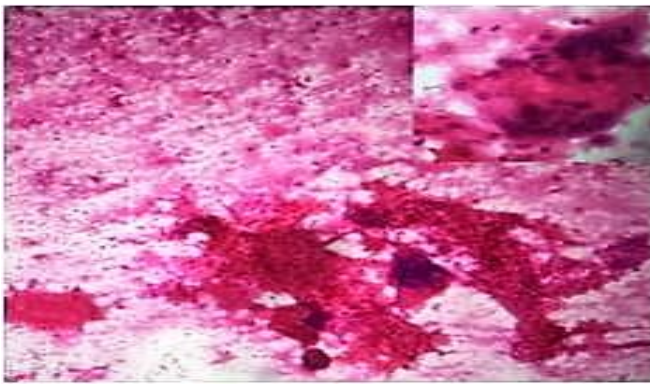

Fig.3. H&E (100X with inset 400X) - Keratinizing SCC: Dispersed keratinizing malignant cells, refractile eosinophilic cytoplasm with necrotic debris and giant cell reaction.

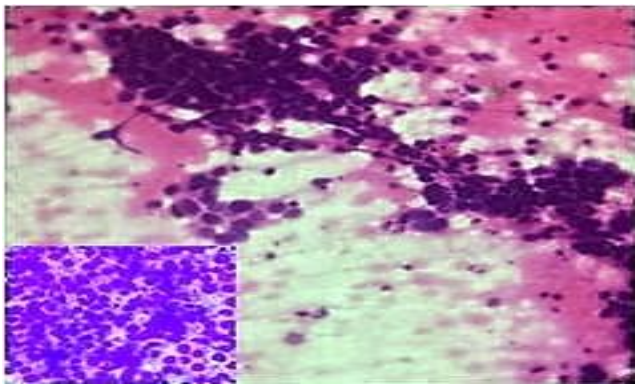

Fig.4. H&E (400X) - SCC: Small to medium sized dispersed cells with little cytoplasm, nuclear moulding & irregularity. Finely granular chromatin, Streaking of nuclear material, numerous apoptotic bodies & mitotic figures. (Inset MGG 400X)

RESULTS

A total n-522 cases of pulmonary mass lesions were studied, out of which n-426 were males (81.60%) and n-96 were females (18.40%). Age range varied from 16 to 90 years. There were n-12 cases below 30 years of age. Majority of cases in our study were smokers (n-308 cases) i.e. 59 %.

In our study adequacy of smears was found in n-471 cases i.e. 90.23%, out of which n-398 (76.24%) cases were malignant, n-25 (4.79%) cases were suspicious for malignancy and n-48 (9.20%) cases were benign lesions (Table 1). Our study shows malignancy as the predominant lesion. The male to female distribution of smoking habits were recorded (Table 2). Detailed clinical history of each patient was taken & analysed (Table 3). Radiological finding by HRCT/CECT were examined for any mass lesion & associated lung disease if any (Table 4). For further calculations, we have omitted all the cases other than primary pulmonary malignancies. Out of total n-398 (76.24%) cytologically proven cases of primary pulmonary malignancy, n-319(80.15%) were males and n-79 (19.85%) were females showing a significant male preponderance with male to female ratio 4.03:1.

On further classification according to WHO Classification of Lung Tumors 2015 and IASLC/ATS/ERS Classification for Cytology, most common type was Adenocarcinoma n-194 cases i.e.48.75% (Fig.1-A, Fig.1-B), followed by squamous cell carcinoma n-134 cases i.e. 33.67% (Fig.2-A, Fig.2-B, Fig.3) & small cell carcinoma n-35 cases i.e.8.79% (Fig.4). n-30 cases (7.54%) were of non-small cell carcinoma- not otherwise specified (NSCC-NOS) and n-05 cases (1.25%) were of non-small cell carcinoma with neuroendocrine morphology (NSCC with NE morphology) are tabulated (Table 5). Now age wise distribution of primary pulmonary malignancies was done (Table 6) along with their sex wise distribution (Table 7).

While adenocarcinoma was found in both smokers and non-smokers, the incidence of squamous cell carcinoma were showing strong association with the smoking habits, chronicity & per day usage. Radiological and clinical correlation of all the cases were done. During our study the incidence of modality induced complication was negligible and was resolved with conservative management.

Table 5: Classification Of Primary Pulmonary Malignancies According To IASLC/ATS/ERS Classification For Cytology

TYPES	TOTAL NUMBER	PERCENTAGE (%)
Adenocarcinoma	194	48.75
Squamous cell carcinoma	134	33.67
Small cell carcinoma	35	8.79
non-small cell carcinoma-not otherwise specified (NSCC-NOS)	30	7.54
non-small cell carcinoma with neuroendocrine morphology (NSCC with NE morphology)	05	1.25

Table 6: Agewise Distribution Of Primary Pulmonary Malignancies

Age in years	<20	21-30	31-40	41-50	51-60	61-70	71-80	>80
Adenocarcinoma	0	4	15	43	51	69	10	2
Squamous cell carcinoma	0	0	4	14	33	59	21	3
Small cell carcinoma	0	0	1	4	12	14	4	0
non-small cell carcinoma-not otherwise specified (NSCC-NOS)	0	0	1	1	8	16	4	0
non-small cell carcinoma with neuroendocrine morphology (NSCC with NE morphology)	0	0	1	0	2	1	1	0

Table 7: Sexwise Distribution Of Primary Pulmonary Malignancies

	NO MALE	%	NO FEMALE	%
Adenocarcinoma	151	37.94	43	10.80
Squamous cell carcinoma	110	27.64	24	6.03
Small cell carcinoma	28	7.03	7	1.76
non-small cell carcinoma-not otherwise specified (NSCC-NOS	25	6.28	5	1.26
non-small cell carcinoma with neuroendocrine morphology (NSCC with NE morphology	5	1.26	0	0
TOTAL	319	80.15	79	19.85

DISCUSSION

CT guided TTFNAC is now a first line diagnostic procedure and completely reliable due to high accuracy rate in terms of its sensitivity & specificity.[13] The presence of the pathologist at the time of the procedure leads to a reduction in the number of needle passes, may decrease the pneumothorax rate and increases overall sensitivity & accuracy of tumor typing.[15]

Now a days crucial management decisions are mostly based on cytology reports. So need of biopsy for diagnosis has been replaced by TTFNA, making it a gold standard tool. It is quick, economical procedure and is associated with low morbidity complaints. It spares a more invasive surgical procedure. Surgical intervention, infact can be avoided in upto 50% of patients with clinically suspected lung cancer[16], except all those where mass reduction is needed for symptomatic relief (especially in centrally placed lesions). FNA has shown to have a high degree of positive predictive value (99%) in a large study.[17] A negative result, generally is less reliable and most reports document a false negative rate of 10-20% for lung aspiration cytology.[13]

In developing countries like India, the incidence of lung cancer is increasing rapidly and shifting from squamous cell to adeno-carcinomatous pattern with younger age of presentation.[18] Currently lung cancer in India is one of the most lethal cancers and ranked fourth largest cause of cancer mortality with its rising trend in females.[19] In our study we found that the mean age of lung carcinoma presentation is 56.5 years. Which is comparable to study done by Krishnamurthy A et al.[18] The peak age of lung cancer in our study was within sixth & seventh decades, which is comparable to studies from the west.[2]

Present study showed the increasing incidence of adenocarcinoma among most of the age groups (i.e. from 21 to 70 years of age), while it was squamous cell carcinoma in more than 70 years of age. Our study is in concordance with many other studies[13,18] and data given by Christopher D.M. Fletcher, fourth edition.[2] As study conducted by Krishnamurthy et al, we have also found a significant correlation between advanced age at presentation and history of smoking in cases of squamous cell carcinoma.[18]

The present study showed a significant male preponderance with male to female ratio 4.03:1. which is comparable to other studies. However many earlier Indian studies were showing sex ratio 5.76:1 to 6.67:1. This over the years change in ratio can be explained due to rising trends of lung malignancies in females, while most of them were never smoker or passive smokers.

The most common etiological association of lung carcinoma found worldwide is tobacco consumption in form of smoking, with increasing risk by early age at initiation, duration and per day use. By the present study we found that 59% of lung cancer patients were smokers. Hence there is a strong need of conduction of more awareness programmes and tobacco control regimens.

Our study showed a higher number of adenocarcinomas i.e. 53.44% of all NSCLC, while Squamous Cell Carcinoma comprised 36.91% of all NSCLC. These results favouring a morphological shift from Squamous Cell Carcinoma to adenocarcinoma of lung, which has been confirmed by many other studies.[14,18]

The possible hypothesis given were:

(1) The changing patterns in smoking i.e. the switch from unfiltered to filtered cigarettes, may lead to altered depth of inhalation. Smoke from unfiltered cigarettes may be shallowly inhaled, resulting in central deposition of chemical carcinogens in the bronchial area and giving rise to Squamous Cell Carcinoma. Smoke from filtered milder cigarettes may be more deeply inhaled and possibly carcinogens reaching more peripherally, giving rise to adenocarcinomas.

(2) Related to the nature of carcinogens present in consumed tobacco i.e. decreased use of carcinogenic polycyclic aromatic hydrocarbons (PAHs) which are Squamous Cell Carcinoma inducers and increased use of carcinogenic tobacco-specific N-nitrosamines (TSNAs) via filtered cigarettes which are adenocarcinoma inducers.[20-22]

The increasing incidence of adeno-carcinomas may not solely related to changing pattern of cigarette smoking but may also be related to other factors like environmental and genetic changes. Hence more population based epidemiological studies are mandatory.

Adenocarcinoma of lung probably involves complex interplay of genetic and environmental mechanism that lead to progressive accumulation of genetic lesion.[23-25] Proof of this is the occurrence of these tumors in children and non-smokers.[2] Former commonly used classification as small and non-small cell carcinoma was for clinical purpose and available treatment at that time. Now with recent development of personalised therapies, this division is no more in use. More specific sub-typing of non-small cell group is required, at least adeno-carcinoma versus squamous cell carcinoma, as this determines eligibility for certain types of molecular testing and therapeutic strategies.[26] The discovery of specific genetic alterations which are amenable to control with Tyrosine Kinase Inhibitors (TKI) has given main impact for need of revised molecular genetic classification. EGFR gene mutation and rearrangement in the anaplastic lymphoma kinase (ALK) gene are the most common genetic alterations found in lung adenocarcinomas. Presence of EGFR gene mutation confer better response to TKI, hence EGFR testing is recommended in all carcinomas of lung.ALK gene rearrangement is associated with young non-smoker having adenocarcinoma morphology. K-RAS mutation found in 15% to 30% of lung adenocarcinomas and is the marker of resistance to TKI therapy.

CONCLUSION

CT guided TTFNAC is safe, less expensive, simple, fast and reliable technique for the diagnosis of pulmonary mass lesions with 93 to 96% accuracy and may reach up to 100% if aided with immune-cytochemistry (ICC) on cellblocks.

Cellblock preparation is now not an ancillary technique, it should be a routine practice and should prepared with every lung FNAC. As it helps in early diagnosis, improved staging and better management, it should be used as a first line investigation in all cases of pulmonary mass lesions. Present study suggests that the incidences of lung adeno-carcinomas are on rise both in non-smokers and smokers of both sexes (41% of total cases were non-smokers). Our study also reflecting the global trend of rising adenocarcinoma pattern. Due to the advent of molecular and genetic studies, better personalised therapies are available for various subtypes of lung malignancies. Hence more population based studies with multidisciplinary approach are needed:-

(1) To establish this rising trend of adenocarcinoma.

(2) To channelize the resources for development of molecular and genetic testing lab setups for effective public health interventions.

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