Changing histological pattern of lung malignancy in India

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Abstract   Previously Squamous cell carcinoma was more common in males and in smokers in india but, the incidence of Adenocarcinoma has increased significantly in last 2 decades. Adenocarcinoma is now the most common form of lung cancer in women and in many studies, in men also. The basis of this change is unclear. A possible factor is the increase in female smokers, but this only highlights our lack of knowledge about why a woman develops more adenocarcinomas. One possibility is that changes in cigarette type (Filter tips, lower tar and nicotine) have caused smokers to inhale more deeply and thereby expose more peripheral airways and cells(with a predilection to adenocarcinoma) to carcinogens. In Our Study out of 48 patients with Adenocarcinoma seen in 36 patients (75%) is most common subtype found followed by squamous cell carcinoma in 09 patients (18.75%) followed by Small cell carcinoma 03 patients(6.25**%**). The reason may be changing smoking pattern and more filtered smoke cigarettes in market and increased in number of female smokers, Adenocarcinoma is most common histological subtype found.
Keywords: Histological Pattern, India, Lung Malignancy.

Access this article online	
Quick Response Code:	Website: www.statperson.com
	DOI: 07 October 2016

INTRODUCTION

The National Cancer Registry Programme of the Indian Council of Medical Research, which collected data from six different parts of the country, both rural and urban areas, showed varying figures in different areas. While cancer of the trachea, bronchus and lungs was the most common form of malignancy in males in 1989 from Bombay, Delhi, and Bhopal, it was the second most common in Madras and third in Bangalore, and was most unusual in Barshi, a rural area. The disease was uncommon in females and only in Bombay it was the sixth common malignancy while in Bhopal, it was the seventh in rank.[1] Hospital data from different parts of the country has also shown different patterns. Behera and Kashyap analyzed the pattern of malignancy in patients admitted to PGIMER Chandigarh from 1973 to 1982 and found that of the 223,930 hospital admissions, there were 863 lung cancer cases (0.38%). Lung cancer was the fifth common cancer after lympho-reticular malignancy, carcinoma cervix, oro-pharyngeal cancer and carcinoma of breast. The total number of lung cancer admissions steadily rose from 1973.[2] As of 1st July 2002 a total of 41,000 cases of lung cancer would have been diagnosed for that year in India as per the ICMR data from its Cancer Registry[1]. According to Globocon 2008, In India, lung cancer is the commonest and most lethal cancer among males accounting for 10.9% of all cancer cases and 13% of cancer related mortality[3]. Previously Squamous cell carcinoma was more common in males and in smokers, the incidence of Adenocarcinoma has increased significantly in last 2 decades. Adenocarcinoma is now the most common form of lung cancer in women and in many studies, in men also. The basis of this change is unclear. A possible factor is the increase in female smokers, but this only highlights our lack of knowledge about why women develops more adenocarcinomas. One possibility is that changes in cigarette type (Filter tips,

lower tar and nicotine) have caused smokers to inhale more deeply and thereby expose more peripheral airways and cells(with a predilection to adenocarcinoma) to carcinogens[4]. There are various methods are available eg Conventional Smear method, Cytospin or Cytocentrifuge method, Cell block method which can be carried on pleural fluid. Every methods has its advantages and disadvantages. Conventional Smear method is most commonly performed method in many institutes as it is rapid, cost effective.

Table 1: Comparative clinical features and cell type patterns in different Indian studies

Authors	Total	M:F	Age (Yrs)	SM: NS	Squam	Anapla	Adeno	Uncla
Viswanathan et al 1962[7]	95	--	--	--	50.5	--	28.4	21.1
Wig et al 11961[8]	65	4.9	55.8	--	--	--	--	--
Basu et al 1971[9]	24	7	48.3	5	62.5	8.3	25	4.2
Sinha et al 1961[10]	33	4.5	57.1	--	--	--	--	--
Karai et al 1967[11]	100	24	52.1	--	41	--	20	39
Shankar 1967[12]	20	All M	54	5.7	73.3	6.7	20	--
Nagrath et al 1970[13]	35	4	47.7	1.9	25.7	--	34.3	40
Reddy et al 1970[14]	46	6.4	50	0.1	50	25	25	--
Guleria et al 1971[15]	120	7.6	57.2	2	46.2	36.5	17.3	--
Jha et al 1972[16]	25	2.9	46.6	5.3	44	20	20	20
Nafae et al 1973[17]	25	All M	51	7.3	56	20	12	12
Malik et al 1976[18]	136	5.2	48.5	3.5	40.4	21.3	16.9	7.3
Narang et al 1977[19]	58	8.7	51.3	4.8	37.9	51.8	10.4	--
Jindal et al 1979[20]	150	5.5	51.7	2.4	32.5	19.3	15.8	21.9
Notani et al 1974[21]	520	--	--	3.9	27.5	11.3	7.3	53.4
Garg et al 1973[22]	82	--	--	--	46.3	28	20.7	--
Malhotra et al 1986[23]	70	7.8	49.6	4.8	50	17	14.3	17.1
Jindal and Behera 1990[24]	1009	4.5	54.3	2.7	34.3	27.6	25.9	12.2
Arora et al 1990[25]	100	4.05	40-60	1.2	27	1	21	41
Rao et al 1992[26]	539	--	--	--	--	--	--	--
Rajasekaran et al 1993[27]	232	7.9	53	2.7	72	4.3	3.9	15.1
Gupta et al1998[28]	279	7.41	56.7	4.5	42.3	32.2	19.9	5.6
Thiappanna et al 1998[29]	160	8.4	40-60	4	67.5	8.8	18.7	5.1
Arora et al 1998[30]	200*	--	--	--	--	--	--	--
Gupta et al 2001[31]	265	7.8	50-70	3.6	60	21.5	16.2	23
Kashyap et al 2001[32]	638**	6.17	54.6	2.4	58.3	--	10.81	--

*Data described only for those below 40 years of age; **:Personal communication. Age (yrs)- Mean Age Of presentation, M:F=Male: Female ratio; Sm: NS=Smoker: non-smoker ratio; squam=Squamous cell carcinoma; Adeno=Adenocarcinoma; Anapla=Anaplaste carcinoma; Uncla=Unclassified.[33]

In 2013, Prabhat et al, in his study called clinico-pathologic profile of Lung cancer, found that the median age of the study population with lung carcinoma was 55 years (23-84years). Majority of the patients were between 50-70 years of age. Male to female ratio was 4.6:1. Out of the total population, 295 patients (67.97%) were smokers (active or former). Bidi (an indigenous form of tobacco) was the commonest mode of smoking (55.25%). There were 370 (85.25%) cases of NSCLC and 64 (14.75%) cases of SCLC and Adenocarcinoma(39%) was comonest histological subtype. 68% patients had history of smoking. Most common presenting symptom in both NSCLC and SCLC was cough (57.03% and 57.8% respectively) followed by chest pain (51.89%and 48.44%).[34] In 2010 N Kirmani et al, in his study found that most common age group of patients with lung malignancies was 51-60 (33.33%).Most common histological subtype was found to be squamous cell carcinoma (44.73%) followed by Adenocarcinoma (30.26%) of lung. Most common age group of patients with lung malignancies was found to be 51-60 years (33.33%.).[35] In 2013 study conducted by Sanjeet Kumar Mandal et al found that, most of the patients with lung cancer were more than 60 years of age(67.8%), Patient with lung cancer had Male :Female ratio was 1.09:1, Smoker: Non- smoker ratio was 3.7:1, 91.9% patients had history of smoking, 16.3% patients had history of tuberculosis, Most common symptom was cough (36.6%), Right lung(60.3%) had affected more than left lung, Most common histological subtype was found to be Squamous cell carcinoma(49.1%) followed by Adenocarcinoma (30.8%).[36]

MATERIALS AND METHODS

Place: Tertiary Care Hospital.

Study population

Patients admitted under department of pulmonary medicine and department of medicine with features suggestive of lung malignancies eg Haemoptysis, recurrent pleural effusion, Cervical and mediastinal lymphadenopathy and Patients presenting with undiagnosed lung masses on radiology.

Study Design: The present study is prospective, hospital based, descriptive study.

Study Period: 18 months from 01-01-2013 to 30-06-2014.

Inclusion Criteria

Patients admitted under department of pulmonary medicine and department of medicine with features suggestive of lung malignancies eg Haemoptysis, Recurrent pleural effusion, Cervical and mediastinal lymphadenopathy and Patients presenting with undiagnosed lung masses on radiology.

Exclusion Criteria

Diagnosed patients with lung malignancies are excluded from study.

Figure 1: H and E Stained slide of conventional Smear Hematoxylin-Eosin staining method for conventional method

After making smear from sediment on slide, slide is fixed in methanol after that slide dip in Hematoxylin for 15 min. then slide washed with tap water and dip in eiosin for 1 min. Slide mount with DPX and observed under microscope.

OBSERVATIONS AND RESULTS

The Interpretation of conventional smear and cell block.

The samples were studied in detail, taking into account the available clinical data, various investigation reports and microscopic details. The samples were categorized as

1. Positive For Malignancy(PFM)
2. Suspicious for malignancy(SFM)
3. Negative for Malignancy (NFM).

The morphological criteria that were taken into account, included the

1. Cellularity,
2. Arrangement of the cells (acini, papillae and cell balls)
3. Cytoplasmic and the nuclear details of suspicious or malignant cells
4. Presence of inflammatory cells like lymphocytes, polymorphs, Mesothelial cells.

All these criteria were put together and they were used for the categorization of the sample. The cytomorphological characters were studied in detail to identify the malignancy. A comparative evaluation of the CS versus the CB techniques was conducted.

Interpretation of conventional smear.

1. POSITIVE FOR MALIGNANT CELLS (PFM).
2. SUSPOCIOUS FOR MALIGNANCY(SMF).

3. NEGATIVE FOR MALIGNANCY(NFM).
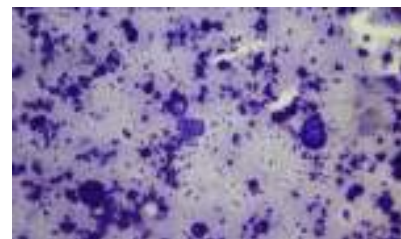
Figure 2: Low power (10x) H and E-Pleural Fluid Cytology.

Smear study shows presence of Round to Oval atypical cells arranged in groups against inflammatory and mucinous background. Diagnosis given- Suspicious For Malignant Cells. (SFM)
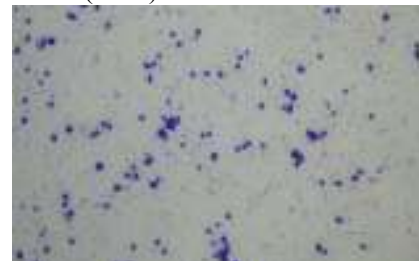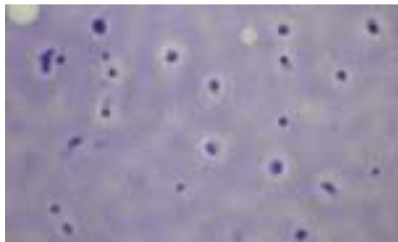

Figure 2: Low Power H and E- Pleural Fluid Cytology on conventional smear

Smear study shows Scattared Round to Oval tumor cell over background of RBCs and inflammatory cells. Diagnosis Was Given- Suspicious Of Malignancy (SFM). (Adv: Cell Block Cytology) block Cytology.) Possible-Adv: Cell
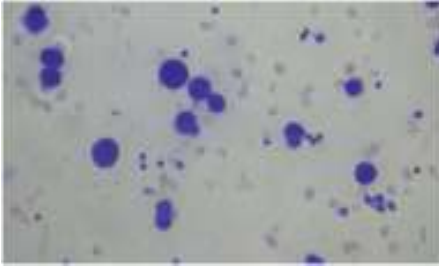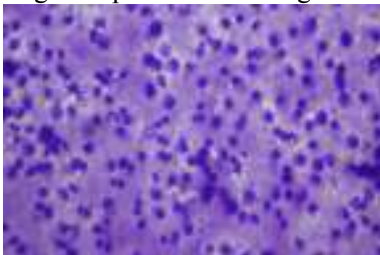
Figure 3: High power H and E Pleural Fluid Cytology

Smear study shows presence of Round to Oval tumor cells having hyperchromatic,Pleomorphic nuclei and scant cytoplasm against haemorrhegic background. Diagnosis given Positive For Malignant cells (PFM).
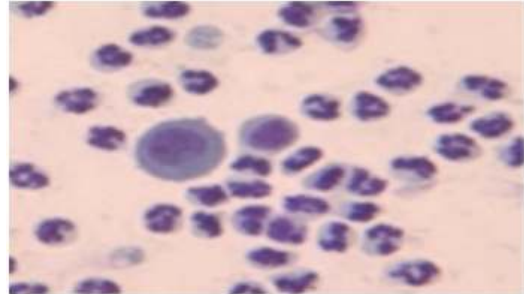

Figure 4: Pleural Fluid Cytology- High power H and E Smear study shows atypical cells with eccentric nuclei with moderate amount of cytoplasm

Diagnosis was given- positive for maliganat cells (PFM).

**Figure 6:** Pleural Fluid Cytology

High power Hand E stained- Smear study shows Many Large cells Having Hyperchromatic Pleomorphic Nuclei and Scanty cytoplasm on necrotic background material. Diagnosis was Given- Positive For Malignant cells(PFM)- Typing Not possible.


Figure 6: H and E High Power-Pleural Fluid Cytology-Smear study shows presence of plenty of polymorphs, a reactive msothelial cell

Diagnosis given was –Negative For Malignancy (NFM)-- /Inflammatory Smear. Interpretation Of Cell Block Cytology Smear which are Positive and Suspicious For Malignancy are processed on cell block. Due to better architectural pattern, cellularity, greater nuclear and cytoplasmic details typing of Lung Malignancies were possible. Smears interpreted as, positive for malignant cells-And Given Further histological typing.eg adenocarcinoma of lung, squamous cell carcinoma lung, small cell carcinoma lung etc.
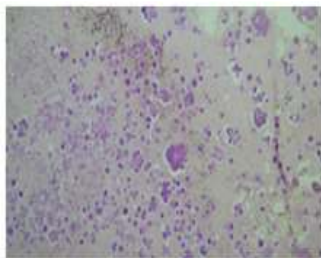

Figure 7: Low Power H and E : Cell Block Cytology from pleural fluid sediments-- Smear shows round to oval tumor cells arranged in acinar, Glandular pattern positive for malignant cells (pfm) s/o adenocarcinoma lung.
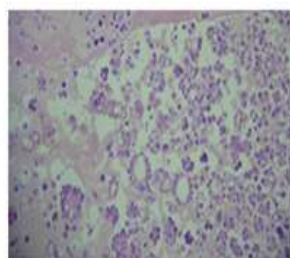
Figure 8: low power- h and e smear shows tumor cells arranged in glandular and at places papillary pattern. positive for malignant cells (pfm) s/o adenocarcinoma
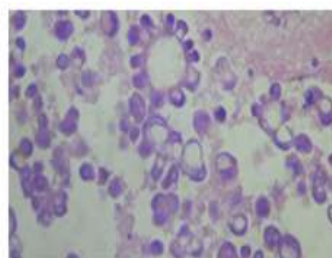
Figure 9: High Power-H and E-Smear shows presence of tumor cells having hyperchromatic, pleomorphic, eccentric nuclei and moderate amount of cytoplasm arranged in glandular pattern.positive for malignant (PFM)cell S/O Adenocarcinoma lung.
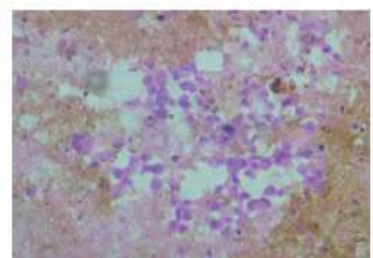
Figure 10: Cell Block cytology H and E High power- Smear shoes presence of tumor cells having hyperchromatic pleomorphic nuclei and moderate amount of eiosinophilic cytoplasm arraned in sheets and clusters. Positive For Malignant (PFM) cells- SQUAMOUS CELL CARCINOMA LUNG.

RESULTS

In this study, 75 cases were studied during January 2013 to June 2014. All samples of patients with suspected lung malignancies are processed on conventional smear and cell block.

The following results were made with regard to:

Table 1: Histological Type of Lung Malignancies found during study as Small cell Lung Cancer And Non -Small Cell lung cancer (n=48)

Sr. No	Type Of Lung Cancar	No. of patients	Percentage (%)
1	Small Cell Lung Cancer.	03	6.25%
2	Non-small cell lung cancer	45	93.75%
	Total	**48**	**100%**

Out of 48 patients with lung malignancies, 3 patients (6.25%) are of small cell lung cancer and remaining 45 patients (93.75%) are Non-small cell lung cancer patients.

Table 2: Overall histological Sub type of Lung Malignancy Found during Study (Male + Female) (n=48)

Sr. No	Histological Subtype	No of patients	Percentage%
1	Adenocarcinoma.	36	75%
2	Squamous cell Carcinoma.	09	18.75%
3	Small Cell Carcinoma.	03	6.25%
4	Large Cell Carcinoma	00	00%
5	Other	00	00%
Total		**48**	**100%**

As described in above table**,** Adenocarcinoma seen in 36 patients (75%) is most common subtype found followed by squamous cell carcinoma 09 patients (18.75%) followed by Small cell carcinoma 03 patients(6.25%). Due to changing pattern and more filtered smoke cigarettes in market, increased in number of female smokers, Adenocarcinoma is most common histological subtype found. Adenocarcinoma may be the commonest subtype in this part of India. Analysis of a larger cohort from multiple institutions would reflect the true pattern
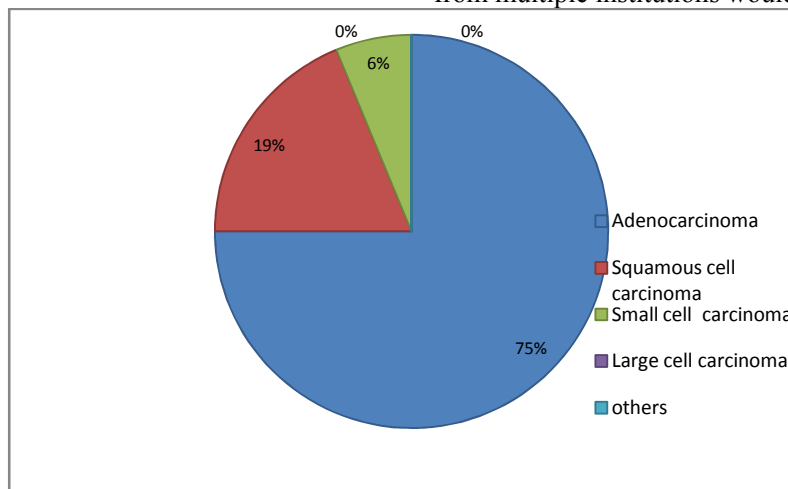
Figure 1: Showing distribution of histological sub type of lung malignancy

DISCUSSION

In this study, 10% Alcohol- Formalin is used as a fixative for modified cell block preparation, by this better cellularity is obtained compared to conventional smear as formalin minimizes cell loss by forming protein cross links.

Table 3: Comparative study of Histological subtype of lung malignancy found during study

Sr No	Authors	Histological Subtype Found.			
		Adenocarcinoma	Squamous cell carcinoma	Small cell carcinoma	Other
1	N Kirmani et al 2010[35]	30.26%	44.73%	5.26%	9.73%
2	Prabhat et al 2013[34]	39%	25%	15%	21%
3	Sanjeetkumar et al 2013[36]	30.83%	49.11%	14.75%	5.28%
4	Present Study.	75%	18.75%	6.25%	00

In study done by N Kirmani et al [35] 2010, found in his study, most common lung malignancy was squamous cell carcinoma (44.73%), followed by Adenocarcinoma (30.26%). In study done by Prabhat et al[34] 2013, noted Adenocarcinoma (39%) is most common histological

subtype found followed by squamous cell carcinoma (25%). Sanjeetkumar et al[36] 2013, found that Squamous cell carcinoma (49.11%) was most common subtype followed by Adenocarcinoma (30.83%). In our study, we found Adenocarcinoma (75%) is most common

histological subtype of lung malignancy. Changing pattern of smoking, more female smokers, filtered cigarettes may be the result for change in histological subtype of lung cancer. But some indian studies still conclude that Squamous cell carcinoma is common histological subtype eg N Kirmani *et al*[35] 2010, found in his study Squamous cell carcinoma (44.73%) was commonest histological subtype of lung malignancy and Sanjeetkumar *et al*[36]2013, also found squamous cell carcinoma(49.11%) was most common.

SUMMARY
We conducted study of diagnosis of lung malignancy by cell block method, we study total 75 samples from clinically suspected patients with lung malignancies. We found 48 patients with lung malignancy.
We found in our study,

1. Due to changing pattern, filtered smoke cigarettes in market, increased in number of female smokers and more exposure of females to household environmental carcinogens, Adenocarcinoma (75%) is most common histological subtype found.
2. There is paradigm shift in the pathological profile of lung cancer in India. Adenocarcinoma may be the commonest subtype in this part of India. Analysis of a larger cohort from multiple institutions would reflect the true pattern. Outcome of these patients are still poor because there presentation in advanced stage of disease.

CONCLUSION
1. With increasing prevalence of smoking, lung cancer has reached epidemic proportions.
2. In addition to smoking, occupational exposure to carcinogens, indoor air pollution and dietary factors has presently implicated in causation of lung malignancy.
3. Various modalities for early detection through screening are being investigated. Majority of patients have locally advanced or disseminated disease at presentation and are not candidates for surgery.
4. Chemotherapy applied as an adjuvant with radiation improves survival and quality of life hence appropriate histological diagnosis is needed for proper treatment.
5. New anticancer drugs, which have emerged during the last decade, have shown an improved efficacy in treatment of lung malignancy.
6. In view of our large population, the burden of lung cancer will be quit enormous in India.

7. Drastic measures aimed at discouraging people from smoking must be taken to reduce the morbidity and mortality due to lung malignancy.

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