

## Study of diagnostic procedures and histopathology in primary malignancies in a tertiary care centre

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### Abstract

**Background:** Primary lung cancer is a leading cause of cancer related death all over the world. In Indian scenario lung cancer is increasingly diagnosed because of beedi and cigarette smoking and majority of times diagnosed in an inoperable stage resulting in poor prognosis.

**Materials and Methods:** In this study we have analysed the diagnostic modalities and histo-pathological analysis of the specimen obtained and correlated with the smoking status and age of the patients. A total of 113 patients having clinical and radiological profile suggestive of primary lung cancer are taken in to the study. Among them only 100 patients were diagnosed as malignancy by histopathological examination. For the confirmation of the diagnosis transthoracic needle aspiration biopsy with the help of ultrasonography and CT scan, bronchoscopic biopsy and bronchial washings, lymph node biopsy and pleural fluid analysis were undertaken.

**Results:** Positive specimens were obtained by TTNA in 54%, Bronchoscopic biopsy and washings in 30%, pleural fluid analysis in 12% and lymph node biopsy in 4% of patients. 82% are males and 18% are females. 82% are smokers and 18% are nonsmokers. 68 patients presented with mass lesions and 73% of them presented with a mass of >5cm in diameter. 27% presented as mass lesions less than 5cm in diameter. Smokers have more mass lesions and more N3 disease and the values are statistically significant. (p<.001). Squamous cell carcinoma is the commonest variety found (48%) followed by adenocarcinoma (34%), small cell carcinoma in 10% and others 8%. Increased age increased the prevalence of both squamous cell carcinoma and adenocarcinoma and the values are statistically significant at p-value of 0.05. Among males commonest cancer is squamous cell carcinoma (53.65%), followed by adenocarcinoma in 31.17%, small cell carcinoma in 7.31%. Among females both squamous cell and adenocarcinoma are equally present contributing to 33.33% each.

**Summary and Conclusions:** Primary lung cancer is a disease of older age. Smoking both active and passive or nonsmoking forms of tobacco are important aetiological factors. Predominant number of patients are males. Diagnosis of lung cancer requires a multi-disciplinary approach. Squamous cell carcinoma is more common among smokers. Adenocarcinoma is more common among nonsmokers. Among females both squamous and adenocarcinoma occurred equally. All the cases of small cell carcinoma occurred among smokers. As majority of the patients presented in late stages clinical outcome is poor. Prevention of smoking and mass campaigning against smoking in the rural areas can decrease the prevalence of lung cancer in India. Discouraging nonsmoking forms of tobacco is equally important.

**Keywords:** Squamous cell carcinoma, Adenocarcinoma, Small cell carcinoma, Smokers, Nonsmokers.

### Introduction

Lung cancer is a leading cause of cancer related deaths through out the world both in males and females accounting for 11.6% of all cancers and 18% of cancer related deaths [1]. In India primary lung cancer is frequently diagnosed with a mean age of 56 years both among smokers and non smokers and male: female ratio is 3.5:1 [2]. Cigarette and beedi smoking is rampant in rural India and has increased in the age group of 15 to 29 years among men [3]. Active and passive smoking along with exposure to biological fuel and other substances probably is responsible for increased incidence of lung cancer [4]. Many a time the disease is diagnosed in an advanced stage where curative surgical therapy is not possible and only palliative treatment is given to prolong the life span and improve quality of life.

Early diagnosis is important in identifying pulmonary malignancy where in surgical and combined modalities of treatment can result in better outcome. Radiology and histopathology together can determine the stage and ultimate prognosis and available mode of treatment.

### Materials and Methods

After taking the approval of the ethical committee of Katuri Medical College, Guntur and having taken the consent from the patients studied in a proper form we have examined 113 patients having symptoms, clinical signs and radiological findings suggestive of primary pulmonary malignancy. Among them in only one hundred patients diagnosis of primary malignancy was made. We examined the histological pattern from the specimens obtained by various diagnostic procedures and correlated the result with their smoking status. Among the 100 patients 82 patients are males and 18 patients are female. CT guided transthoracic lung biopsy for the lung masses, accessible lymph node cytology by aspiration or surgical biopsy, ultrasound guided cutting needle biopsy of lung lesions, pleural fluid analysis, bronchoscopic endobronchial biopsy and analysis of bronchial washings were performed for the diagnosis.

## Results

**Table 1:** No. of cases present as mass lesions n= 68

Size of the Mass lesions	No. of Patients	Smokers	Nonsmokers
5cm and below in maximum diameter	18 (26.47%)	13	05
5cm and above in maximum diameter	50 (73.57%)	43	07
Total	68	56	12

The chi-square statistic is 1.7288. The p-value is .188566. The result is not significant at  $p < .05$

Patient with Positive Lymph nodes above 1cm in CT scan

61 patients out of hundred presented with subcarinal, contralateral hilar and contralateral mediastinal nodes suggesting N3 disease. 39 patients presented with N1 and N2 disease (intrapulmonary, ipsilateral hilar and ipsilateral mediastinal nodes by the resources available.

**Table 2**

Lymph node status	No. of Patients	Smokers	Nonsmokers
N1, N2 Disease	39	25 (64.10%)	14(35.90%)
N3 Disease	61	57 (93.44%)	04 (6.56%)
Total	100	82	18

The chi-square statistic is 13.8749. The p-value is .000195. The result is significant at  $p < .05$

**Table 3:** Diagnostic procedure employed

Diagnostic procedure	No. of patients (n=100)	Percentage
Lymph node Biopsy	4	4%
Pleural fluid cytology	12	12%
CT guided TTB	36	36%
U/S guided cutting needle biopsy	18	18%
Bronchoscopic biopsy, Bronchial Washings and HPE	30	30%

**Table 4:** Histopathological presentation

Histopathological Type	No. of patients	Percentage
Squamous cell Ca	48	48%
Adeno Ca	34	34%
Small cell Ca	10	10%
Others	8	8%

**Table 5:** Distribution of histopathological types with respect to smoking status

Factor	Squamous cell carcinoma	Adenocarcinoma	Small cell carcinoma	Others
Smokers (n=82)	44 (53.65%)	20(24.39%)	10(12.19%)	8(9.75%)
Nonsmokers(n=18)	4(22.22%)	14(77.78%)	0	0

When numbers of squamous and adenocarcinoma were correlated among smokers and nonsmokers smokers have increased prevalence of squamous cell carcinoma and nonsmokers have increased prevalence of adenocarcinoma and the values are statistically significant. Chi-square statistic is 12.5306. The p value is .0004. The result is significant at  $p < .05$ .

**Table 6:** Distribution of histopathological types with respect to Age

Age group in years	Squamous cell carcinoma	Adeno carcinoma	Small cell carcinoma	Others	Total
31-40	2 (2%)	2(2%)	0	0	4
41-50	12 (12%)	4(4%)	2 (2%)	0	18
51-60	14(14%)	22 (22%)	6(6%)	4 (4%)	46
61-70	16 (16%)	4 (4%)	2(2%)	0	22
> 70	4 (4%)	2 (2%)	0	4 (4%)	10
Total	48	34	10	8	100

When the ages of the patients were correlated with the number of patients in the squamous cell carcinoma and adenocarcinoma group there is an increased prevalence of both squamous and adenocarcinoma with increased age. The Chi-square statistic is 11.5921. The p-value is .020657. The result is significant at  $p < .05$

**Table 7:** Distribution of histopathological type in males

Histopathological type	Males (n=82)	Percentage
Squamous cell carcinoma	42	53.65%
Adenocarcinoma	28	31.17%
Small cell carcinoma	6	7.31%
Undifferentiated carcinoma	6	7.31%

**Table 8:** Distribution of histopathological type in females

Histopathological type	Females (n=18)	Percentage
Squamous cell carcinoma	6	33.33%
Adenocarcinoma	6	33.33%
Small cell carcinoma	4	22.22%
Others	2	11.11%

## Discussion

Primary lung cancer is diagnosed relatively late. Because many symptoms are nonspecific many patients are treated for common illness by general practitioners. Our experience suggests that a predominant number of patients are found to be in T3-4 disease and N3 disease and sometimes with metastasis. All these criteria make the patient inoperable and only suitable for palliative treatment. All the general symptoms except for haemoptysis are not viewed seriously by the patient and much precious time is lost before diagnosis [5]. Multi disciplinary approach is needed in thoroughly staging the lung cancer for the purpose of instituting the treatment. Advanced radiological investigations are very important in determining the operability of the tumour [6].

Tissue diagnosis is of utmost importance in the diagnosis and staging of primary lung malignancy especially in nonsmall cell carcinoma of lung. The least invasive procedure should be adopted with a multidisciplinary approach. Flexible bronchoscopic biopsy, radiology guided percutaneous transthoracic needle aspiration, direct lymph node biopsy if accessible and analysis of pleural fluid can yield good results. Combination of procedures and proper processing of specimen are important. Sending the tissue specimen for EGFR and ALK mutations can help in the diagnosis and treatment [7]. We have adopted similar approach but financial limitations of the patients was a limiting factor.

Transthoracic needle aspiration was successful in yielding positive specimen in 54% of cases in our study. Bronchoscopic procedures yielded positive in 30%. Pleural fluid analysis was positive in 12% and accessible lymph node biopsy was possible in only 4% of cases in our study. The utility of TTNA was stressed by several authors but utility of all the available modes of diagnosis can yield better positivity [8]. The utility of ultrasound as a noninvasive procedure in the diagnosis of lung cancer is enunciated by MM Hoosein et al [9].

In our study accessible lymph nodes for biopsy were obtained in 4% of cases. However application of newer methods like trans bronchial biopsy, trans esophageal biopsy (described as medical mediastinoscopy) can improve the diagnosis. Together with PETCT scan can assess the activity of the lymph nodes in separating operable N2 disease from inoperable N3 disease [10].

Nonsmall cell carcinoma accounts for 80% of lung cancer in USA. Adenocarcinoma constitutes 40% of lung cancers, Squamous cell carcinoma 25%, large cell carcinoma 10% and small cell carcinoma 15% and other uncommon types 5%. In the western world adenocarcinoma is more common than squamous cell carcinoma [11]. In Europe, lung cancer is the biggest killer accounting for 20.8% of cancer deaths attributed largely to tobacco smoking [12]. Lung cancer in India is largely attributed to cigarette and beedi smoking. Non smoking forms of tobacco are equally important. In Digambar Behera study from PGI Chandigarh, squamous cell carcinoma is the commonest lung cancer followed by adenocarcinoma. In India among smokers squamous cell carcinoma is higher in incidence and adenocarcinoma is higher in nonsmokers [13]. In western countries adenocarcinoma is the commonest. Males outnumber females by 4.5:1 until 60 years of age. In an Indian study Squamous cell carcinoma accounted for nearly 50% of lung cancers and adenocarcinoma for nearly 20% and anaplastic carcinoma accounted for 24% of cases. Predominant age distribution was in 50-59 years age group. In our study 78% of the patients were in above 51 years age group. Female lung cancer is less correlated with smoking [14]. Our study showed squamous cell carcinoma as the predominant histopathology followed by adenocarcinoma. Another Indian study reiterates that lung cancer occurs in India 15-to 20 years earlier compared to western countries. It is mostly attributed to smoking and nonsmoking form of tobacco consumption. Nonsmall cell lung cancer accounts for nearly eighty percent of lung cancers and majority of them are presented in inoperable stages [15]. We have similar experience in our study as majority of the patients

presented in N3, and T3-4 stages. Lung cancers occur in nonsmokers also and in our study nonsmokers are as high as 18%. In Anurag Agarwal study four fifths of the patients were males. Mass lesion was the predominant mode of presentation. These findings are similar to our study. They have adenocarcinoma as the commonest histopathology, followed by squamous cell carcinoma occurring in 22% and small cell carcinoma of 12%. Most patients were smokers males belonging to 50-70 year age group similar to our study [16].

A large study from Florida suggested that number of cigarettes smoked per day did not influence the type of lung cancer. They found that adenocarcinoma was more frequent among cases of lung cancer detected at earlier ages in both men and women. Incidence of nonsmall cell carcinoma was higher among smoker women [17]. Our study showed more prevalence of squamous cell carcinoma among smokers. Squamous cell carcinoma was seen in more than 50% of smokers, followed by adenocarcinoma in 24% and small cell carcinoma in 12%. Among nonsmokers more than three fourths of patients belonged to adenocarcinoma category and 22% belonged to squamous cell carcinoma group. In our study small cell carcinomas were seen only in smokers group and there was none in nonsmokers group. In our study 72% of squamous cell carcinoma cases, 82% of adenocarcinoma patients and 80% small cell carcinoma patients fall in above 51 years age category. This is consistent with other studies that lung cancers are a disease of older age though they occur around fifteen to twenty years earlier in Indian population. In general it is accepted that cigarette smoking increases the risk of lung cancer several studies did not correlate smoking history and severity of smoking with histopathology [18]. Another British study showed that life long nonsmokers had more adenocarcinoma and less squamous cell and small cell carcinoma and the observation is similar to our study [19].

### Summary of study

Diagnostic modalities employed were thorough radiological examination with chest x ray PA and lateral, Contrast enhanced CT scan chest and ultrasonographic examination of chest and abdomen. PET scan was obtained in selected few patients.

Among 100 patients of primary pulmonary malignancy bronchoscopic brush biopsy, bronchial washings and bronchoscopic biopsy were positive in 30% patients.

Most common diagnostic modality used was CT guided transthoracic biopsy (36%) followed by FOB guided biopsy (30%). Ultra sound guided cutting needle biopsy was done in 18%. 6% of patients were diagnosed by pleural fluid analysis. Only 4% were diagnosed by lymph node biopsy. Biological markers like TTF1, Nap-A, CK5, CK-6, CK-7, CK-20, chromogranin, Synaptophysin, P-63 were used in selective cases when requested by the pathologist. EGFR mutation test by FISH method were sent for two cases of adenocarcinoma and both of them were positive for EGFR mutations.

Histopathological examination revealed squamous cell carcinoma as the commonest primary malignancy of lung in 48% of cases followed by adenocarcinoma in 34%. Small cell carcinoma accounted for 10%. Others that included combined modalities and inconclusive malignancy, large cell carcinoma and salivary gland tumors accounted for 8%.

When histopathological diagnosis is correlated with smoking status among the 48 cases of squamous cell carcinoma 44 (91.66%) cases were seen in smokers and the rest in non smokers (8.34%). Among the cases of adenocarcinoma 20 out of 34 cases (58.82%) occurred among smokers. Nonsmoker adenocarcinomas accounted for 41.18%. All the ten cases of small cell carcinoma are present in smokers. Other 8 malignancies are also present in smokers.

Among males commonest lung cancer is squamous cell carcinoma in whom a majority are smokers. Among females, both squamous and adenocarcinoma were equally distributed in the present study. 100% of small cell carcinoma patients were smokers.

The most common histopathological type in smokers was squamous cell carcinoma and in non-smokers, the most common histopathological type was adenocarcinoma. There was no case of small cell carcinoma among nonsmokers.

Analysis of age distribution of the primary pulmonary malignancies revealed 78% of cases were diagnosed in 51 and above patients. 34 out of 48 cases of squamous cell carcinoma (70.83%) were seen in above 51 years age group and 14 of 48 cases were seen in below 51 years age group (27.17%). 28 out of 34 cases (82.35%) of adenocarcinoma were seen in 51 and above age group and six out of 34 cases of adenocarcinoma were seen in below 51 years age group. 8 out of ten cases of small cell carcinoma (80%) were seen in 51 and above age group.

The peak incidence of adenocarcinoma and small cell carcinoma was found to be in the age group of 51-60 years and in squamous cell carcinoma it was in the age group of 61- 70 years.

### Conclusion

Primary lung cancer is a disease of older age. Smoking both active and passive or nonsmoking forms of tobacco are important aetiological factors. Predominant number of patients are males. Histopathology is important. Diagnosis of lung cancer requires a multi-disciplinary approach. Squamous cell carcinoma is more common among smokers. Adenocarcinoma is more common among nonsmokers. Among females both squamous and adenocarcinoma occurred equally. All the cases of small cell carcinoma occurred among smokers. As majority of the patients presented in late stages clinical outcome is poor. Prevention of smoking and mass campaigning against smoking in the rural areas can decrease the prevalence of lung cancer in India. Discouraging nonsmoking forms of tobacco is equally important.

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obtaining consent from the subjects studied in a proper form.

**Conflict of Interests:** None.

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