Original Article

The spectrum of Lung and Pleural Neoplasms in Patients Presented to a Referral Hospital In Nepal

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ABSTRACT

Background: Lung cancer is one of the most common cancers worldwide. Lung and pleural biopsies are the most commonly performed procedures for the diagnosis of suspicious lesions in the lungs and pleura. The main objective of the study was to identify the incidence pattern of lung and pleural neoplasms in the tertiary care center of Nepal.

Methods: A hospital-based cross-sectional study was carried out from April 20, 2019, to April 19, 2020, taking the histopathological specimens with suspicion of lung or pleural neoplasms. Demographic data, type of biopsy obtained, laterality of involvement, smoking status, and histopathological diagnosis in lungs and pleura were collected in the pro forma and entered in Microsoft excel. The statistical analysis was done by using SPSS version 16.

Results: Out of 7859 biopsies and resection specimens, 272 (3.5%) cases of lung and pleural specimens were obtained during the study period, out of which 101 (37.1%) were lung and 16 (5.9%) were pleural neoplasms altogether constituting 117 (43.01%) cases of the total lung and pleural biopsies. The mean age for lung and pleural neoplasms was 63.38 (SD±12.5) years. Male predominance was seen with M:E ratio of 1.6:1 and 1.3:1 in lung and pleural neoplasms respectively. Out of 117 cases, trucut biopsy was done for 104 (88.9%) cases and 62 (53%) cases specimens were obtained from the right side. Among the lung neoplasms, 87 (86.1%) were epithelial tumors among which 38 (43.7%) cases were Squamous cell carcinoma. Among the pleural neoplasms, 9 (56.3%) cases were metastatic tumors. Smokers with more than 20 pack years were at significant risk of developing epithelial lung neoplasms (p=0.042). The adjusted odds ratio for epithelial lung neoplasm was 15.26 [95% Confidence Interval (CI) 2.91-20.07] in persons who smoke.

Conclusion: Lung and pleural neoplasms were more prevalent in males in this study. Squamous cell carcinoma is the commonest histological type of lung cancer, closely followed by Adenocarcinoma in our study. Metastatic tumors were the most common among the pleural neoplasms in our study. Smokers were 15 times more likely to have epithelial lung neoplasms than non-smokers.

Keywords: *Hematoxylin and eosin, lung neoplasms, pleural neoplasms*.

ARTICLE INFORMATION	**Source of Support**: Nil	**Conflict of Interest**: None
Received: 8 March 2022	**Accepted**: 25 August 2022	**Published Online**: 30 August 2022

INTRODUCTION

Lung cancer, commonest of all cancers is the leading cause of death due to cancer worldwide.[1] Globally lung cancer is shown to affect 2.09 million population, and is also the most common cause of cancer-related death contributing 1.76 million deaths in the year 2018 and in Nepal, lung cancer deaths are 1.64% of total deaths and the age-adjusted death rate is 12.99 per 100,000 of population.[2]

Tobacco-related cancers contributed to more than three-fourths of cancers among men and

more than half of cancers for women.[3] Age of the patient, gender, radon exposure, and pre-existing lung diseases like asthma, tuberculosis, and chronic obstructive pulmonary disease are also important risk factors.[4] In the analysis done by UK GP research database, incidence rates of lung cancer per 10,000 person-years were around four-fold higher in patients with prior chronic obstructive pulmonary disease (COPD) increasing from 45 to 64 in men and from 29 to 48 in women compared with the general population (from 10 to 15 in men and 5 to 10 in women).[5] Indoor coal burning is also a risk factor for lung cancer.[6] However, some cancer may occur due to genetic influences.[7]

The clinical presentation of cases of lung cancer varies greatly. Common symptoms are cough, weight loss, chest discomfort, difficulty in breathing, hemoptysis and occasionally incidental finding after the radiological examination.[8]

Imaging techniques like X-ray, Computed tomography, ultrasonography, bronchoscopy, mediastinoscopy are used extensively to establish the location of lesion. These techniques even help the extraction of the specimen for further evaluation as they cannot differentiate benign or malignant lesions. With the view to provide proper diagnosis, cytological examination of sputum, pleural fluid, broncho-alveolar lavage, bronchial brushing and CT guided fine needle aspiration are commonly performed procedures.[9,10]

Histopathological examination is gold standard procedure considered in the diagnosis of lung neoplasms.[11] Percutaneous needle aspiration , conventional bronchoscopy, flexible bronchoscopy (FB), electromagnetic navigation (EMN) bronchoscopy, radial endobronchial ultrasound (R-EBUS)-guided needle aspiration, transthoracic needle aspiration (TTNA), transbronchial needle aspiration (TBNA) are various methods applied for obtaining biopsy. It is very essential to type the lung carcinomas for estimate of prognosis and choice of treatment.

Broadly lung cancers are divided as non-small cell carcinomas (NSCLC) and small cell carcinomas (SCLC). NSCLC accounts for approximately 84% of all lung cancers. Adenocarcinoma (ADC) and Squamous cell carcinoma (SCC) are predominant histological types among NSCLC. Pleural lesions commonly include mesothelioma and metastasis. Similarly, pleural lesions can also occur frequently. Proper and timely diagnosis of the lung and pleural neoplasms can aid in the management of the cases. The present study was conducted to identify the incidence pattern of lung and pleural neoplasms in the tertiary care center of Nepal.

MATERIALS AND METHOD

A hospital-based cross-sectional study was carried out for one year. All biopsies(Ultrasound/Computed tomography-guided Bronchoscopic, Transbronchial trucut biopsy), as well as resection specimens (Pneumonectomy, lobectomy, wedge resection) with the diagnosis of lung and pleural neoplasms reported at the Histopathology unit at the Department of Pathology, TUTH, over a period of 1 year (April 20, 2019 to April 19, 2020), were studied. The study was initiated after obtaining Institutional Review Board clearance. Written informed consent was taken from all the participants.

All the cases diagnosed as neoplastic lung and pleural diseases are included in the study. The cases that have been treated with neo-adjuvant therapy for lung/pleural cancer, those with inconclusive or normal lung biopsy results, those with infective pathology and also who were diagnosed before were excluded from the study. The diagnosis was based upon the Haematoxylin and Eosin stained slides and even immunohistochemistry was performed whenever applicable that helped in further evaluation and confirmation of diagnosis. The cases with the neoplastic diagnosis were documented along with consent and history taking in the proforma developed for the study.

Statistical Analysis

Data collected were entered in MS Excel sheet and analysis was done in SPSS version 16. *p*-value less than 0.05 was considered to show significant association between two variables, and that less than 0.001 was considered to show highly significant association between two variables.

RESULTS

During the study period of one year, from 20 April, 2019 to 19 April 2020, total 7859 biopsies and resection specimens received. Total 272 (3.5%) lung and pleural biopsies as well as resection

specimens were received among which 117 cases (43.01%) were diagnosed histologically as lung and pleural neoplasms. Among the neoplasms, 113 cases (96.6%) were malignant, and 4 cases (3.4%) were benign. Hundred and one cases were lung neoplasms and sixteen cases were pleural neoplasms.

The mean age of the participants was 63.38±12.5 years with the range of 15-84 years (Fig.1).

Maximum number of cases was in the age group of 61-70 year which was 40 cases (34.12%). Maximum number of cases of lung and pleural neoplasm in males was reported at the age after 70 years whereas that in female was reported between the age group of 61 to 70 years (Fig.1).

Among 101 cases of lung neoplasms majority were epithelial tumor, comprising 87 cases (86.1%), out of which 62 cases (71.3%) were seen in the population above 60 years of age (Table 1).

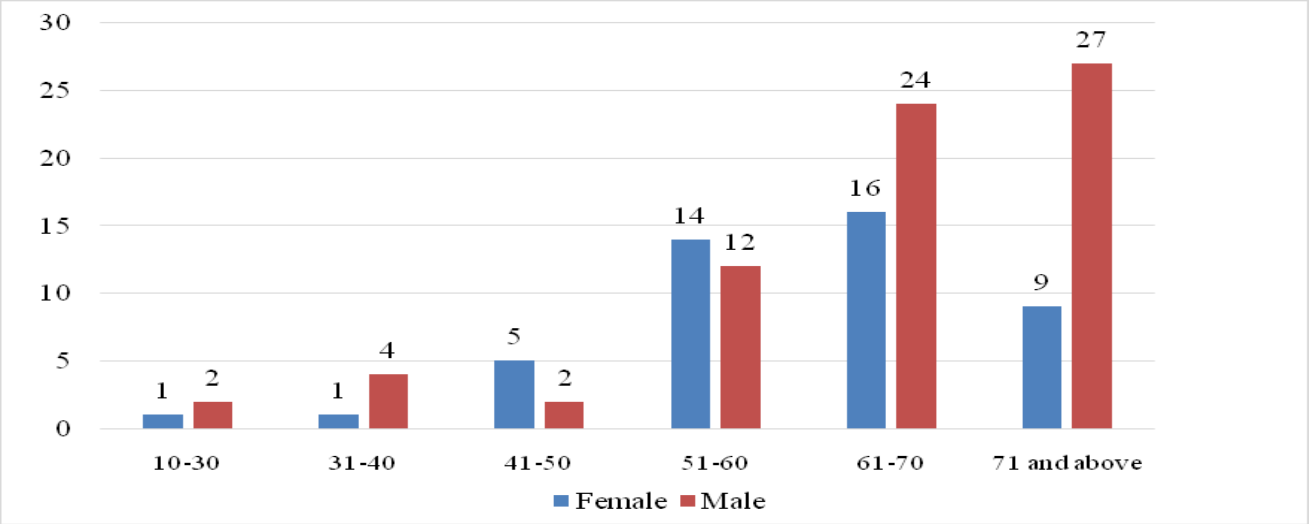

Figure 1: Age and Sex distribution of Lung and pleural neoplasms

Table 1: Association between Age and Lung neoplasms (n=101)

Age Interval	Lung Neoplasms		Total	*p*-value
	Epithelial tumor(%)	Non-Epithelial tumor(%)		
≤60	24 (23.8%)	8(7.9%)	32(31.7%)	0.027
>60	63(62.4%)	6(5.9%)	69(68.3%)	
Total: n(%)	87(86.1%)	14(13.9%)	101(100%)	

Table 2: Age Distribution for Pleural neoplasms (n=16)

Age Interval	Pleural Neoplasms				Total (%)
	Mesothelial tumor (%)	Lymphoproliferative tumor (%)	Mesenchymal tumor (%)	Metastatic tumor (%)	
<30	0(0)	0(0)	0(0)	1(11.1)	1(6.3)
30-60	0(0)	1(100)	2(50)	5(55.6)	8(50)
>60	2(100)	0(0)	2(50)	3(33.3)	7(43.7)
Total (%)	2(100)	1(100)	4(100)	9(100)	16(100)

Of 16 cases of pleural neoplasm, 8 cases (50%) were recorded at 30-60 years age group. Among these 8 cases, 5 cases (62.5%) were diagnosed as metastatic tumor in this age group (Table 2).

Of the 117 cases enrolled, 71 cases (60.7%) were males and 46 cases (39.3%) were females. Both lung and pleural neoplasms were predominantly diagnosed in males with male to female ratio of 1.6:1 and 1.3:1 respectively. Total of 101 cases of lung neoplasm were recorded, out of which, 62 cases (61.2%) were males and 39 cases (39.8%) were females. Among 16 cases of pleural neoplasm, 9 cases (56.3%) were in males whereas 7 cases (43.7%) were females (Table 3).

Out of 87 epithelial tumors, 52 cases (59.8%) were males whereas 35 cases (40.2%) were females (Table 4). Of the total 101 cases of the lung neoplasm, 90 cases (89.1%) were trucut biopsies (Ultrasound guided, CT guided, Transbronchial), 7 cases (6.9%) were lobectomy specimens, and 2 cases (1.9%) of each pneumonectomy and wedge resection specimens were obtained (Fig. 2).

Among 16 pleural biopsies, 14 cases (87.5%) were trucut biopsies and 2 cases (12.5%) were wedge resection specimens. Lung and pleural specimens collected were mainly from right side, constituting 62 cases (53%) and that from left side constituted 55 cases (47%). Of the 101 cases of lung neoplasm most common was epithelial tumors comprising 87 cases (86.1%) and metastatic tumors comprised 7 cases (6.9%). Among the epithelial tumors, SCC was the most common comprising 38 cases (37.7%), followed by ADC constituting 36 cases (35.7%), neuroendocrine tumors being 10 cases (9.9%) and one case (0.9%) each of adenosquamous carcinoma, spindle cell carcinoma and mucoepidermoid carcinoma (Table 5).

The neuroendocrine tumors include five cases of small cell carcinoma, three cases of large cell neuroendocrine carcinoma and two cases of carcinoid. The metastatic tumors include two immunohistochemistry proven metastatic tumor from renal origin, one case each of morphologically favoring metastasis from salivary gland and renal origin and three cases of unknown primary. Seven cases were diagnosed as spindle cell tumor, unclassifiable. Two of the spindle cell tumors were benign and five were morphologically malignant. They were categorized as spindle cell tumor; unclassifiable as further sub-categorization of the tumor was not possible as the tissue was sub optimal for IHC and in some cases the block was taken by the patients to other referral centers. (Table 5)

Table 3: Sex Distribution for Lung and Plural neoplasms (n=117)

Gender	**Lung Neoplasms**	**Pleural Neoplasms**	**Total (%)**
Female (%)	39(39.8)	7(43.7)	46(39.3)
Male (%)	62(61.2)	9(56.3)	71(60.7)
Total: n (%)	101(100)	16(100)	117(100)

Table 4: Sex Distribution for Epithelial Lung neoplasms (n=87)

Gender	**Epithelial Lung Neoplasms**				**Total (%)**
	ADC (%)	**SCC (%)**	**NET (%)**	**Others (%)**	
Female (%)	14(38.8)	14(36.8)	4(40)	3(100)	35(40.2)
Male (%)	22(61.2)	24(63.2)	6(60)	0(0)	52(59.8)
Total: n (%)	36(100)	38(100)	10(100)	3(100)	87(100)

ADC: Adenocarcinoma, SCC: Squamous cell carcinoma, NET: Neuroendocrine tumors

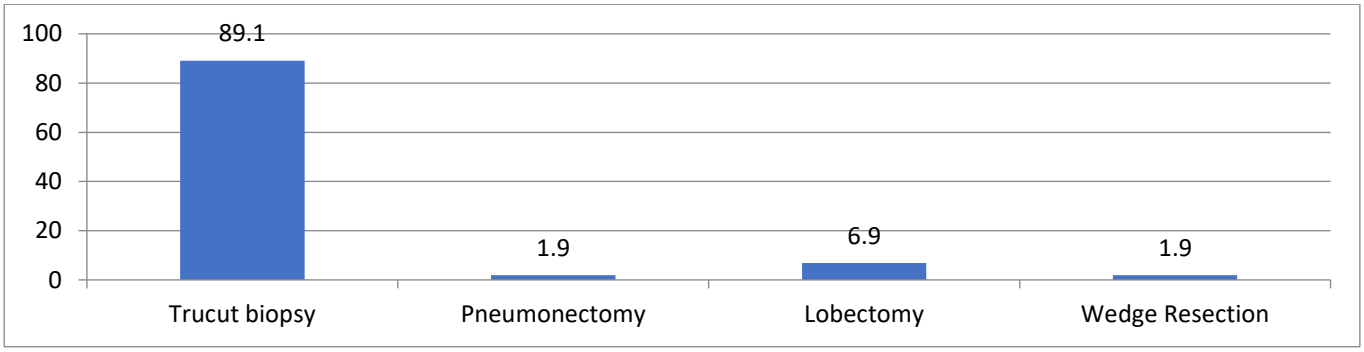

Figure2: Various specimens obtained from lung

Table 5: Histopathological spectrum of Lung neoplasms

Histopathological diagnosis	Frequency	Percent (%)
1. Epithelial tumor	87	86.2
Squamous cell carcinoma (SCC)	38	37.8
Adenocarcinoma (ADC)	36	35.8
Neuroendocrine tumors	10	9.9
Adenosquamous carcinoma	1	0.9
Spindle cell carcinoma	1	0.9
Mucoepidermoid carcinoma	1	0.9
2. Metastatic tumor	7	6.9
3. Spindle cell tumor, unclassifiable	7	6.9
Total	101	100

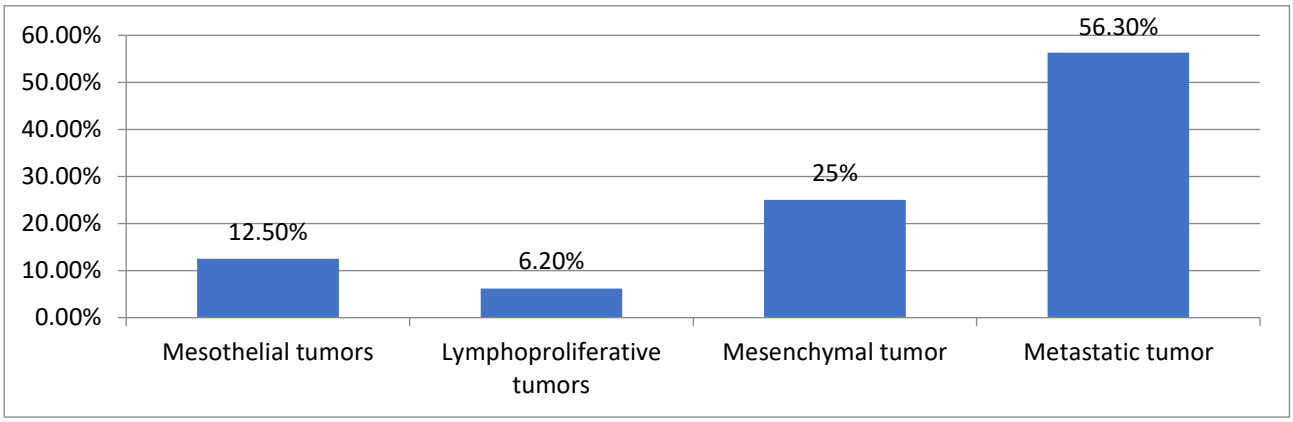

Figure 3: Histopathological spectrum of Pleural neoplasms

Out of 16 cases of pleural neoplasms, most common were metastatic tumors, comprising 9 cases (56.3%) which include five immunohistochemistry proven metastatic adenocarcinoma, one metastatic tumor from breast and one metastatic small cell carcinoma. This is followed by 4 cases (25%) of mesenchymal tumors, which include one case each of schwannoma, solitary fibrous tumor and synovial sarcoma and one unclassified case, 2 cases (12.5%) of mesothelioma, and 1 case (6.2%) of lymphoproliferative tumor which was T-cell non-Hodgkin lymphoma. (Fig. 3)

Table 6: Association of smoking with Lung neoplasms

Smoking status	Lung Neoplasms			Chi square value	*p*-value
	Epithelial tumors (%)	Metastatic tumor (%)	Spindle cell tumor, unclassifiable (%)		
Non-Smoker (%)	6(6.8)	3(42.8)	2(28.5)	11.055	0.004
Smoker (%)	81(93.2)	4(57.2)	5(71.5)		
Total: n (%)	87(100)	7(100)	7(100)		

Table 7: Association of Pack years with Epithelial Lung neoplasms

Pack years	Epithelial lung neoplasms				X^2-value	*p*-value
	ADC (%)	SCC (%)	NET (%)	Others (%)		
≤20	9 (29)	6 (15.7)	6 (60)	1 (50)	8.194	0.042
>20	22 (71)	32 (84.3)	4 (40)	1 (50)		
Total (%)	31 (100)	38 (100)	10 (100)	2 (100)		

ADC: Adenocarcinoma, SCC: Squamous cell carcinoma, NET: Neuroendocrine tumors

Table 8: Unadjusted and adjusted OR and 95% CI for epithelial lung neoplasms with smoking status

Variables	COR	AOR	*p*-value	95% CI
Smoking Status	6.750	15.255	0.001	2.913-20.77

COR: Crude Odds Ratio, AOR: Adjusted Odds Ratio

Out of 101 cases of lung neoplasms, 89.2% were smokers. History of smoking is significantly associated with lung neoplasms especially associated with epithelial tumors of lung. (*p*-value <0.05) (Table 6). Pack year is significantly associated with epithelial neoplasms of lung. (*p*-value <0.05) (Table 7). (Photomicrograph 1-4) Smokers were 15 times more likely to have epithelial lung neoplasms than those who do not smoke. Socio-demographic variables like age and gender are the adjusted variables. Smoking is not statistically significant in pleural neoplasms.

DISCUSSION

Lung cancer is the most common cause of cancer related deaths worldwide. Smoking is the most important risk factor among others. Due to availability of various treatment modalities on the molecular level, typing of lung and pleural neoplasms are revised. Further classification of non-small cell carcinoma into specific Adenocarcinoma (ADC), Squamous cell carcinoma (SCC) and others are of utmost importance.

Adequate material must be obtained primarily to arrive at proper histological diagnosis and also for subsequent immunohistochemical and molecular analysis.[12] Various methods are practiced for obtaining biopsy, like image guided biopsy including conventional bronchoscopy, flexible bronchoscopy (FB), electromagnetic navigation (EMN) bronchoscopy, radial endobronchial ultrasound (R-EBUS)-guided needle aspiration, transthoracic needle aspiration (TTNA) or biopsy, image guided percutaneous lung biopsy and pleural biopsy. Bronchoscopy remains the primary tool being quick and safe procedure for obtaining biopsy. This can be performed with minimal complication, but this greatly depends upon the location. Study done by Popovich et al. revealed 96% overall yield for central tumors whereas 75% for peripheral nodules.[13] Flexible bronchoscopy is proven valuable for proximal tumors whereas CT-guided lung biopsy is of more value to peripheral tumors.[14]

During the study period of one year between April 20, 2019 to April 19, 2020 total 272 lung and pleural biopsies as well as resection specimens were received out of which 117 cases (43.01%) (includes 113 malignant i.e., 96.6% and 4 benign i.e., 3.4%) as were enrolled in the study. Among them, 101 were lung neoplasms (ADC, SCC, neuroendocrine carcinoma, adenosquamous carcinoma, mucoepidermoid carcinoma, spindle cell carcinoma, metastatic tumors and spindle cell tumor, unclassifiable), and 16 were pleural neoplasms (mesothelioma, lymphoproliferative, mesenchymal and metastatic).

In our study the age of patients for lung and pleural biopsies or resection ranged from 15 to 84 years with a mean age 63.38 and median age of 65 years.

Maximum numbers of cases were in the age group of 61-70 years, with 40 cases. Maximum number of cases of lung and pleural neoplasms in males were reported at the age after 70, whereas that in female was reported between the age group of 61 to 70. Study done by Mallik et al. analyzed 434 pathologically confirmed lung cancer, with median age 55 years.[15]

Study done by Howlader et al., found median age group for lung cancer to be 66, which is similar to our study.[16] Of the 117 cases enrolled in our study, 71 cases (60.7%) were males and 46 cases (39.3%) were females, male to female ratio being 1.5:1. Both lung and pleural neoplasms were predominantly diagnosed in males with male to female ratio of 1.6:1 and 1.3:1 respectively. Study done by Houston et al., found that incidence of lung cancer in men to be 53.8% while that of female is 46.2%, male to female ratio being 1.16:1 which is similar to our study.[17]

Study done by Mallik et al. had enrolled cases with male to female ratio of 4.6:1 which is very high as compared with ours.[15] In a recent study done by Hellyer and Patel, there was higher lung cancer incidence in young women than young men in United States. They also showed continued sex-based incidence disparities and presented compelling evidence that these discrepancies may not be attributed to smoking behavior.[18]

In our study maximum specimens collected were from right side, constituting 62 cases (53%) followed by left side that constituted 55 cases (47%). Study done by MK Piya showed that carcinoma of right lung was frequent (62%) compared to the left lung (38%).[19] Of the 101 cases of lung cancer involved in our study, there were 38 cases (37.8%) of SCC closely followed by 36 cases (35.8%) of ADC which contrasts to the five-year study done by Khan et al., in which SCC was observed in 77.3%, while 17.1% had small cell carcinoma.[20]

One of the studies done by Krishnamurthy et al. with 258 cases of proven diagnosis of lung cancer, non-small-cell lung cancer (NSCLC) was the most common histology in 224 patients and the remaining 34 patients were small-cell carcinoma. Similar common histology in our study is NSCLC however among them SCC is predominant, which is not coherent with this study where ADC is more common.[21] In the study done by Singh et al., the commonest histological type is SCC (34.8%), ADC (26.0%) and small cell carcinoma (18.4%), which is comparable to our study.[22]

Of the 101 cases of lung neoplasms, the most common was epithelial tumors comprising 87 cases (86.2%), and metastatic tumors comprised 7 cases (6.9%). Among the 87 cases of epithelial tumors, SCC was the most common comprising 38 cases (43.7%), followed by ADC constituting 36 cases (41.4%), neuroendocrine tumors being 10 cases (11.6%) and one case (1.1%) of adenosquamous carcinoma, spindle cell carcinoma and mucoepidermoid carcinoma. Among the neuroendocrine tumors, small cell carcinoma was the most common comprising five cases (50 % of neuroendocrine tumors).

In a study done by Komaki, Tsao and Mehran, Non-small cell lung cancer (NSCLC) accounted for about 80 % of these cases, which is similar to our study.[23] In a study titled "Lung Cancer in India: Challenges and Perspectives", the most common of histological diagnosis was SCC (34.3%) followed by ADC (25.9%), which is similar to our study.[24] The histological typing of lung cancer and its incidence varied over time. Incidence of SCC, large cell carcinoma and small cell carcinoma rates continued to decrease for all gender/race combinations, whereas ADC rates is comparatively constant in males but the incidence is increasing in females, as revealed by a study done by Meza et al.[25]

In a study done by Dela Cruz, Tanoue and Matthay, non-small cell carcinoma accounted for 85% of lung cancers out of which 38.5% were ADC, 20% were SCC, large cell carcinoma accounted for 2.9% and 15% small cell carcinoma.[26] In our study epithelial lung cancer occurred at significantly higher age group (61 above) constituting 62 cases (61.4%) of all the lung cancer cases, with SCC being the most common affecting 32 cases (51.6%) which is similar to the study done by Dey et al. which revealed that the occurrence of SCC is frequent in higher age group (60.84±12.16 years) (35.1%) compared to other subtypes.[27] Study done by Yang et al. revealed that the most common histological type among both sexes was ADC however; the proportion of ADC differed significantly between males and females (45.36% and 77.14%, respectively).[28] In contrast, our study showed the most common histological types among both the sex as SCC, closely followed by ADC with proportion of ADC among males and females, 42.3% and 40% respectively.

There was total 16 cases of pleural neoplasm in our study, most common among all was Metastatic tumors comprising 9 cases (56.3%), followed by 4 cases (25%) of Mesenchymal tumors, 2 cases (12.5%) of Mesothelial tumors, and 1 case (6.2%) of T-cell Non-Hodgkin Lymphoma. There were total of 35 cases of pleural neoplasm that included 15 (42.9%) primary pleural neoplasms and 20 (57.1%) metastatic carcinoma cases in a study done by Venkatachala et al. which supports our study findings that metastatic neoplasms are common among the pleural tumors.[29]

Study done by Karpathiou and Peoc'h concludes that malignant pleural mesothelioma is the most common primary epithelial neoplasm of pleura. Solitary fibrous tumor is the most common mesenchymal tumor and metastasis from lung followed by lymphoid neoplasms are the most common of all others.[30] Study done by Shroff et al. stated that pleural metastases are associated with tumors of lung, breast, pancreas and stomach, which is comparable with the study done by Smart and Hinson, which had 20% of the pleural metastases from lung, 20% from breast, 10% lymphoma and others metastatic tumors from ovary, gastric, neuroblastoma, kidney, bladder, osteosarcoma and endometrium as well.[31,32] Of the 101 cases of lung cancer involved in our study, 90 cases (89.1%) were smokers. Among epithelial tumors of lung, 38 cases of SCC, all had history of smoking whereas 31 cases (86.1%) of ADC cases had history of smoking. The proportion of smoking is statistically significant.

In a five-year study done by Khan et al., SCC was observed in 77.3%, while 17.1% had small cell carcinoma. Smoking history was present in 88% of the patients.[20] The study done by Krishnamurthy et al. stated that the 60.5% patients with lung carcinoma were smokers.[21] This study similar to ours found a very significant correlation with SCC among the smokers compared to non-smokers.[21]

CONCLUSION

Lung and pleural neoplasms were more prevalent in males in this study. Squamous cell carcinoma closely followed by Adenocarcinoma is the common histological types of lung cancer in our study. Metastatic tumors were the most common among the pleural neoplasms in our study. Smokers were 15 times more likely to have epithelial lung neoplasms than those who do not smoke.

ETHICAL APPROVAL: Ethical approval was taken from Institutional review board at Tribhuvan University Teaching Hospital, Maharajgunj.

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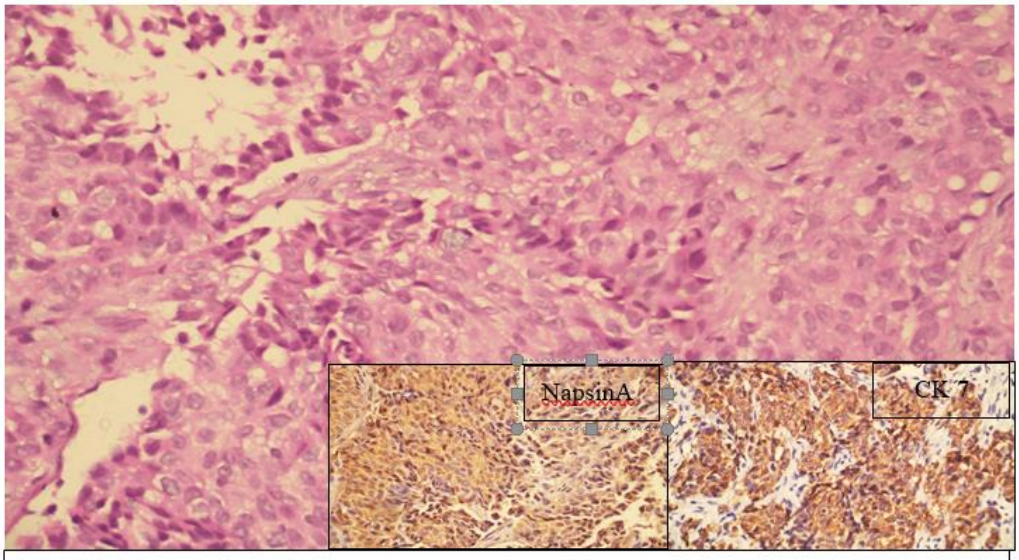
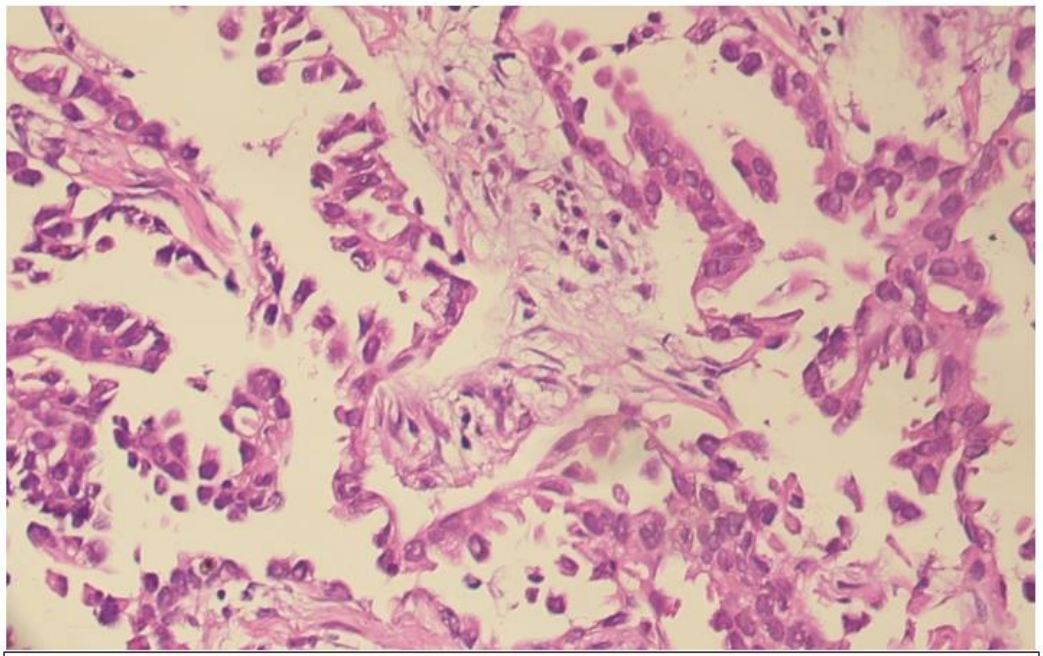
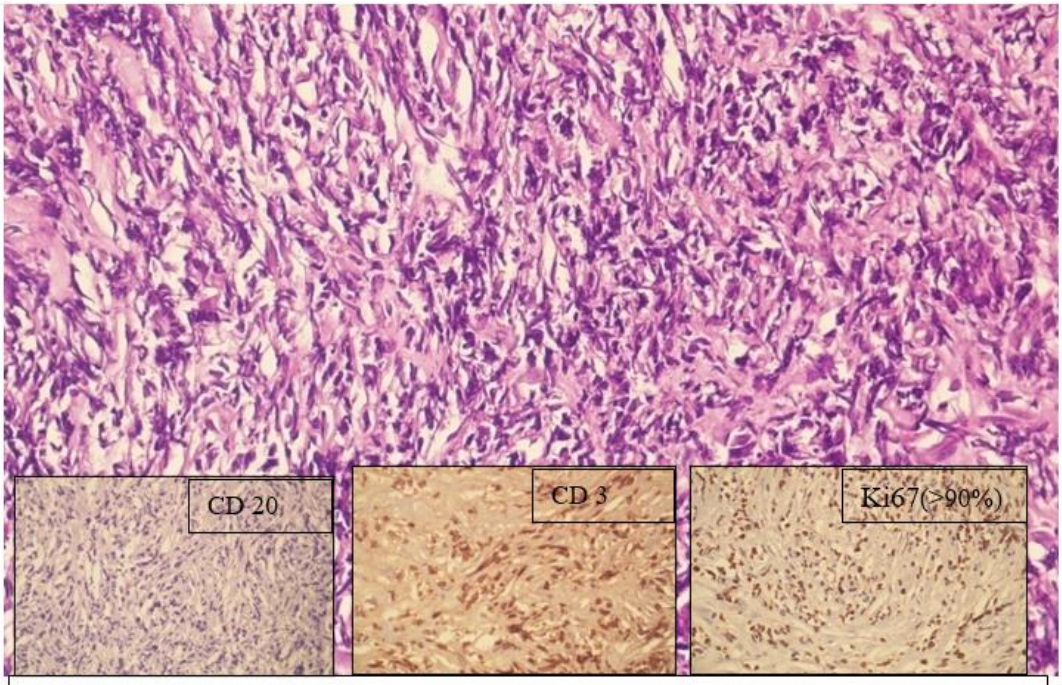


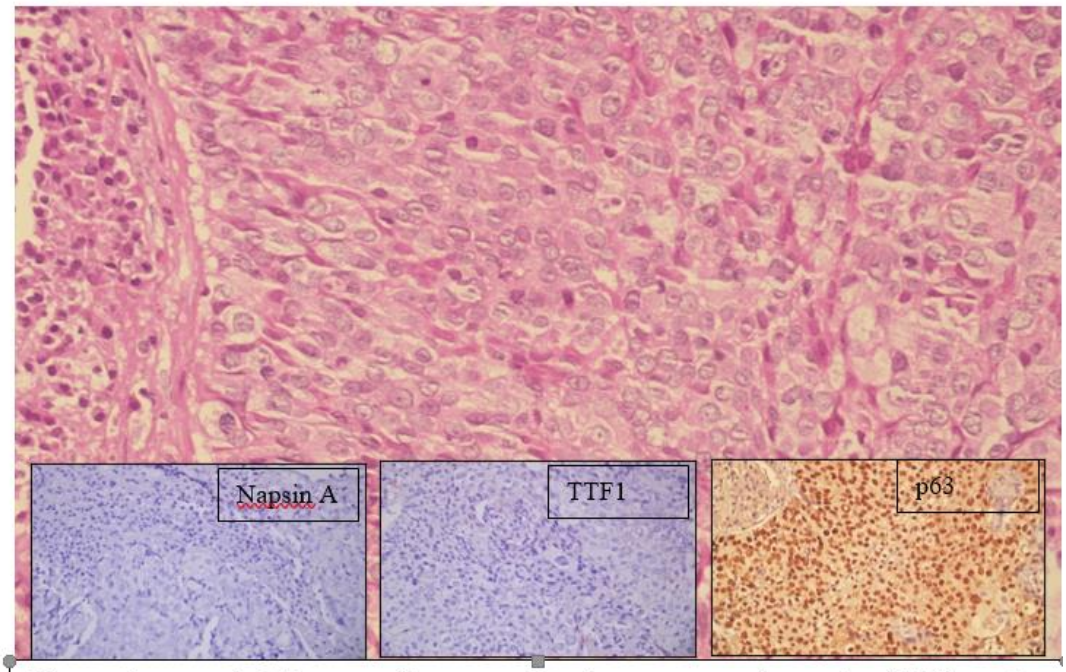
Photomicrograph 1: Tumor cells arranged in diffuse sheets and nests in Adenocarcinoma (H&E,x40). NapsinA and CK7 expression in adenocarcinoma.



Photomicrograph 2: Tumor cells are seen along the surfaces of alveolar walls in Lepidic adenocarcinoma (H&E X40).



Photomicrograph 3: Pleura infiltrated by atypical lymphoid cellsin T-cell Non-Hodgkin lymphoma (H&E, x40) with CD3 expression. Ki67 showing high-proliferative index (Ki67 >90%).



Photomicrograph 4. Tumor cells arranged in sheets, nests and occasional ill formed glands in Poorly differentiated Squamous cell carcinoma (H&E, x40) with p63 expression. NapsinA and TTF1 in Squamous cell carcinoma showing no immunoreactivity.