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A 5 Year Tertiary Centre Experience of Frequency & Risk Factors Association with Primary and Secondary Lung Cancers

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ABSTRACT

Introduction: Lung cancer is one of the commonest cancers worldwide having either small cell or non-small cell types and smoking is its major risk factor. We intend to study distribution of various lung malignancies and their association with various risk factors in a Pakistani population sample.

Aims & Objectives: To evaluate the frequency of types of primary and secondary lung cancers in a sample of the Pakistani population and see their association with age, gender, and smoking.

Place and duration of study: The department of Pulmonology, Shaikh Zayed Hospital, Federal Postgraduate Medical Institute, Lahore, Pakistan, from August 2017 to August 2022 (5 years).

Material & Methods: Analysis of retrospective data of 156 consecutive patients age 40-70 years diagnosed with primary or secondary lung cancers. Data were stored and analyzed using IBM-SPSS version 23.0. Diagnosis was established through fibreoptic (FOB), or rigid bronchoscopies or CT and U/S guided percutaneous lung biopsies, P-value<0.05 was taken as significant

Results: There were 156 samples, among them 37.8% were found with age group 41 – 60 years old, 31.4% with age group 61 – 70 years old, mean age of subjects was 58.3 (SD=±14.9) years. 82.1% were of male gender, 42.9% were non-smokers, 25% were found with less than or equal to 25 smoking pack years, median smoking pack years were 30 with range 5 – 100 smoking pack years. Distribution of primary lung malignancy revealed; 28.8% having Squamous cell carcinoma, 35.3% with Adenocarcinoma, 13.5% with small cell carcinoma, 2.6% with large cell carcinoma and 5.8% with primary lung carcinoid tumors. Secondary deposits of cancer in lungs were found in 22 (14.1%) subjects. Pearson Chi Square test showed significant association of primary type of cancer with age group, gender, and smoking pack years (p <0.01).

Conclusion: Adenocarcinoma was most frequent lung malignancy followed by Squamous cell carcinoma and small cell carcinoma was less frequent. Advancing age, male gender and cigarette smoking are strongly associated with the diagnosis of lung cancer.

Keywords: Biopsy, interventions, lung cancer, primary, secondary.

INTRODUCTION

Lung cancer is among the most common cancers worldwide. It is generally classified as either small cell (20%, mostly central tumors with falling incidence) or non-small lung cancer (NSCLC) accounting for the remaining 80%[1]. Within NSCLC, adenocarcinoma (30% to 35%), mostly a peripherally located tumor is the most common cell type having rising incidence in never smokers; squamous cell carcinoma (20% to 25%) that mostly occurs in smokers as a central tumor which may cavitate and large cell carcinoma (10% to 15%), again a peripheral tumor, while the remainders are unclassified or poorly differentiated lung cancers[1,2]. Globally tobacco smoking is responsible for 80% to 90% of the cases of lung cancer but advancing age, chronic obstructive pulmonary disease (COPD) and exposure to chemicals like nickel, arsenic, chromium, asbestos, radon, polycyclic hydrocarbons and chloromethyl ether have also proven to be causative of lung cancer[2]. It has been observed that in Pakistan, lung cancer is the

second most common cancer in men and the third most common cancer in both sexes combined[3].

We have carried out a retrospective analysis of data saved over the past five years to see the distribution of various types of lung cancer and their association with common risk factors. Our research also highlights that majority of patients with lung cancer usually present late in the course of their disease (stage III/IV) in contrast to patients in the Western world who are diagnosed at earlier stages.

MATERIAL AND METHODS

The study was a descriptive case series, carried out in the Department of Pulmonology at Shaikh Zayed Hospital, Federal Postgraduate Medical Institute, Lahore, Pakistan, during August 2017 to August 2022. All patients diagnosed to have primary or secondary lung cancers only during this period were included. Excluded were patients with benign airways/pulmonary neoplasms as well as malignancies involving the mediastinum and pleura. A total of 156 biopsy proven cases of malignancy who underwent interventional procedures including FOB, rigid bronchoscopies and percutaneous tumor/lung biopsies to obtain malignant tissue for histopathological diagnoses were included. Rigid bronchoscopies (Karl Storz® Rigid Bronchoscope 10318-C) for tumor diagnostic sampling (excisional/non-excisional biopsy) were done in operation theatre under general anesthesia in 9 (5.8%) patients. FOB biopsies (Fujinon® EB-270T flexible bronchoscope) were carried out in 138 (88.5%) subjects, and percutaneous lung/tumor biopsies (Monopty® Disposable Core Biopsy Instrument 14G) were done in 9 (5.8%) subjects, at the Departmental Interventional Pulmonology's procedure suite. FOB and percutaneous lung/tumor biopsies were performed using local anesthesia (lignocaine 2% spray during FOB for topical anesthesia in the airways/to suppress cough, and lignocaine 2% to infiltrate intercostal space for percutaneous lung/tumor biopsies) and procedural analgesia & sedation were achieved using intravenous midazolam ± morphine or fentanyl (depending upon the availability in the hospital). All procedures were performed according to specified protocols including obtaining informed written consents, using prophylactic oxygen during procedure and monitoring of oxygen saturation, heart rate and blood pressure. In patients in whom FOB was used to obtain tumor tissue for histopathology, majority (129 subjects 82.7%) required endobronchial tumor biopsies while 9 (5.8%) underwent transbronchial lung biopsy to collect tumor tissue for histopthological analyses.

Data Analyses:

Data were stored and analyzed using IBM-SPSS version 23.0. Counts with percentages were reported on age group, gender, Smoking Packs, Primary & Secondary types of lung Cancer and procedures were used. Association of cancer type was tested with age, gender and smoking packs of studied samples using Pearson Chi Square test. P-values less than 0.05 were considered statistically significant. Bar diagrams and Pie charts were also used to give graphical presentation of study outcomes.

RESULT

In the present study there were 156 samples among them 37.8% were found with age group 41 – 60 years old, 31.4% with age group 61 – 70 years old, mean age of samples was 58.3 (SD=±14.9) years. 82.1% were male gender, 42.9% were non-smokers, 25% were found with less than or equal to 25 smoking pack years, median smoking pack years were 30 with range 5 – 100 smoking pack years (Table-1). Table-2 reports the descriptive on types of cancer and procedures; in patients presenting with primary lung cancers, 35.3% were found to have Adenocarcinoma, 28.8% were found to have Squamous cell carcinoma, , 13.5% with small cell carcinoma, 2.6% with large cell carcinoma and 5.8% with primary lung carcinoid.

Secondary deposits of cancer in lungs were diagnosed in 22 (14.1%) subjects and distribution included 2.6% having non-Hodgkin's lymphoma, 1.3% with Hodgkin's lymphoma, 1.9% with metastatic hepatocellular carcinoma, 2.6% with metastatic carcinoma of unknown origin, 2.6% with metastatic sarcoma, 0.6% with metastatic carcinoma of esophagus, and 0.6% with metastatic adenoid cystic carcinoma.

Whereas majority (82.7%) patients were diagnosed using FOB with predominant technique being Endobronchial Biopsy (EBB), remaining diagnostic modalities included Trans-bronchial Lung Biopsy (TBLB), rigid bronchoscopic biopsy and percutaneous lung mass biopsy in 9 (5.8%) subjects each. All types of cancers were predominantly found in male subjects. Table-3 represents that among Squamous cell cancer 37.8% with age 41 – 60 years old, 97.8% were male gender, and 48.9% with history of more than 25 smoking pack years; for adenocarcinoma 40% with age 41 – 60 years, 76.4% with male gender,

and 21.8% with more than 25 smoking pack years; for small cell cancer 42.9% with age group 61 – 70 years old, 95.2% were male gender, and 57.1% with more than 25 smoking pack years; for large cell cancer 50% with age more than 70 years old, 75% were male gender, and 50% with more than 25 smoking pack years, whereas for primary lung carcinoid all nine samples with age less or equal to 40 years, 66.7% were female, and 11.1% were less or equal to 25 smoking pack years. Pearson Chi Square test showed significant association of primary type of cancer with age group, gender, and smoke packs ($p < 0.01$).

Characteristics		n	%
Age Group	**≤40 years**	20	12.8
	41 - 60 years	59	37.8
	61 - 70 years	49	31.4
	>70 years	28	17.9
	Mean (±SD)	**58.3**	**±14.9**
Gender	**Male**	128	82.1
	Female	28	17.9
Smoking Pack Years	**Nonsmoker**	67	42.9
	≤25 pack years	39	25.0
	>25 pack years	50	32.1
	Median (Range)	**30**	**(5 – 100)**

Table-1: Baseline Characteristics of Studied Samples (n=156).

Variables		N	%
Primary Lung Cancer Type	Primary Lung Cancers (total cases)	134	85.9
	Adenocarcinoma	55	35.3
	Squamous cell Carcinoma	45	28.8
	Small Cell Carcinoma	21	13.5
	Large Cell Carcinoma	4	2.6
	Primary lung Carcinoid	9	5.8
Secondary Lung Cancer Type	Secondary Lung Cancers (total cases)	22	14.1
	Hodgkin's Lymphoma	2	1.3
	Non-Hodgkin's Lymphoma	4	2.6
	Metastatic Renal Cell Carcinoma	2	1.3
	Metastatic Hepatocellular Carcinoma	3	1.9
	Metastatic Pancreatic Cancer	1	0.6
	Metastatic Carcinoma of Unknown Origin	4	2.6
	Metastatic Sarcoma	4	2.6
	Metastatic Esophageal Carcinoma	1	0.6
	Metastatic Adenoid Cystic Carcinoma	1	0.6
Diagnostic Procedure	Flexible Bronchoscopy (EBB)*	129	82.7
	Flexible Bronchoscopy (TBLB)**	9	5.8
	Rigid Bronchoscopy	9	5.8
	Percutaneous Lung Mass Biopsy	9	5.8

Table-2: Descriptive on Types of Lung Cancer and Procedures (n=156).

***EBB:** Endobronchial biopsy.

****TBLB:** Trans-bronchial Lung Biopsy.

Characteristics		Primary and Secondary Lung Cancer Type												p-value
		Secondary Lung Cancers (n=22)		Squamous Cell Cancer (n=45)		Adenocarcinoma (n=55)		Small Cell Cancer (n=21)		Large Cell Cancer (n=4)		Primary lung Carcinoid (n=9)		
		n	%	n	%	n	%	n	%	N	%	n	%	
Age Group	≤ 40 years	5	22.7	-	-	5	9.1	1	4.8	-	-	9	100.0	<0.01*
	41 - 60 years	12	54.5	17	37.8	22	40.0	7	33.3	1	25.0	-	-	
	61 - 70 years	4	18.2	17	37.8	18	32.7	9	42.9	1	25.0	-	-	
	>70 years	1	4.5	11	24.4	10	18.2	4	19.0	2	50.0	-	-	
Gendr	Male	16	72.7	44	97.8	42	76.4	20	95.2	3	75.0	3	33.3	<0.01*
	Female	6	27.3	1	2.2	13	23.6	1	4.8	1	25.0	6	66.7	
Smoking Pack Years	Non Smoker	19	86.4	7	15.6	29	52.7	2	9.5	2	50.0	8	88.9	<0.01*
	≤25	1	4.5	16	35.6	14	25.5	7	33.3	-	-	1	11.1	
	>25	2	9.1	22	48.9	12	21.8	12	57.1	2	50.0	-	-	
*p<0.05 was considered statistically significant using Pearson Chi Square test														

Table-3: Association of primary and secondary lung cancer types with age, gender and smoking pack years.

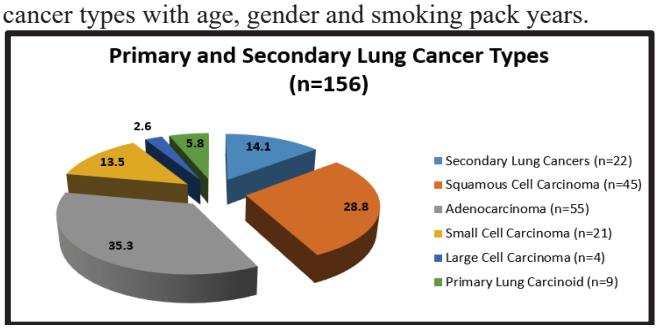

Fig-1: Types of primary and secondary lung cancers.

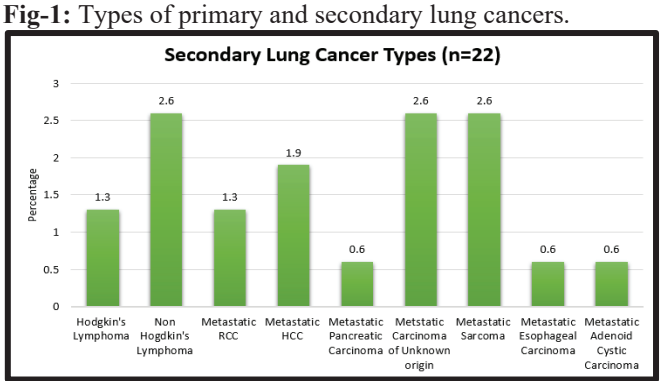

Fig-2: Secondary lung cancer types.

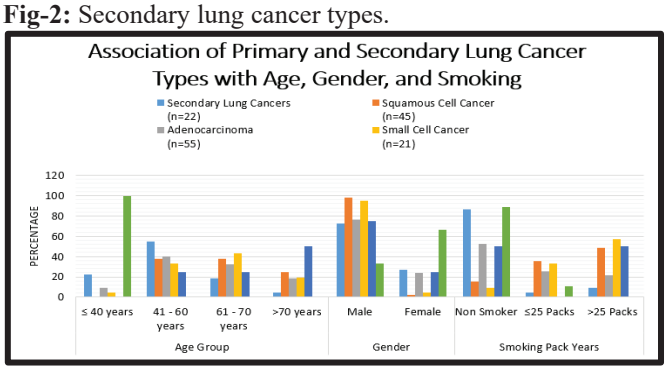

Fig-3: Association of primary and secondary lung cancer types with age, gender and smoking pack years.

DISCUSSION

This retrospective study evaluated the frequency of different types of primary and secondary lung cancers in all consecutive patients having biopsy proven (histologically confirmed) malignancies confined to airways and/or lung parenchyma only. Among 156 subjects with different types of primary and secondary lung cancers, the main diagnostic tool was FOB to perform biopsies form the malignant neoplasms. Similar to our study, conventional flexible diagnostic FOB with forceps biopsy has usually been the modality of choice to obtain adequate biopsy specimen (preferable to a cytological specimen) from all accessible tracheobronchial (central) lesions as well as lesions with suspected airway involvement[4]. In patients with cancer involving the lung parenchyma without any accessible airway lesion/s, TBLB done using FOB (under fluoroscope guidance) can provide good diagnostic yield[5]. Transthoracic/percutaneous needle biopsy involves passing a needle under image guidance (ultrasound/fluoroscope/CT), to biopsy malignant tissue with a sensitivity of 74 to 90 percent for suspected lung lesions[6]. Whereas majority (129, 82.7%) of our study patients were diagnosed using FOB with predominant technique being EBB, remaining diagnostic modalities included TBLB, rigid bronchoscopic biopsy and percutaneous lung mass biopsy in 9 (5.8%) subjects each. We utilized rigid bronchoscope to consider large/excisional biopsy (along with therapeutic tumor debulking) of the malignant bronchogenic cancers associated with complications including airway obstruction and ipsilateral lung atelectasis, recurrent hemoptysis and severe dyspnea; similar to international recommendations[4, 7].

In this study, among NSCLC types (Fig-1, Table-3), adenocarcinoma was the most frequent cancer followed by squamous cell lung cancer, and the least frequent were large cell cancers, again almost similar to the global prevalence for different types of bronchogenic cancers.[1] Majority of our patients with all types of primary and secondary lung cancers were males probably because of more smoking prevalence in males, also found across the world. [3, 4, 8] However, primary bronchial/lung carcinoids (neuroendocrine tumors) were predominantly found in females (6 patients, 66%) out of 9 cases, global prevalence for lung carcinoid tumors has also been high in female gender.[9]

Lung cancer is predominantly a disease of elderly population. However, in our study, age distribution among primary and secondary lung cancers varied. Majority (75.6%) of cases of squamous cell lung cancers were found in subjects 41-70 years of age and none below 40 years old. Adenocarcinoma distribution was found in all age groups including 5 subjects (9.1%) being less than 40 years old. The lowest aged subject with NSCLC was a never-smoker 35-year-old male having adenocarcinoma histology.[10] Large cell lung cancer was found only in 4/156 patients, 2 in subjects >70 years old. In contrast to NSCLC, majority (9, 42.9%) small cell cancers were found in subjects with age >70 years. Similar to other studies, carcinoid tumors were found only in younger individuals less than 40 years old[9]. In comparison to our study, an old epidemiological study (1998) of 182 patients from Shaukat Khanum Cancer hospital Lahore showed age more than 50 years being the frequent age in NSCLC patients with 75% being smokers.[11] Almost similar to our study, US data from National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program showed that of all primary lung cancer cases (other than carcinoid tumors), 70.4% occur in persons over the age of 65, with approximately half of those in persons over the age of 75 and only 7.7% of cases in those less than 45 years of age.[12]

The venous return containing lymphatic fluid from body tissues flows into the lungs through the pulmonary vascular system; thus, all malignant tumors have the potential to metastasize into the lungs. Secondary/metastatic tumors in the lungs are seen in 20-54% of extrathoracic malignancies, with the breast, colorectal, kidney, head and neck, and uterus cancers being the most common primary tumors with lung metastasis at autopsy. [13] In contrast, in our study, lung/bronchial metastatic cancers were diagnosed in 22 (14.1%) subjects and had a different frequency including highest numbers from Non-Hodgkin's lymphoma (4 subjects, 2.6%), Metastatic Sarcoma (4 subjects, 2.6%), Metastatic Carcinoma of Unknown Origin (4 subjects, 2.6%) followed by Metastatic Hepatocellular Carcinoma (3 subjects, 1.9%) followed by Hodgkin's lymphoma (2 subjects, 1.3%) and metastatic renal cell carcinoma (2 subjects, 1.3%) and the least frequent being metastatic carcinoma of esophagus, metastatic pancreatic carcinoma and metastatic adenoid cystic carcinoma having 1 subject (0.6%) each (Fig-2). More than half of patients with nodal lymphoma have lung involvement as was also

diagnosed in 6 out of 22 patients in our study population[14].

The primary risk factor for the development of lung cancer remains tobacco smoking, estimated to account for approximately 90 percent of all lung cancers[3,15]. The risk of lung cancer increases with both the number of cigarettes smoked per day (pack-years) as well as the lifetime duration of smoking[16]. The same phenomenon was observed in our research, majority of patients with small and NSCLC had history of more than 25 smoking pack-years except adenocarcinoma that was found slightly more in subjects with less than 25 smoking pack-years (Fig-3, Table-3). On the other hand, despite the predominance of tobacco smoking as its presumed etiology, lung cancer is also a significant health problem in never smokers[17]. In our study, 4 out of 5 subjects less than 40 years old were never smoker females having advanced stage (III-IV) adenocarcinoma histology. It has already been revealed that the subset of patients with NSCLC under the age of 40 has a higher proportion of women, adenocarcinoma histology, and representation of Asian/Pacific Islanders, and is more likely to present with distant metastases.[18] However, not all people with these risk factors develop lung cancer, and some without any known risk factor do, indicating the importance of genetic influences. Future advances in understanding and treating lung cancer will be based on genetic analysis.

CONCLUSION

Lung cancer is among the most common cancers across the globe comprising of small versus NSCLC. Conventional FOB (EBB/TBLB) is the initial diagnostic tool for majority of individuals and rigid bronchoscope can be utilized when the tumor is associated with airway occlusion, post obstructive pneumonia and recurrent hemoptysis. In our study Adenocarcinima has been the most frequent lung cancer followed by Squamous cell carcinoma and small cell carcinoma. Advancing age, male gender and smoking is strongly associated with the occurrence of lung cancers.

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