Original Article

Clinical profile of lung cancer in North India: A 10-year analysis of 1862 patients from a tertiary care center

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ABSTRACT

Introduction: Over the past few years, the demographic profile of lung cancer has changed. However, most reports are limited by small numbers, short follow-up period, and show an inconsistent pattern. A comprehensive evaluation of changing trends over a long period has not been done. **Materials and Methods:** Consecutive lung cancer patients were studied over a 10-year period from January 2008 to March 2018 at the All India Institute of Medical Sciences, New Delhi, and relevant clinical information, and survival outcomes were analyzed. **Results:** A total of 1862 patients were evaluated, with mean (SD) age of 59 (11.1) years, and comprising 82.9% males. Majority were smokers (76.2%) with median smoking index of 500 (interquartile range [IQR]: 300–800). Adenocarcinoma (ADC) was the most common type (34%), followed by squamous cell carcinoma (SCC – 28.6%) and small cell lung cancer (SCLC) (16.1%). Over the 10-year period, ADC increased from 9.5% to 35.9%, SCC from 25.4% to 30.6%, and non-small cell lung cancer -not otherwise specified (NSCLC-NOS) decreased from 49.2% to 21.4%. The proportion of females with lung cancer increased although smoking rates remained similar. Majority of NSCLC (95%) continued to be diagnosed at an advanced stage (3 or 4). Epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements were present in 25.3% and 11.5% ADC patients, respectively. The median overall survival was 8.8 months (IQR 3.7–19) for all patients and 12.57 (IQR 6.2–28.7) months among the 1013 patients who were initiated on specific treatment (chemotherapy, targeted therapy, radiotherapy, or surgery). Never-smokers were younger, more likely to be female and educated, had a higher prevalence of ADC and EGFR/ALK mutations, and had better survival. **Conclusion:** Among this large cohort, our center seems to follow the global trend with increasing incidence of ADC. EGFR mutation positivity was similar to existing reports, while higher ALK positivity was detected. A characteristic phenotype of never-smokers with lung cancer was elucidated which demonstrated better survival.

KEY WORDS: India, lung cancer, smoking, trends

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INTRODUCTION

Lung cancer is the leading cause of cancer-related death in the world and likely to remain so in the foreseeable future. According to the GLOBACON report 2018, lung cancer affected about 2.1 million persons (11.6% of all cancers) and caused 1.8 million deaths (which comprised 18.4% of all cancer-related deaths. The above report also estimated that in India, a total of 67,795 new lung cancer cases occurred (5.9% of all cancers) in 2018, of which 48,698 (8.5%) occurred in males.[1] Further, lung cancer caused 63,475 deaths, comprising 8.1% of all cancer-related deaths.[1]

Although the global mortality due to lung cancer has started to decline, probably reflecting the decrease in smoking habits, the prevalence in India appears to be increasing.[2] According to the Indian Council of Medical Research cancer registry, there were 57,795 new cases of lung cancer in 2012, which is projected to rise to 67,000 new cases annually by the year 2020.[3] More importantly, the high disease-attributable mortality makes this condition an important public health issue.

In recent years, there has been a great interest in the histological characterization and genomic classification of lung carcinoma due to the availability of several new targeted therapeutic modalities.[4] The previously accepted broad classification of lung cancer into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) is now considered inadequate. Subtype analysis for mutations such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) rearrangements, ROS-1 translocation, or expression of programmed death receptor-1 (PD-1)/PD ligand-1 now forms the basis of targeted therapy/immunotherapy for lung cancer. The morphology of lung cancer also appears to be changing, with adenocarcinoma (ADC) equaling or even overtaking squamous cell carcinoma (SCC) in terms of the frequency of occurrence in most Western and some Asian countries.[5,6] However, the clinical and pathological profile of lung cancer in India appears to show a wide variability. Furthermore, long-term trends in lung cancer demographics have been sparsely reported, and most centers reported outcomes over relatively short periods. The present study, thus, aimed to perform a comprehensive evaluation of the clinicopathological and molecular profile of a large cohort of lung cancer patients in a tertiary care health-care center in North India and to study trends of important variables over a 10-year period.

MATERIALS AND METHODS

This was an ambispective observational study that included consecutive patients with pathologically (biopsy or cytology) proven lung cancer diagnosed between January 1, 2008, and March 31, 2018, in the Department of Pulmonary, Critical Care, and Sleep Medicine, All India Institute of Medical Sciences, New Delhi. Patients who had thoracic metastatic disease from a nonpulmonary primary cancer were excluded. Prior approval was taken from the Institutional Ethics Committee.

The clinical details were recorded in a predesigned structured proforma which comprised of demographic and socioeconomic characteristics, a detailed smoking history (reformed or current smoker, bidi, cigarette or hookah smoking, smoking index, and pack-years), previous treatment history, details of imaging findings, and diagnostic investigations [transthoracic ultrasound or computed tomography (CT)-guided fine-needle aspiration or biopsy, bronchoscopic, or endobronchial ultrasound (EBUS)-guided fine-needle aspiration, or biopsy using radial-probe EBUS, thoracoscopy (rigid or semi-rigid)-guided biopsy, pleural fluid analysis, peripheral lymph node biopsy, or biopsy from any other site for definitive diagnosis], pathological and molecular characteristics of tumor, baseline laboratory investigations, treatment details, and overall survival (OS).

Patients were classified on the basis of morphology using the WHO classification of lung tumors as (1) non-small cell lung carcinoma (SCC, adenocarcinoma, and non-small cell lung carcinoma -not otherwise specified [NSCLC-NOS]); (2) SCLC, and (3) miscellaneous tumors.[7] Patients diagnosed at other centers were required to have their tissue specimens re-reviewed by a pathologist at our center. In case the pathology review was inconclusive, repeat tissue sampling was performed.

Immunohistochemistry (IHC) was started in 2011 in our institute as a routine for lung cancer specimens. Tissue samples in ADC were subjected to appropriate driver mutation studies. EGFR mutations in tissue were tested using Qiagen ARMS scorpion PCR assay. ALK rearrangements were determined by IHC or fluorescence *in situ* hybridization method. Disease staging was done using either a whole-body positron emission tomogram-computerized tomogram (PET-CT) or CT scan of chest and upper abdomen, bone scan, and magnetic resonance imaging/CT Brain. In NSCLC, the disease was staged according to the American Joint Committee on Cancer (AJCC) 7th edition tumor-node-metastasis (TNM) staging system for patients diagnosed on or before December 31, 2016, and IASLC (the International Association for the Study of Lung Cancer)-AJCC-UICC TNM staging (8th edition) if diagnosed after January 1, 2017.[8,9] In SCLC, the disease was classified according to the Veterans Administration Lung Group 2-stage system, as limited disease and extensive disease.[10]

The performance status of patients was noted using the modified Karnofsky Performance Scale (KPS) and Eastern Cooperative Oncology Group scale (ECOG).[11] Patients were treated with a multidisciplinary approach in consultation with radiotherapist, radiologist, nuclear medicine specialist, and surgeon. Details of treatment, i.e., surgical resection, chemotherapy, radiotherapy, or targeted therapy were noted. Overall survival (OS) was calculated from the date of definitive diagnosis to the date of death or date of the last follow-up. Patients were considered on continuous follow-up if the last visit fell within 1 month of data censoring (July 31, 2018). In

case where the last visit was more than 1 month ago, attempts were made to contact the patient by telephone. Patients were followed from the date of registration to the date of death and were censored at the date they were last known to alive, i.e., date of the last follow-up either in person or telephonically. In the retrospective part of the study, an attempt was made to obtain the treatment response and survival detail from the patient or relatives telephonically.

Statistical analysis

Data were recorded on a predesigned proforma and managed on an Excel spreadsheet. Quantitative variables were checked for approximate normality. Variables following normal distribution were expressed as mean (standard deviation), and variables that followed skewed distribution were expressed as median (interquartile range [IQR]). Categorical variables were expressed as frequency (%). Median OS was estimated using Kaplan–Meier survival curve. The association between the two categorical variables was compared by Chi-square test and Student's *t*-test was used to compare the difference in the mean age of two independent data sets. Statistical analysis was performed using StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP, and a $p < 0.05$ was considered statistically significant.

RESULTS

A total of 1862 patients with lung cancer were included in the study. Table 1 shows the main demographic and baseline characteristic of the study group.

Majority of the patients were males (82.9%), in the age bracket of 46–70 years, with mean (SD) age of 58 (11.1) years. The mean age remained relatively unchanged over the study time-period [Figure 1]. The proportion of females showed an increasing trend, from 7.9% in 2008 to 27.2% in 2018. Majority of patients (54.7%) were either illiterate or received primary education only. Smokers comprised 76.2% of all patients and among them, 69.2% were heavy smokers with median smoking index of 500 (IQR, 300–800). Flexible bronchoscopy was the most common diagnostic modality (50.2%), followed by CT or ultrasound-guided interventions (32.6%), pleural fluid analysis/thoracoscopic biopsy (6.5%), and peripheral lymph node fine-needle aspiration/biopsy (5.6%).

The most common symptoms were cough (81.3%), loss of appetite (65.9%), dyspnea (64.9%), fatigue (60.4%), weight loss (58.1%), chest pain (48.9%), and hemoptysis (36.1%). Significant physical findings included digital clubbing (18.7%), peripheral lymphadenopathy (13.3%), neurological manifestations (2.1%), and superior vena cava obstruction (3.4%).

The right and left upper lobes were the most commonly affected lobes (26.9% and 24.4% respectively); 8.3% of patients had predominant mediastinal involvement. Adenocarcinoma (ADC) was the most common pathological

Table 1: Demographic and baseline characteristics of lung cancer patients

Variable	Sub-group	*n* (%)
Age (years) (*n*=1862)	≤45	256 (13.8)
	46-70	1410 (75.7)
	>70	196 (10.5)
Sex (*n*=1862)	Male	1544 (82.9)
	Female	318 (17.1)
Education level (*n*=1518)	Illiterate	416 (27.4)
	Primary level	415 (27.3)
	Secondary level (matric)	370 (24.4)
	Higher secondary	150 (9.9)
	Graduation	126 (8.3)
	Postgraduation	41 (2.7)
Smoking status (*n*=1788)	Never smoker	425 (23.8)
	Current smokers	697 (39)
	Reformed smokers	666 (37.2)
Smoking index (*n*=1136)	<100	95 (8.4)
	100-300	254 (22.4)
	301-600	385 (33.9)
	>600	402 (35.3)
Diagnostic modality (*n*=1772)	Flexible bronchoscopy	890 (50.2)
	CT/USG-guided FNAC/biopsy (lung)	577 (32.6)
	Thoracoentesis	95 (5.4)
	Thoracoscopic Pleural biopsy	19 (1.1)
	Peripheral lymph node sampling	100 (5.6)
	EBUS	47 (2.7)
	Lung biopsy (surgical)	6 (0.3)
	Others	38 (2.1)
Predominant lobe involved (*n*=1467)	Upper lobe	792 (51.3)
	Right middle lobe/lingula	112 (7.7)
	Lower lobe	326 (22.2)
	Others	277 (18.8)
Pathological type (*n*=1862)	ADC	634 (34.0)
	SCC	532 (28.6)
	NCSLC (NOS)	338 (18.1)
	Small cell carcinoma (SCLC)	300 (16.1)
	Others	58 (3.2)
NSCLC stage TNM staging 7th ed. (before 1st January, 2017)	Stage 1	14 (1.2)
	Stage 2	44 (3.8)
	Stage 3	337 (29.1)
	Stage 4	766 (65.9)
NSCLC stage TNM staging 8th ed. (1st January, 2017 onwards)	Stage 1	7 (1.6)
	Stage 2	8 (1.9)
	Stage 3	127 (30.2)
	Stage 4	279 (66.3)
Small cell carcinoma stage (*n*=275)	Limited stage	68 (24.8)
	Extensive stage	207 (75.2)
ECOG (*n*=1493)	0, 1	758 (50.8)
	2	484 (32.4)
	≥3	251 (16.8)
KPS (*n*=1567)	≤60	388 (24.8)
	70	344 (21.9)
	80-100	835 (53.3)
EGFR mutations (*n*=257)	Positive	65 (25.3)
	Negative	192 (74.7)
ALK rearrangement (*n*=192)	Positive	22 (11.5)
	Negative	170 (88.5)

CT: Computed tomography, USG: Ultrasound, FNAC: Fine-needle aspiration cytology, EBUS: Endobronchial ultrasound, ECOG: Eastern cooperative oncology group, KPS: Karnofsky Performance Status Scale, EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, ADC: Adenocarcinoma, SCC: Squamous cell carcinoma, SCLC: Small cell lung cancer, NSCLC: Non-SCLC, TNM: Tumor node metastasis, NOS: Not otherwise specified

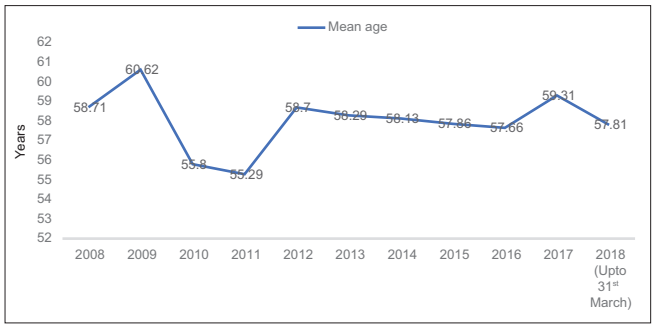

Figure 1: Year-wise mean age of patients over time period of study. The mean (standard deviation) age of patients over first 5-year block (2008–2012) compared to the next 5-year block (2013 to March 2018) was similar, (57.7 [10.3] years vs. 58.3 [11.3] years), respectively, (P = 0.42)

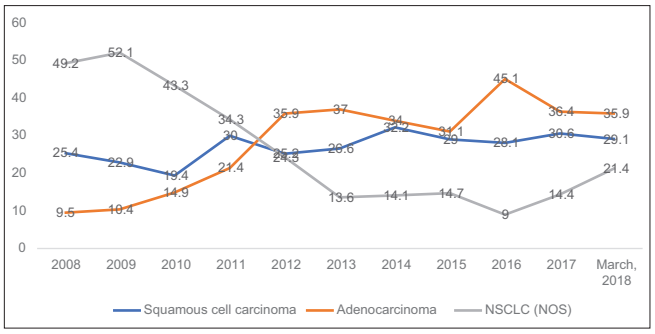

Figure 2: Depicts the year-wise distribution (%) of adenocarcinoma, squamous cell carcinoma and non-small cell lung cancer (not otherwise specified) over the study period from 2008 to 2018

Table 2: Year-wise distribution of various pathologic types of lung cancer

Years	SCC	ADC	NSCLC (NOS)	SCLC	Others
2008 (n=63)	16 (25.4)	6 (9.5)	31 (49.2)	10 (15.9)	0 (0)
2009 (n=48)	11 (22.9)	5 (10.4)	25 (52.1)	7 (14.6)	0 (0)
2010 (n=67)	13 (19.4)	10 (14.9)	29 (43.3)	15 (22.4)	0 (0)
2011 (n=70)	21 (30)	15 (21.4)	24 (34.3)	10 (14.3)	0 (0)
2012 (n=103)	26 (25.2)	37 (35.9)	25 (24.3)	14 (13.6)	1 (1.0)
2013 (n=154)	41 (26.6)	57 (37.0)	21 (13.6)	33 (21.4)	2 (1.4)
2014 (n=233)	75 (32.2)	79 (34.0)	33 (14.1)	40 (17.2)	6 (2.5)
2015 (n=286)	83 (29.0)	89 (31.1)	42 (14.7)	59 (20.6)	13 (4.6)
2016 (n=359)	101 (28.1)	162 (45.1)	32 (9.0)	51 (14.2)	13 (3.6)
2017 (n=376)	115 (30.6)	137 (36.4)	54 (14.4)	54 (14.4)	16 (4.2)
Upto March 2018 (n=103)	30 (29.1)	37 (35.9)	22 (21.4)	7 (6.8)	7 (6.8)

ADC: Adenocarcinoma, SCC: Squamous cell carcinoma, SCLC: Small-cell lung cancer, NSCLC: Non-SCLC, NOS: Not otherwise specified

type (34.0%), followed by (SCC-28.6%), NSCLC-NOS (18.1%), and SCLC (16.1%). Other tumors included neuroendocrine morphology (0.9%), adenoid cystic carcinoma (0.6%), sarcomatoid carcinoma (0.4%), mesothelioma (0.4%), and mesenchymal carcinoma (0.1%) [Table 1].

Majority of patients had good performance status, i.e., ECOG 0 or 1, and KPS >70. Among NSCLC, >90% had advanced disease (stage 3 or 4), while 75.2% of SCLC had extensive stage.

EGFR mutation positivity was detected in 65/257 (25.3%) of ADC patients, whereas ALK rearrangements were detected in 22/192 (11.5%) patients. Among patients in whom typing of EGFR mutations was available (42 patients), 32 patients (76.2%) had exon 19 deletions, 8 patients (19.0%) had exon 21 point mutations, while 2 patients (4.8%) demonstrated T790M mutations in exon 20.

Table 2 shows the year-wise distribution of various pathological types of lung cancer patients over 10 years. ADC showed increasing trend over time, comprising 9.5% of all lung cancers in 2008 to 36.4% in 2017 and 35.9% in the first quarter of 2018, while SCC increased from 25.4% in 2008 to 30.6% in 2017 and 29.1% in 2018 [Figure 2]. The frequency of NSCLC (NOS) declined from 49.2% in 2008 to 14.4% in 2017 and 21.4% in 2018. We found a significant shift in morphological pattern of NSCLC between the first five years (2008-2012) and the next five (2013-2018), showing increase of ADC from 20.8% to 37.1%, SCC from 24.8% to 29.4%, and decrease of non-small cell carcinoma (NOS) from 38.18% to 13.5%.

The prevalence of smoking among males ranged between 73.3% and 93.5%, and in females, between 23% and 50% over the study period [Figure 3]. Among females, the prevalence of lung cancer increased in spite of the smoking prevalence remaining relatively the same.

As shown in Table 3, smokers with lung cancer were significantly older, more likely to be male, had poor educational status, less advanced stage of disease, lower EGFR and ALK positivity, and were less likely to receive treatment compared to nonsmokers. No significant difference in performance status was noted. SCC was the most common histology in smokers (34.9%), whereas ADC was most common in nonsmokers (62.3%). NSCLC (NOS) and small cell carcinoma were less prevalent in nonsmokers compared to smokers (13% and 7.5% vs. 19.5% and 19.1%, respectively). Among the 1013 patients who received treatment, median (IQR) OS was significantly higher in never-smokers than smokers (17.6 months [7.4 – not reached] vs. 10.7 months [5.9–20.3], P < 0.001).

Table 4 depicts the histology differences based on gender and smoking status. In female smokers, the prevalence of ADC and SCC was almost identical (33.3% vs. 32.3% respectively). Among all nonsmokers, females had higher ADC and small cell carcinoma compared to males (66.5% and 14.6% vs. 58.5% and 8.1%, respectively). Adenocarcinoma morphology was commoner in male as well as female non-smokers compared to their counterparts who smoked; however, no significant difference was found in NSCLC morphology between male and female smokers (P = 0.09) or between male and female nonsmokers (P = 0.46).

Among the total 1803 patients, treatment details were available for 1013 patients, with the most common treatment modality being chemotherapy (87.5%) followed by radiotherapy (15.3%), targeted therapy (8.6%), and

surgery (3.0%). The most common chemotherapy regimens were carboplatin-paclitaxel (53.4%), cisplatin-etoposide (18.4%), carboplatin-gemcitabine (7.4%), and carboplatin-pemetrexed (9.0%). The median OS was 8.8 months (IQR, 3.7–19) for all patients, and 12.6 (IQR, 6.2–28.7) months among the 1013 patients who underwent specific treatment (chemotherapy, targeted therapy, radiotherapy, or surgery) and had at least one additional follow-up visit.

A comparative analysis of the demographic profile of the patients in the current study with other Indian and International reports showed that our patients were younger, had higher male preponderance, lesser smoking rates, and higher prevalence of SCC compared to western studies [Table 5].

Table 3: Comparison of characteristics between smokers and nonsmokers with lung cancer

Characteristics	Smokers	Nonsmokers	*P*
Age >60	797/1363 (58.5)	154/425 (36.2)	<0.001
Female	96/1363 (7)	203/425 (47.8)	<0.001
Education (above primary level education)	489/1120 (43.7)	182/358 (50.8)	0.018
Morphology			
ADC	340/1363 (24.9)	265/425 (62.3)	<0.001
SCC	476/1363 (34.9)	42/425 (9.9)	
Small cell carcinoma	261/1363 (19.1)	32/425 (7.5)	
NSCLC-NOS	266/1363 (19.5)	55/425 (13)	
EGFR mutation positivity, *n* (%)	23/129 (17.8)	37/117 (31.6)	0.012
ALK rearrangement positivity, *n* (%)	5/94 (5.3)	15/84 (17.9)	0.014
ECOG 0, 1	555/1099 (50.5)	191/371 (51.5)	0.744
Stage			
NSCLC (before January 1, 2017)			
Stage 1 or 2	46/788 (5.8)	8/239 (3.4)	<0.001
Stage 3	274/788 (34.8)	35/239 (14.6)	
Stage 4	468/788 (59.4)	196/239 (82.0)	
Ist January, 2017 onward			
Stage 1 or 2	9/263 (3.4)	6/122 (4.9)	<0.001
Stage 3	97/263 (36.9)	20/122 (16.4)	
Stage 4	157/263 (59.7)	96/122 (78.7)	
Small cell carcinoma			
Limited stage	62/244 (25.4)	6/26 (23.1)	0.794
Extensive stage	182/244 (74.6)	20/26 (76.9)	
Treatment received	733/1334 (54.9)	249/399 (62.4)	0.008
Median overall survival (months)	8.0 (3.23-16.6)	14.4 (4.9-NR)	<0.001

All values in *n* (%). NR: Not reached, ECOG: Eastern cooperative oncology group, EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, ADC: Adenocarcinoma, SCC: Squamous cell carcinoma, SCLC: Small-cell lung cancer, NSCLC: Non-SCLC, NOS: Not otherwise specified

DISCUSSION

To the best of our knowledge, this 10-year analysis is the largest single-center study to evaluate the clinical spectrum of lung cancer in India and revealed some interesting trends. The average age of our patients was 58 years, which is similar to that reported in previous Indian studies,[14,20,25,28] but almost 10 years less than the mean age reported in most Western studies.[30,33,34] No changing trend in age was seen during the study period.

Similarly, the male predominance in our study was similar to other Indian reports but higher than Western studies.[15,21,23,25,26,28] This may be a reflection of higher smoking prevalence in females in the West or possibly due to the fact that males tend to seek medical attention more frequently than females in our societal setup.[29,31-34] However, we observed a definite increase in the proportion of females from 7.9% in 2008 to 20.6% in 2017. Interestingly, the smoking prevalence among females did not increase proportionally during the same period. The likely explanation may be due to increase in females seeking medical attention over the last decade, or exposure/susceptibility to other unknown risk factors.

Most patients had poor educational status, with as many as 54.7% being either illiterate or educated up to primary level only. The prevalence of smoking in our study (80%) is comparable to other Indian studies[13,17,25,28] but lower than most Western data, which have reported smoking prevalence between 87% and 93%.[30,32,34] This observation supports the possibility of other contributing factors in lung cancer etiology, such as genetic predisposition, passive smoking, air pollution,

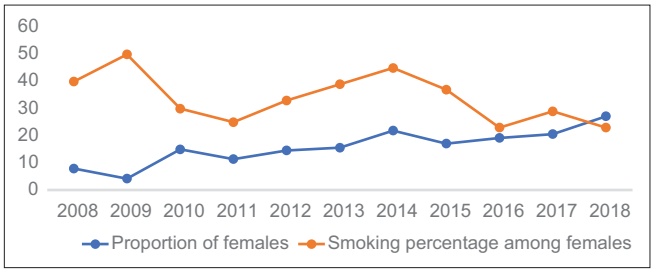

Figure 3: Year-wise proportion of female among total population and smoking prevalence among females over the time period of the study. The difference of proportion of females over first 5 years (2008–2012) compared to the next 5 years (2013–March 2018) was statistically significant (11.4% vs. 18.4%, *P* = 0.002); however, the smoking % in females over the two 5-year blocks was not significantly different (32.5% vs. 32.0%, *P* = 0.95)

Table 4: Histology differences in male and female according to their smoking status

Histology	Male smokers (*n*=1267)	Male nonsmokers (*n*=222)	Female smokers (*n*=96)	Female nonsmokers (*n*=203)
SCC	445 (35.1)	23 (10.4)	31 (32.3)	19 (9.4)
ADC	308 (24.3)	130 (58.5)	32 (33.3)	135 (66.5)
NSCLC (NOS)	256 (20.3)	31 (14.0)	7 (10.4)	24 (12.0)
Small cell carcinoma	240 (18.9)	18 (8.1)	21 (21.9)	14 (14.6)
Others	18 (1.4)	20 (9.0)	2 (2.1)	11 (11.5)

All values given in *n* (%). ADC: Adenocarcinoma, SCC: Squamous cell carcinoma, SCLC: Small-cell lung cancer, NSCLC: Non-SCLC, NOS: Not otherwise specified

Table 5: Comparison of Lung cancer demographics between various Indian and other international studies

Author (reference)	Place/country, year	Total	Male:female	Mean age (years)	Smokers (%)	SCC (%)	ADC (%)	SCC:ADC	SCLC
Jindal and Behera[12]	Chandigarh, 1990	1009	4.5:1	51	63	34.3	25.9	1.3	25.9
Gupta *et al*.[13]	Rajasthan, 1998	279	6.1:1	57	81.6	42	20	2.1	14
Prasad *et al*.[14]	Lucknow, 2004	400	4.3:1	57	71	46.5	18.5	2.5	18.2
Khan *et al*.[15]	Kashmir, 2006	321	11.3:1		88.4	77.3	5.3	14.5	17.1
Prasad *et al*.[16]	Lucknow, 2009	799	4.75:1	--	80.4	47.3	18.2	2.6	13.7
Rawat *et al*.[17]	Uttarakhand, 2009	203	8.2:1	56.4	81.77	44.83	19.38	2.2	16.75
Sheikh *et al*.[18]	Kashmir, 2010	783	6.98:1	57.8	68.1	71.3	2.6	27.9	20.8
Singh *et al*.[19]	Chandigarh, 2012	654	5:1	58.2	76.9	38.1	27.5	1.38	20.5
Dey *et al*.[20]	Kolkata, 2012	607	4.1:1	57.9	67.2	35.1	30.8	1.1	16.5
Noronha *et al*.[21]	Mumbai, 2012	489	3.5:1	56	52	26.2	43.8	0.60	8
Krishnamurthy *et al*.[22]	Tamil Nadu, 2012	258	3.5:1	56	60.5	15.8	42.6	0.37	13.2
Sharma *et al*.[23]	Himachal Pradesh, 2012	105	10.6:1	62.7	89.5	37.1	36.2	1.02	
Malik *et al*.[24]	New Delhi, 2013	434	4.6:1	55	67.9	32.1	37.1	0.86	14.7
Mandal *et al*.[25]	Manipur, 2013	466	1.09:1	58.5	73	49.1	30.8	1.6	14.8
Baburao and Narayanswamy[26]	Bangalore, 2015	96	3:1		69.7	47.9	28.1	1.7	
Mohan *et al*.[6]	New Delhi, 2016	397	7.4:1	57.8	79	25.1	24.1	1.04	14.6
Murali *et al*.[27]	Chennai, 2017	678	3.17:1	-	53.4	16.1	51.2	0.31	9.0
Kaur *et al*.[28]	Chandigarh, 2017	1301	4.6:1	58.6	76.9	36.4	36.4	1	19.2
Perng *et al*.[29]	Taiwan, 1996	10,910	5.57:1	62.1	75.7	37.1	38.3	0.97	12.2
Gadgeel *et al*.[30]	USA 1999	1012	NA	65	90	48	18	2.67	9.5
Minami *et al*.[31]	Japan 2000	1242	2.7:1	64.1	89	45	48	0.94	NA
Radzikowska *et al*.[32]	Poland 2002	20,561	6.1:1	62.18	92.5	51	23	2.22	19
Fu *et al*.[33]	USA, 2005	2,28,572	1.8:1	66	NA	44	36	1.22	NA
Stewart *et al*.[34]	USA, 2008	10,95,305	1.2:1	68	87	22.2	36.4	0.61	15.4
Zou *et al*.[35]	China, 2014	15,427	Males only	60	NA	32	43	0.74	15
Present study	Delhi, 2019	1862	4.9:1	58	76.2	28.6	34	0.84	16.1

ADC: Adenocarcinoma, SCC: Squamous cell carcinoma, SCLC: Small cell lung cancer, NA: Not available

and biomass fuel that is commonly used in rural India.[36,37] However, the prevalence of smoking in our cohort remained largely unchanged over 10 years.

Although majority of patients in our study had a reasonably good performance status at the time of initial presentation (50.8% had ECOG 0 or 1; and 53.3% had KPS more than 70), but this was lower than most Western reports.[38,39] This may be due to morbidity associated with more advanced stage of the disease at the time of diagnosis and seeking medical care.

In the initial years of this study, SCC dominated the morphological type of NSCLC but was overtaken by ADC in 2012, and this trend continued till 2018. It should be noted, however, that the distribution of SCC and SCLC remained largely unchanged, while the frequency of NSCLC- NOS declined. This occurred most likely due to the changing practices of pathological reporting keeping in tune with the advancement in immunohistochemical techniques and based on the revision of guidelines for pathological reporting for lung cancer.[40] Another contributory factor may be an increase in the proportion of females over the 10-year period.

Several studies, including from our group, have previously reported that ADC has surpassed SCC as the most common histological subtype of lung cancer. This shift seems to be attributable partly to the changed smoking pattern and the increasing incidence of lung cancer in females and nonsmokers. At the same time, it is worthwhile to note that most previous Indian studies have described SCC as the most common pathological subtype.[12,13,16,17,25]

Although bronchoscopy and transthoracic-guided sampling remain the most common diagnostic modalities for LC, the past decade has seen the emergence of newer techniques such as convex-probe EBUS, radial probe EBUS, and thoracoscopy with impressive diagnostic yield and sensitivity.[41,42] Among our patients, EBUS provided the diagnosis in 2.7% of individuals, while thoracoscopy was the diagnostic modality in 1.1% individuals. With increasing usage, this number is likely to further increase.

Unfortunately, lung cancer continues to be diagnosed at an advanced stage in India in contrast to most Western literature, where 30%–50% of cases are diagnosed at a relatively early stage which is potentially operable.[32,43] Less than 3% of our patients underwent surgery, and this probably reflects the relatively poor survival among our patients.

The tissue EGFR positivity rate among our patients was 25.3%, which is similar to that reported in Indian studies but higher than most Western reports.[44-53] However, the ALK positivity rate of 11.5% observed in our study is higher than most previous reports (5% in Western and 1.45%–7.6% in Indian individuals).[53-55] Whether this observation represents a true high prevalence of ALK rearrangements in this geographical region remains unknown yet, and more population-based data is required before we can draw definite conclusions.

Among all patients, 56.2% (1013/1803) received disease-specific treatment (chemotherapy, targeted therapy,

radiotherapy, and surgery). The remaining participants were either unwilling for chemotherapy, unsuitable due to poor performance status, opted for alternative systems of medicine, (ayurvedic or homeopathic) or were those in whom treatment details were not known. Other Indian studies have also reported a high proportion of patients unwilling or unsuitable for cancer-specific treatment for reasons similar to what we observed.[15] The median OS in our study was 8.8 months (IQR 3.7–19 months), which is similar to that reported in various other Indian studies (6.0–7.8 months), especially in advanced NSCLC.[24,27,56] However, the OS of the patients who received at least some cancer-specific treatment was higher at 12.6 (6.2–28.7) months.

Our results revealed some other important clinical observations as well. The never-smokers in our cohort were younger and were diagnosed at a more advanced disease stage than smokers. Previous reports on this aspect have shown conflicting results.[21,57-59] Differences in smoking history, family predisposition, and delay in diagnosis of lung cancer in nonsmokers may explain some of these discrepancies. Compared to smokers, a greater proportion of nonsmokers received treatment in our study, possibly due to a higher occurrence of EGFR/ALK mutations in this group, that allows prescription of oral TKI therapy even in patients with poor performance status. Never-smokers had a better survival even after adjusting for treatment received.[58,59]

CONCLUSION

Our center appears to be following the global trend with increasing incidence of ADC. The proportion of females is increasing, whereas smoking rates and mean age at diagnosis remained unchanged over time. EGFR mutation positivity and survival were at par with most existing reports, while higher ALK positivity was detected. A characteristic phenotype of never-smokers with lung cancer was elucidated which demonstrated better survival.

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Conflicts of interest

There are no conflicts of interest.

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