# Clinical profile of small-cell lung cancer in North India: A 12-year analysis from a tertiary care center

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## ABSTRACT

Introduction: The small cell variant is a relatively uncommon but aggressive form of lung cancer. The present study aims to analyse the clinical characteristics, treatment outcomes and prognostic factors of an ambispectively enrolled large cohort of small cell lung cancer (SCLC) in the Indian population over a decade-long period. Materials and Methods: All patients diagnosed with SCLC between 2008 and 2020 at a tertiary care lung cancer clinic were included. The clinical details, demographics, details of investigations, treatment and survival outcomes were recorded and analysed. Results: A total of 361 patients were included. The majority were males (86.4%) with a mean (SD) age of 57.3 (12.3) years. Further, 34.9% were current smokers, with the median smoking index being 520 (interquartile range [IQR]: 260-1000). The majority had good performance status, that is, the Eastern Cooperative Oncology Group scale (ECOG) 0 or 1 (65%), and Karnofsky Performance Scale (KPS)  $\geq$  70 (85.9%). Also, 73.3% had extensive stage disease. The median time from symptom onset to definitive diagnosis was 91 days. Treatment details were available for 179 patients: chemotherapy only (n = 128), combined chemo-radiotherapy (n = 41) and radiotherapy only (n = 10). The median (IQR) progression-free survival (PFS) was 182 (94 to 306) days and the median (IQR) overall survival (OS) was 205 (94 to 429) days. On univariate analysis. factors that significantly affected survival included smoking index and performance status. However, on multivariate analysis, only the performance status significantly affected PFS, whereas none of these factors were significant for OS. **Conclusions:** SCLC predominantly affects males with a heavy smoking index. The diagnosis is usually made late; survival remains poor and is predominantly affected by the performance status.

KEY WORDS: India, small-cell lung cancer, smoking, survival

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## **INTRODUCTION**

Lung cancer is one of the leading causes of cancer in the world, with an estimated 2.2 million new cancer cases and 1.8 million deaths in 2020.<sup>[1]</sup> Lung cancer is

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histologically divided into two main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The small cell type is an aggressive variant arising from

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the neuroendocrine cells with distinct clinico-radiological and pathological characteristics. Globally, including in India, SCLC comprises about 13 to 15% of lung cancer cases.<sup>[2]</sup> Over the years, the incidence of SCLC has declined compared to NSCLC, with a proportionate rise in females, possibly due to changing smoking patterns across the globe.<sup>[3]</sup> The phenotypes and survival predictors in SCLC have been less studied, with most previous studies being relatively small, with a short enrolment period and follow-up. The trends in this morphological pattern over a prolonged time are also not well elucidated, especially in the Asian population. The largest study from a Chinese registry has mainly focused on epidemiological trends over 9 years with respect to SCLC.<sup>[4]</sup> However, the present study aims to analyse the change, if any, in the incidence and clinico-demographic profile over 12 years and also identify variables impacting survival in a North Indian population.

## **METHODOLOGY**

Patients with pathologically (histology or cytology) proven SCLC diagnosed between 2008 and 2020 in the Lung Cancer Clinic of the tertiary care hospital in India were included. Data were collected and collated both retrospectively and prospectively; the collected data were used for analysis. Prior approval was taken from the Institutional Ethics Committee.

Relevant demographics, clinical details, details of investigations, treatment administered and survival outcomes were retrieved and recorded. Patients were classified using the World Health Organisation (WHO) classification of lung tumours as SCLC.<sup>[5]</sup> If the diagnosis of SCLC was made in another centre, their tissue specimens were re-examined by a pathologist at our centre for confirmation. In case of pathology review being inconclusive, a repeat tissue sampling was performed. The disease was classified as a limited disease or extensive disease as per the Veterans Administration Lung Group 2-stage system.<sup>[6]</sup>

Modified Karnofsky Performance Scale (KPS) and Eastern Cooperative Oncology Group scale (ECOG) were used to assess the performance status of patients.<sup>[7]</sup> Various forms of treatment administered such as chemotherapy, radiotherapy, both, or only palliative care were recorded. The overall survival (OS) was calculated from the date of definitive diagnosis to the date of death or last known follow-up. In cases where the last follow-up was within a month of data censoring, the patients were considered to be on continuous follow-up. If the patient did not follow up for more than a month, attempts were made to contact the patient telephonically. Patients were followed from the date of registration to the date of death and were censored at the date they were last known to be alive, that is, the date of the last follow-up either in person or 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 are expressed as mean (standard deviation), and variables that followed skewed distribution are expressed as median (interquartile range [IQR]). Categorical variables are expressed as frequency (%). Median OS and progression-free survival (PFS) were estimated using Kaplan-Meier survival curve. 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 361 patients with SCLC were included in the study over 12 years. The major clinical and demographic details at baseline are depicted in Table 1.

The majority of patients were males (86.4%). Patients in the age bracket 46–70 years represented around a third-fourth of the whole group, with the mean (SD) age being 57.3 (12.3) years. One-third of patients were illiterate. Reformed smokers comprised 42.7% of the patients, whereas 34.9% were current smokers, with the median smoking index being 520 (IQR: 260–1000). More than 60% of the patients were heavy smokers (smoking index of more than 300). Almost 50% of the patients were diagnosed using flexible bronchoscopy, and approximately one-third used image-guided procedures (CT guidance [24.0%] and USG guidance [7.6%]).

The most common symptoms were cough (84.4%), fatigue/weakness (83.0%), loss of weight (76.6%), shortness of breath (74.1%), loss of appetite (72.8%) and chest pain (71.8%). Also, 4.8% of patients presented with SVC syndrome. Six percent of all patients had diabetes and hypertension each. Approximately one-third (33.6%) of the patients had received anti-TB treatment for a variable duration before the diagnosis of cancer. Location-wise, the right and left upper lobes were the most commonly affected lobe (51.6% together); 5.7% of the patients had a predominantly mediastinal mass. There were 5 patients with brain metastasis and 35 patients with bone metastasis at the time of initial presentation. The majority of patients had good performance status, that is, ECOG 0 or 1, and KPS  $\geq$  70. However, 73.3% of the patients had extensive stage disease. Overall, SCLC comprised 14.3% of all lung cancer cases diagnosed over the 12 years. However, the proportion of SCLC among all lung cancers declined from 15.9% in 2008 to 8.0% in 2020 [Figure 1].

The mean (SD) duration from symptom onset to the first doctor visit was 66 (21) days, and the first doctor visit to the first visit at our tertiary care hospital was 122 (34) days. The various timelines from the course of diagnosis until treatment are highlighted in Figure 2.

study group	<u> </u>	(0/)
Variable	Subgroup	n (%)
Age (years) ( <i>n</i> =361)	≤45	56 (15.5)
	46-70	273 (75.6)
	>70	32 (8.9)
Sex ( <i>n</i> =361)	Male	312 (86.4)
	Female	49 (13.6)
Education level	Illiterate	121 (33.5)
( <i>n</i> =361)	Primary	50 (13.8)
	Secondary (matric)	97 (26.9)
	Higher secondary	49 (13.6)
	Graduate	28 (7.5)
	Postgraduate	16 (4.4)
Smoking status	Never smoker	78 (22.3)
( <i>n</i> =349)	Current smoker	122 (34.9)
	Reformed smoker	149 (42.7)
Smoking index	<100	18 (9.3)
( <i>n</i> =193)	100-300	46 (23.8)
	301-600	52 (26.9)
	>600	77 (39.9)
Diagnostic modality	Flexible bronchoscopy	167 (50.8)
( <i>n</i> =329)	CT-guided FNAC/biopsy	79 (24.0)
	USG-guided FNAC/biopsy	25 (7.6)
	Pleural fluid aspiration	23 (7.0)
	Lymph node FNAC/biopsy	14 (4.3)
	Others	21 (6.4)
Predominant lobe	Upper lobe	126 (51.6)
involved (n=244)	Right middle lobe/lingula	7 (2.9)
	Lower lobe	56 (22.9)
	Combination of lobes	36 (14.8)
	Mediastinum	14 (5.7)
	Others	5 (2.0)
Staging (n=300)	Limited	80 (26.7)
	Extensive	220 (73.3)
ECOG (n=223)	0,1	145 (65.0)
LCOG (n 225)	2	60 (26.9)
	_ ≥3	18 (8.1)
KPS (n=248)	<u>≤</u> 60	35 (14.1)
111.5 (.1 2.10)	70	68 (27.4)
	80-100	145 (58.5)
Clinical symptoms	Cough $(n=347)$	293 (84.4)
and signs	Shortness of breath $(n=343)$	254 (74.1)
und bighb	Hemoptysis $(n=336)$	122 (36.3)
	Chest pain $(n=344)$	247 (71.8)
	Fever $(n=338)$	122 (36.1)
	Wheezing $(n=328)$	34 (10.4)
	Fatigue-weakness $(n=342)$	284 (83.0)
	Loss of appetite $(n=342)$	249 (72.8)
	Loss of weight $(n=342)$	262 (76.6)
	- · · · · ·	
	Dysphagia $(n=24)$ SVC sundrome $(n=215)$	6(25.0)
Comarkiditi	SVC syndrome ( <i>n</i> =315)	15 (4.8)
Comorbidities	Diabetes	19 (6.0)
( <i>n</i> =315)	Hypertension	19 (6.0) 24 (7.6)
04	Others	24 (7.6)
Others	ATT received before treatment ( $n=351$ )	118 (33.6)

 Table 1: Demographic and baseline characteristics of the study group

CT: Computed tomography, USG: Ultrasound, FNAC: Fine-needle aspiration cytology, ECOG: Eastern cooperative oncology group, KPS: Karnofsky Performance Status Scale, SVC: Superior Vena Cava, ATT: Anti tubercular treatment

Among the 361 patients, treatment details were available for 179 patients (49-limited stage and 130-extensive stage). The most commonly administered treatment modalities were chemotherapy only (n = 128), combined chemo-radiotherapy (n = 41), and radiotherapy only (n = 10). Among the 49 patients with the limited-stage

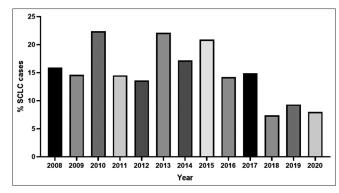


Figure 1: Year-wise distribution of small cell lung carcinoma (SCLC) cases among all lung cancer cases over the period of study

disease, 34 received chemotherapy only, 3 patients received only radiotherapy and 12 patients received combined chemo-radiotherapy. Among the patients with extensive stage disease, 94 received chemotherapy only, 7 received only radiotherapy and 29 received combined chemo-radiotherapy. The most common chemotherapy regimen was cisplatin + etoposide administered intravenously every three weeks for up to a maximum of six cycles. The most common sites for radiotherapy were bone, the primary lesion and the brain. Thirty-two patients had disease progression and received second-line chemotherapy. The most commonly used second-line agent was docetaxel.

Using the Kaplan–Meier survival curve, the median (IQR) PFS time was calculated as 182 (94 to 306) days [Figure 3a], and the median (IQR) OS time as 205 (94 to 429) days [Figure 3b].

A univariate and multivariate analysis was performed to analyse the factors affecting the OS and PFS [Tables 2 and 3]. On univariate analysis, factors that significantly affected PFS and OS included a smoking index of 301–600 and ECOG  $\geq$ 3. A KPS score  $\geq$ 70 significantly affected PFS, whereas KPS  $\geq$ 0 significantly affected OS. However, on multivariate analysis, only KPS significantly affected PFS, whereas none of these factors were significant for OS.

A comparative analysis of the demographic profile of patients in the current study with other Indian and International reports is shown in Table 4.

## **DISCUSSION**

Our study is one of the largest cohorts of patients of SCLC collected over 12 years in the Indian population. Overall, the Indian data are similar to the global reports in many aspects. Globally, the incidence of SCLC has shown a decline from around 17% in the late 1980s to around 13% in 2002.<sup>[3]</sup> Our data show a similar trend, with the proportion of cases dropping to half from 16% in 2008 to around 8% in the early quarter of 2020 [Figure 1]. A change in smoking habits could possibly explain this trend.<sup>[16]</sup>

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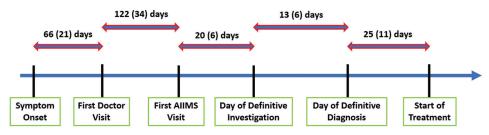


Figure 2: Delays during the patient diagnostic timeline. Days are represented as mean (SD)

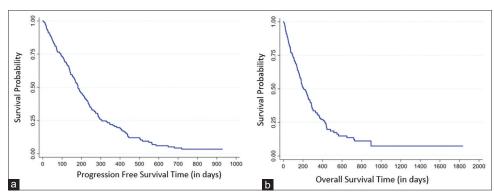


Figure 3: Kaplan-Meier survival plots. (a) Progression-free survival. (b) overall survival

Variable	Subgroup	n	Median PFS days	Univariate analysis		Multivariate analysis	
				HR (95% CI)	Р	HR (95% CI)	Р
Age (years) ( <i>n</i> =361)	≤45	56	196	1		-	-
	46-70	273	191	1.11 (0.54-2.72)	0.77		
	>70	32	134	1.63 (0.73-3.63)	0.24		
Sex (n=361)	Male	312	182	1		-	-
	Female	49	190	0.99 (0.66-1.51)	0.98		
Education level (n=361)	Up to primary level	171	183	1		-	-
	Above primary level	190	182	0.99 (0.74-1.35)	0.98		
Smoking status (n=349)	Never smoker	78	198	1		-	-
e ( )	Current smoker	122	177	1.03 (0.58-1.81)	0.92		
	Reformed smoker	149	183	1.00 (0.57-1.77)	0.99		
Smoking index (n=193)	<100	18	302	1		1.01 (0.99-1.02)	0.23
6	100-300	46	182	2.32 (0.83-6.49)	0.11		
	301-600	52	183	2.93 (1.05-8.21)	0.04*		
	>600	77	210	2.34 (0.81-6.23)	0.12		
Staging (n=300)	Limited	80	169	1		-	-
	Extensive	220	189	1.03 (0.72-1.47)	0.86		
ECOG (n=223)	0,1	145	190	1	0.98 0.92 0.99 0.11 0.04* 0.12	0.90 (0.62-1.30)	0.58
	2	60	213	0.99 (0.69-1.43)	0.97		
	≥3	18	113	2.48 (1.62-3.80)	0.00*		
KPS ( <i>n</i> =248)	≤60	35	134	1		0.97 (0.95-0.99)	0.00*
	70	68	207	0.59 (0.39-0.89)	0.01*		
	80-100	145	252	0.46 (0.32-0.67)	0.00*		
Comorbidities (n=315)	No comorbidity		169	1			
	Diabetes	19	218	0.87 (0.50-1.51)	0.61		
	Hypertension	19	181	1.09 (0.60-1.98)	0.78		
	Others	24	182	1.25 (0.40-3.96)	0.70		

#### Table 2: Univariate and multivariate analysis of factors influencing progression-free survival

PFS: Progression free survival, OS: Overall survival, ECOG: Eastern cooperative oncology group, KPS: Karnofsky Performance Status Scale

The mean age of our patients was 57.3 years, which is approximately a decade earlier compared to the Western data. This has been observed in previous Indian reports as well involving SCLC and NSCLC cohorts.<sup>[17,18]</sup> Our study showed that close to 80% of the patients were former or reformed smokers, making it the single most important factor associated with SCLC. It is also pertinent to note that 65% of the patients in our study were heavy smokers (smoking index more than 300), further reiterating the role of smoking and its intensity in the development of SCLC.<sup>[19]</sup> An interesting point to note is that around 20% of the cases were non-smokers and still developed

Variable	Subgroup	п	Median OS days	Univariate analysis		Multivariate analysis	
				HR (95% CI)	Р	HR (95% CI)	Р
Age (years) ( <i>n</i> =361)	≤45	56	196	1			
	46-70	273	232	1.16 (0.51-2.63)	0.72		
	>70	32	134	1.94 (0.79-4.82)	0.15		
Sex (n=361)	Male	312	203	1			
	Female	49	287	0.84 (0.52-1.34)	0.46		
Education level ( <i>n</i> =361)	Up to Primary Level	171	238	1			
	Above Primary Level	190	191	1.05 (0.76-1.44)	0.77		
Smoking status (n=349)	Never Smoker	78	198	1			
8	Current Smoker	122	196	0.99 (0.54-1.83)	0.98		
	Reformed Smoker	149	213	1.01 (0.54-1.85)	0.99		
Smoking index (n=193)	<100	18	302	1		1.00 (0.99-1.01)	0.28
	100-300	46	203	3.17 (0.7613.24)	0.11		
	301-600	52	213	4.39 (1.06-18.13)	0.04*		
	>600	77	253	3.14 (0.76-12.97)	0.11		
Staging (n=300)	Limited	80	191	1			
8 8 9	Extensive	220	205	1.12 (0.77-1.63)	0.56		
ECOG ( <i>n</i> =223)	0,1	145	271	1		1.29 (0.88-1.89)	0.19
	2	60	286	0.95 (0.63-1.43)	0.81	· · · · ·	
	≥3	18	113	2.17 (1.39-3.40)	0.00*		
KPS ( <i>n</i> =248)	≤60	35	154	1		0.99 (0.97-1.01)	0.67
	70	68	250	0.67 (0.44-1.03)	0.07		
	80-100	145	302	0.51 (0.35-0.76)	0.00*		
Comorbidities (n=315)	No Comorbidity		183	1			
	Diabetes	19	239	0.94 (0.52-1.72)	0.85		
	Hypertension	19	198	1.29 (0.71-2.36)	0.39		
	Others	24	182	1.54 (0.49-4.86)	0.46		

#### Table 3: Univariate and multivariate analysis of factors affecting overall survival in SCLC

PFS: Progression free survival, OS: Overall survival, ECOG: Eastern cooperative oncology group, KPS: Karnofsky Performance Status Scale

Author (reference)	Place/country, year	Sample size	Male:female	Mean age	Smokers (%)	
Prasad et al.[8]	Lucknow, 2004	73	5.6:1	-	84.8%	
Sheikh et al. <sup>[9]</sup>	Kashmir, 2010	163	5:1	59.2 years	77.7%	
Dey <i>et al</i> . <sup>[10]</sup>	Kolkata, 2012	100	4.9:1	57.4 years	77.7%	
Malik et al. <sup>[11]</sup>	New Delhi, 2013	64	9.7:1	55.5 years	87.5%	
Mandal et al. <sup>[12]</sup>	Manipur, 2013	67	0.8:1	-	77.6%	
Murali et al. <sup>[13]</sup>	Chennai, 2017	62	-	-	82%	
Perng et al. <sup>[14]</sup>	Taiwan, 1996	1329	10.5:1	63.9 years	-	
Radzikowska et al.[15]	Poland 2002	3479	4.6:1	59.8 years	97.3%	
Present study	Delhi, 2022	361	6.4:1	57.3 years	77.6%	

SCLC. Although it is difficult to ascertain the exact reasons for the same, there is evidence that prolonged exposure to particulate matter 2.5  $\mu m~(PM_{2.5})$  in ambient air is associated with an increase in the risk of lung cancer, especially in low and middle-income countries.<sup>[20]</sup>

In our study, we found that a total of almost half of the patients of SCLC were either illiterate or educated up to the primary level only. It has been shown that the incidence of lung cancer is influenced by education level possibly because education influences smoking habits and the ability to quit smoking.<sup>[21]</sup> Furthermore, lower educational status negatively impacts the likelihood of patients undergoing definite investigations and disease-specific treatment, thereby translating into delayed diagnosis and higher mortality.<sup>[22]</sup>

Staging of SCLC is based on Veterans' Administration (VA) classification into limited and extensive stage SCLC.<sup>[6]</sup> It has been reported that almost a third of SCLC are initially

diagnosed in the limited stage.<sup>[23]</sup> In our cohort, only 26.7% had a limited stage at diagnosis. This may possibly be due to a delay in referral to a specialist physician and due to initial wrong treatment with anti-TB drugs.<sup>[11]</sup>

Performance status (PS) is another important parameter, which influences prognosis in SCLC.<sup>[24]</sup> Our study found that a majority of patients had good PS (65% ECOG 0–1, 58.5% KPS  $\geq$  80) although this is lesser than some of the global data that have reported a good baseline PS in more than 80% of subjects.<sup>[25]</sup> Overall, performance status is a simple and reliable tool for rapid and accurate assessment of prognosis in lung cancer and is now a routine component of all lung cancer clinics.

The high prevalence of tuberculosis in Indian settings leads to a significant delay in the diagnosis of lung cancer due to prescriptions of inappropriate empirical anti-TB therapy. In our study, 33.6% of patients received empirical treatment with anti-tubercular medicines before definite diagnosis and treatment. Similar reports have emerged from other studies. In a study from south India, approximately 18% of physicians made a wrong diagnosis of tuberculosis, of which, 88% prescribed anti-tubercular therapy. Similarly, another study found that around 20% of patients received the wrong treatment with anti-TB drugs.<sup>[26,27]</sup> An important outcome of treatment errors (especially anti-TB drugs) is reported to delay the institution of cancer-specific therapy.<sup>[28]</sup> In our study, the maximum time delays occurred between patient referrals from his primary doctor to our referral centre (122 days). One of the primary reasons for this could be the lack of pulmonary medicine specialists involved in the initial management of such patients or simply a lack of clinical suspicion due to the high burden of TB in our population.<sup>[26]</sup> We feel that this is an area that needs urgent reform and education about the high-risk groups and their symptoms, which will enable early and timely referral of patients with suspected lung cancer to specialist centres.

Out of the 361 patients, only 50% received cancer-specific treatment. Although this appears very low, globally it has been seen that the utilisation of anti-cancer treatment is highly variable, ranging from 80% in some countries such as the USA and dropping to 50% in Ireland and New Zealand.<sup>[29]</sup> Several possible explanations may be offered, such as unsuitability for specific therapy due to extensive disease and poor performance status, socio-economic reasons, preference for alternative forms of treatment and advanced age. Although old age in itself is not a contraindication to therapy, it has been seen that the proportion of untreated patients with SCLC was higher in this group.<sup>[30]</sup>

The recommended treatment for SCLC depends on the stage of the disease. Among our 49 patients with the limited-stage disease, 34 patients received only chemotherapy, whereas 12 received combined CT-RT. A possible reason for the lack of receipt of combined chemo-radiotherapy is the long waiting period for radiotherapy in our centre, thus making it logistically difficult to administer CT-RT concurrently. None of our patients with a limited-stage SCLC underwent surgery. Although the role of surgery in this context is debatable, there are a few studies that have shown its utility.<sup>[16]</sup>

The median OS in our study was 205 days, which is lower than most previous reports globally.<sup>[31]</sup> Several reasons may explain this poor outcome: Firstly, only 50% of the patients received cancer-specific therapy for reasons already discussed above; secondly, more than 50% of patients with limited-stage SCLC did not receive concurrent chemo-radiotherapy, which is known to improve survival; and thirdly, it could simply reflect the real-world scenario demonstrating the dismal prognosis of this aggressive cancer.<sup>[16]</sup>

We also analysed various factors, which affected the survival of SCLC. A heavy smoking index (301-600)

and poor performance status (ECOG/KPS) adversely impacted survival. The adverse effect of smoking has been previously reported not just on the PS and effectiveness of chemo-radiotherapy but also on survival.<sup>[32,33]</sup> On univariate analysis, only PS, that is, KPS >80 and ECOG <3 was associated with better OS. This has been seen in other studies as well.<sup>[34-36]</sup> A better PS is an important factor, which determines suitability for administering definitive therapy.<sup>[37]</sup> This is likely to translate into improved survival. However, none of these factors were found to influence survival on multivariate analysis.

We acknowledge the limitations of this study. Although PCI (prophylactic cranial radiotherapy) is SOC (standard of care) for most patients post-chemo who have partial/complete remission, the data for PCI were not available in our records and hence were not mentioned. Some important data such as patient outcomes were missing in several patients and this could have influenced the results. The numbers of subjects with treatment-related follow-up were relatively small, hence conclusions cannot be drawn regarding reliable prognostic factors. In addition, there was significant variability in the treatment modalities; hence, their effect on clinical outcomes cannot be reliably commented upon. However, this is one of the largest studies on SCLC from the Asia-Pacific region and perhaps the only one to have included patients and demonstrate incidence trends over a long 12-year period.

## **CONCLUSIONS**

The proportion of incidence of SCLC in our area appears to be declining over the last decade. In spite of several diagnostic advancements, the definitive diagnosis continues to be made late, survival remains poor and is predominantly affected by the performance status.

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## **Conflicts of interest**

There are no conflicts of interest.

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