Original Article

Clinicopathological characteristics and treatment outcome in small cell lung cancer: A single institutional experience from India

Sandip Ganguly[1], Bivas Biswas[1], Sayanika Bhattacharjee[1], Joydeep Ghosh[1], Sumit Mukhopadhyay[2], Divya Midha[3], Deepak Dabkara[1]

[1]Department of Medical Oncology, Tata Medical Center, Kolkata, West Bengal, India, [2]Department of Radiology, Tata Medical Center, Kolkata, West Bengal, India, [3]Department of Pathology, Tata Medical Center, Kolkata, West Bengal, India

ABSTRACT

Background and Objectives: Small cell lung cancer (SCLC) constitutes 14%–20% of all lung cancers. Clinical data on SCLC are scarce in literature. To report clinical features and treatment outcome of SCLC treated at our center. **Materials and Methods:** This is a single institutional data review of SCLC patients treated between June 2011 and December 2018. Patients were staged as either localized or extensive disease after appropriate staging work-up. Patients with localized disease were treated with concurrent chemoradiation with platinum-based chemotherapy. Those with extensive disease were treated with platinum based palliative chemotherapy. Clinicopathological characteristics, treatment details, and outcome were recorded in this study. Patients who received at least one cycle of chemotherapy were included for survival analysis as intent-to-treat analysis. **Results:** A total of 181 were patients registered with a median age of 62 years (range: 35–86 years) and male: female ratio of 166:15. Eighty-seven percent (*n* = 157) of patients had smoking history and 15% (*n* = 28) of patients had symptom of superior vena cava obstruction at baseline. Twenty-seven (15%) patients had localized disease at presentation. One hundred and twenty (66%) patients took systemic chemotherapy. Chemotherapy regimen was carboplatin only in 9 (7%), etoposide-carboplatin in 54 (45%), and cisplatin-etoposide in 57 (48%). Patients received median cycle number of 6 (range: 1–6). Of the evaluable 87 (73%) patients, initial response was complete response in 4, partial response in 57, stable disease in 20, and progressive disease in 6. Twenty patients received second-line chemotherapy at time of disease progression. After a median follow-up of 8.8 months (range: 0.3–46.1), median progression-free survival (PFS) of the whole population was 9.3 months. **Conclusions:** Small cell carcinoma in our series had a high incidence of advanced stage (85%) and 13% of patients were nonsmoker. Only 66% of patients received palliative chemotherapy and achieved high disease control rate (>75%) in the evaluable patients with median PFS of 9.3 months.

KEY WORDS: Chemotherapy, lung cancer, small cell

Address for correspondence: Dr. Sandip Ganguly, Department of Medical Oncology, Tata Medical Center, 14 Mar EW Arterial Road, Newtown, Kolkata - 700 160, West Bengal, India.
E-mail: dr.babumashai@gmail.com

Access this article online

Quick Response Code:

Website:
www.lungindia.com

DOI:
10.4103/lungindia.lungindia_370_19

INTRODUCTION

Lung cancer is top in terms of incidence and mortality according to latest GLOBOCAN 2018. It amounts to 11.6% of all cancer cases and 18.4% of all cancer-related deaths.[1] Small cell lung cancer (SCLC) constitutes around 14% of all lung cancers.[2] SCLC is a high-grade neuroendocrine cancer with aggressive features. The treatment of SCLC depends on the stage of the disease. They are staged based on the disease inclusion in the radiation field portal into localized disease and extensive disease. Surgery has a limited role in the SCLC. The treatment of localized disease is a combination of systemic chemotherapy and radiotherapy whereas palliative chemotherapy being the only option for extensive disease. They are characterized by high response to systemic treatment but they are notorious for rapid regrowth leading to early relapse and high mortality. Most of the available literatures on lung cancer are mainly on non small cell lung cancer (NSCLC). Very few reports are available on outcome of SCLC in the literature and especially from developing countries, like India. Here, we are reporting clinical profile and outcome of patients with SCLC treated in our institute.

MATERIALS AND METHODS

This is a single institutional data review of patients with SCLC registered and treated in the Department of Medical Oncology of Tata Medical Center, Kolkata, from May 2011 to December 2018. Patients who received at least one cycle of chemotherapy were included for survival analysis in an intent-to-treat analysis. Clinicoepidemiological features and treatment details were analyzed for all patients. Ethical clearance was taken from the institutional review board.

Diagnosis and workup

All patients underwent tissue diagnosis either by biopsy or cytology with cell block from the accessible sites with appropriate immunohistochemistry (IHC). IHC markers which were used are synaptophysin and chromogranin along with Ki-67 Metastatic workup was done with either whole-body ^{18}Fludeoxyglucose positron emission tomography-computed tomography (PET CT) or CT of thorax and abdomen with/without ^{99}technetium bone scintigraphy whenever indicated. Magnetic resonance imaging of the brain was done in patients with symptomatic neurological symptoms and those treated with curative intent for localized extracranial disease.

Treatment and response evaluation

After confirmation of diagnosis and metastatic workup, patients with localized disease were treated with systemic chemotherapy and thoracic radiation therapy (RT). Prophylactic cranial irradiation (PCI) was initially given in patients to all patients who achieved complete or partial response posttreatment. However, post 2016, it was given to patients with only limited disease who had a response to definitive therapy. Patients with extensive disease

underwent systemic treatment if the Eastern Cooperative Oncology Group (ECOG) performance status (PS) was between 0 and 2 and organ functions were within normal limits. In patients with ECOG PS 3 either due to the disease or comorbidity they were initially tried with single-agent carboplatin and in the subsequent cycles, they were given doublet therapy if there was an improvement of their PS. Cis + Eto (intravenous cisplatin 75 mg/m^2 on day 1, etoposide 100 mg/m^2 on day 1–day 3, repeated every 21 days) or carboplatin + eto (intravenous carboplatin area under curve [AUC] 5 on day 1, etoposide 100 mg/m^2 on day 1–day 3, repeated every 21 days) or carboplatin (intravenous carboplatin area AUC 5 on day 1 and cycle repeated every 21 days) were used as preferred first-line treatment. None of the patients with very poor PS were started on chemotherapy and was put on the best supportive care. It was symptom-directed therapy toward pain, decreased appetite, nutrition, respiratory distress, and psychological support. In second-line settings, chemotherapeutic regimes which were used are single-agent irinotecan, paclitaxel, or topotecan.[3] Platinum doublet was rechallenged if the PS was good and disease-free interval was more than 6 months. Toxicities were graded as per the Common Terminology Criteria for adverse events version 4.[4] Patients were assessed every three cycles for response assessment. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were defined according to the response evaluation criteria in solid tumors (RECIST v1.1) criteria wherever applicable.[5] Overall response rate (ORR) was defined as the sum of CR + PR. Clinical benefit rate (CBR) was defined as the sum of CR + PR + SD.

Descriptive statistics were used for demographic and clinical characteristics. Survival was estimated with the Kaplan–Meier method, and survival estimates were compared using the log-rank test. Data were censored on May 14, 2019. Patients who were lost to follow-up were censored at the date of the last contact/follow-up. Patients who were alive on May 14, 2019, were censored for overall survival (OS) analysis. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of clinical or radiological disease progression. OS was calculated from the date of diagnosis to the date of death from any cause. Patients who were lost to follow-up or who had abandoned treatment was also included in the event-free survival and OS analyses, and the outcomes for these patients were confirmed by telephone contact. Patients who received at least one cycle of chemotherapy were included for a modified intent to treat survival analysis. The Cox proportional-hazard model was used in the univariate analysis to detect outcome differences between groups. Stepwise multivariate Cox regression analysis was performed to identify the predictors of outcome. Factors with significance ($P < 0.1$) in the univariate analysis were entered into multivariate analysis. Treatment abandonment was included in the survival analysis in the present study as it has been proposed that patients who do not comply with or who abandon treatment be included in survival

analysis for studies from developing nations to provide a true picture of outcomes from these countries. STATA/SE 11.0 (StataCorp, College Station, Texas, USA) was used for statistical analysis.[6]

RESULTS

Clinicopathological features
Totally 1979 new lung cancer cases were registered in our department over the study period. Of these total cases, 181 (9%) cases were diagnosed with SCLC. Out of them, 154 (85%) patients had extensive disease. The median age of the study population was 62 years (range: 35–86 years) with a majority being male (male:female ratio = 166:15). Majority of the study population were smokers with nonsmokers comprising only 24 (13%) of cases. The baseline characteristics of the patients are shown in Table 1.

Majority of the patients (68%) had a cough as the presenting feature. Other presenting symptoms are shown in Table 1. Features of superior vena cava obstruction (SVCO) were present in 15% of the cases. The most common site of metastases was liver metastases which was 34% closely followed by bone metastases (32%). One hundred and seven (69%) of the patients had more than 1 site of metastases. The tissue diagnosis was established by biopsy

in 112 (61.8%) of patients. Bronchoscopy-guided biopsy was used in 32.1% of cases and CT-guided biopsy of the lung mass was used in 41% of patients. Biopsy from the regional nodal mass was used in 16.9% of cases.

Of 181 patients, only 120 patients took at least one cycle of chemotherapy as shown in Figure 1. They were included in the modified intent to treat survival analysis. Common chemotherapeutics regime which was used were cisplatin-etoposide (48%) followed by carboplatin-etoposide (45%) followed by single-agent carboplatin (7%) in the upfront setting. A total of 21 patients received PCI postcompletion of definitive treatment. For patients with extensive disease neither post-chemotherapy consolidation nor consolidative radiation to the residual disease were given in our cohort.

Progression was documented in 46 patients. Local progression was seen in seven cases. Isolated central nervous system progression was seen in four cases. Systemic multiple sites of progression occurred in 35 patients. Twenty patients only received further chemotherapy on systemic progression with the most common agent being taxane (35%) and irinotecan (35%). Two patients were re-challenged with platinum doublet on progression.

Response assessment and outcome
Interim response assessment was assessed on 86 (72%) patients, CR in 4 (3%), PR in 56 (65%), SD in 21 (24%), PD in 6 (7%) patients with an ORR of 68.6%, and CBR of 93%. End of the treatment response assessment was done

Table 1: Baseline characteristics of the patients

Characteristics	*n* (%)
ECOG Performance Score	
0	3 (2)
1	58 (32)
2	77 (43)
3	35 (19)
4	8 (4)
Symptoms	
Cough	123(68)
Dyspnoea	69 (38)
Chest pain	44 (24)
Hemoptysis	24 (13)
SVCO	28 (15)
Comorbidities	
Diabetes	39 (21.5)
Hypertension	54 (29.8)
Coronary artery Disease	8 (4.4)
COPD	5 (2.7)
AJCC Staging 8th ed..ition	
IIIA	3 (1.65)
IIIB	9 (4.9)
IIIC	15 (8.2)
IVA	22 (12.1)
IVB	132 (72.9)
Sites of metastases	
Lung	38 (21)
Nodal	40 (22)
Liver	62 (34)
Bone	58 (32)
Brain	20 (11)
Pleura	49 (27)
Others	42 (23)

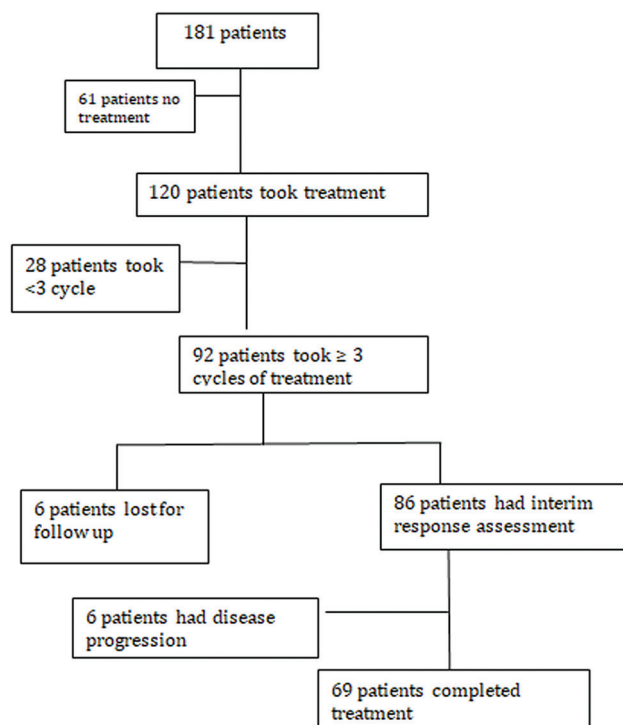ECOG-Eastern Cooperative Oncology Group, SVCO-Superior Vena Cava Obstruction

Figure 1: Consort diagram of the study population

in 69 (60%) patients, CR in 6 (8.7%), PR in 19 (27.5%), SD in 30 (43.6%), and PD in 14 (20.2%) patients. ORR was seen in 36.2% of patients and CBR was seen in 79.7% of patients.

After a median follow-up of 8.8 months (range: 0.3–46.1 months), median PFS of the whole population was 9.3 months as shown in Figure 2a. Median PFS for those who were treated with carboplatin-etoposide was 9.3 months and it was 9.2 months for those who were treated with cisplatin-etoposide as shown in Figure 2b. Median PFS for the localized disease 13.2 months versus 9.1 months in patients with extensive disease is shown in Figure 2c. The median OS of the whole population was 13.1 months as shown in Figure 3a. Median OS for those who were treated with carboplatin + etoposide was 11.5 months and it was 16.2 months for those who were treated with cisplatin + etoposide, as shown in Figure 3b. Median OS for the localized disease 20.6 months versus

12.6 months in patients with extensive disease is shown in Figure 3c. In univariate analysis there was OS advantage with cis+eto based chemotherapy over carbo+eto. But in multivariate analysis it was not there as shown in Table 2.

DISCUSSION

According to the recent GLOBOCAN data, lung cancer is the most common cancer-related mortality in both the sexes.[1] NSCLC comprises majority of all lung cancers. Most of the available literatures are on NSCLC and very few are there on SCLC and treatment outcome.

The median age of the study population was 62 years which is almost similar to 61.8 years of Benna *et al.*[7] Average incidence of SCLC is around 10%–14%, but in our study, it is around 9% similar to the study by Murali *et al.*[8] Smoking incidence was seen in 87% of our cases

Table 2: Univariate and multivariate analysis of Progression free survival (PFS) and overall survival (OS)

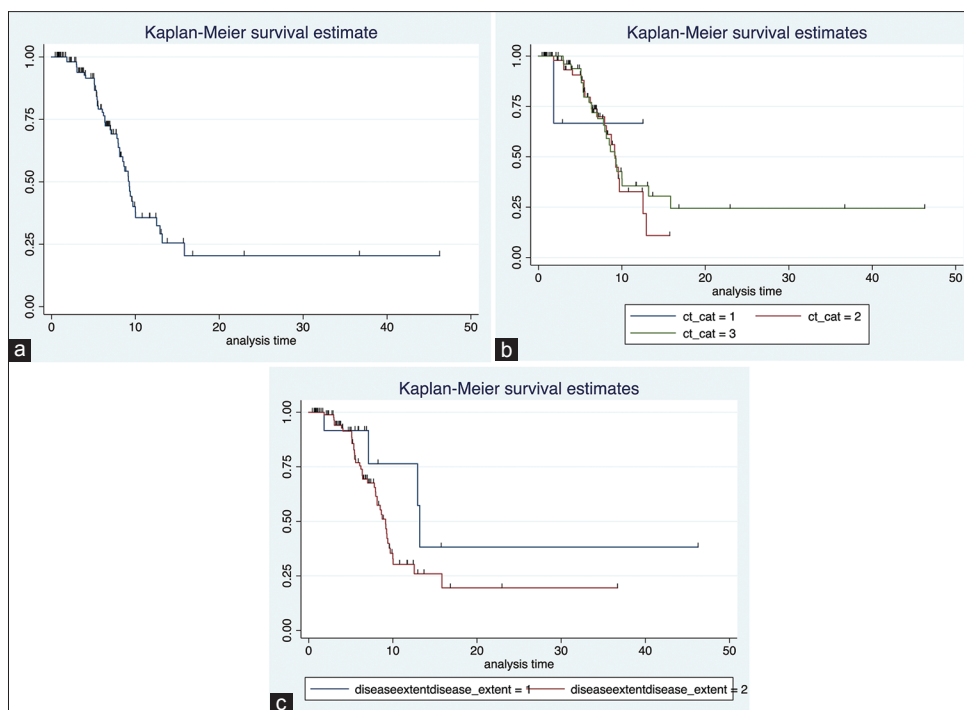| Variables	Category	PFS (univariate)			OS (univariate)			OS (multivariate)		
		HR	CI	P	HR	CI	P	HR	CI	P
Age (years)	≤60 (56)	1		0.66	1		0.66			
	>60 (64)	1.14	0.62-2.1		1.15	0.60-2.01				
Sex	M (110)	1		0.38	1		0.87			
	F (10)	0.53	0.12-2.22		0.91	0.31-2.67				
PS	0-1 (49)	1		0.83	1		0.74			
	2-4 (71)	1.06	0.57-1.96		1.11	0.57-2.14				
Chemo	Carbo+/-eto (63)	1		0.72	1		0.02	1		0.05
	Cis+eto (57)	0.89	0.48-1.6		0.44	0.21-0.9		0.47	0.23-0.97	

Figure 2: (a) Kaplan–Meier graph showing median progression-free survival of the entire cohort. (b) Kaplan–Meier graph showing median progression-free survival among the different chemotherapy subgroups. (Cat 1-single agent carboplatin; Cat 2-VP16 + etoposide; Cat3-cis + etoposide). (c) Kaplan–Meier graph showing the median progression-free survival among disease extent. (1-localized; 2- extensive)

Table 3: Comparison of characteristics between other studies and our

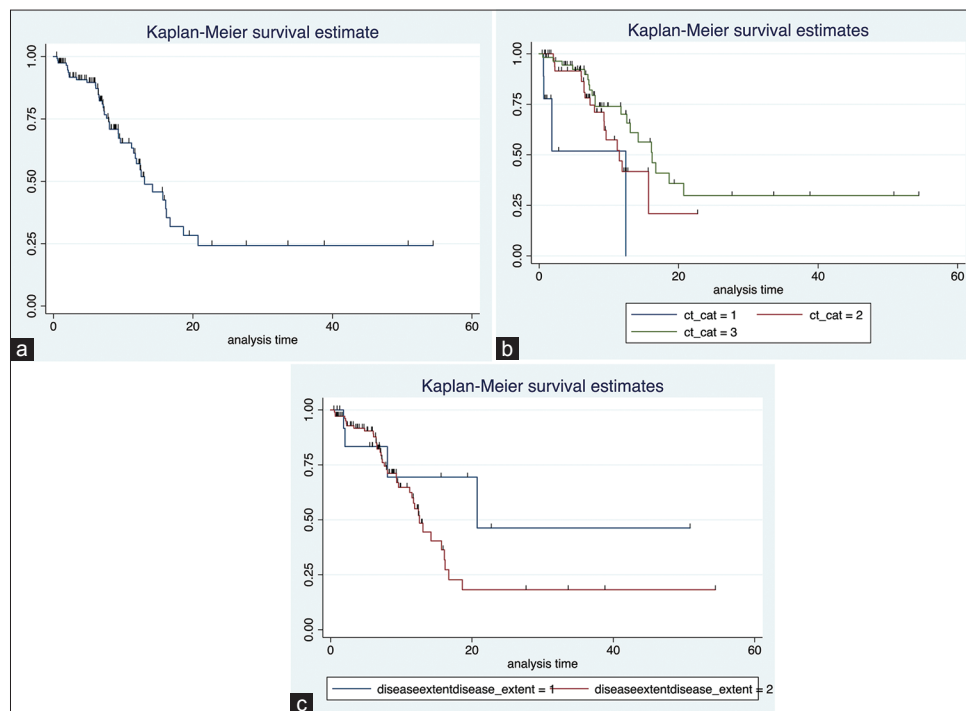| Characteristics	Julka *et al*.[11]	Murali *et al*.[8]	Tunisia study[7]	Malik *et al*.[15]	Our study
Total cases	85	62	60	64	181 (120 treated)
Localized/extensive (%)	40/60	42/58	33.3/66.7	23.4/71.6	15/85
PFS (months)	11.4	6	NA	6.8	9.3
OS (months)	NA	7	10	9.1	13.1

Figure 3: (a) Kaplan–Meier graph showing median overall survival of the entire cohort. (b) Kaplan–Meier graph showing median overall survival among the different chemotherapy subgroups. (Cat 1-single-agent carboplatin; Cat 2-VP16 + etoposide; Cat3-cis + etoposide). (c) Kaplan–Meier graph showing the median overall survival among disease extent. (1-localized; 2- extensive)

which is similar to the published literature.[9] Due to higher incidence of smoking among females, globally SCLC comprises around 30% of lung cancer cases among females.[10] Julka *et al*., in their series had around 13% of SCLC cases were being females.[11] We had a relatively small percentage around 8% of SCLC being females. Majority of the patients presented with symptoms due to the local tumor effect. SVCO was seen in 15% of cases which was more compared to 10% cases of SVCO reported in literature.[12]

In our study, around 85% of patients presented with extensive stage which is higher than that were present in the study done from Tunisia[7] and also from AIIMS.[11] This necessitates the fact that proper staging evaluation is mandatory while working up a patient with SCLC. The higher incidence of extensive stage in our study may be due to referral bias as our institution is a tertiary cancer center. The most common site of metastases was liver (34%) and bone (32%) which was similar to the available literature.[13] Sixty-nine percent of patients had more than one site of metastases which was way higher than other studies where the authors have reported only 19% of cases had more

than one site of metastases.[8] PCI was given only to the patients with localized disease if they had good response to the primary lung lesions as role of PCI in extensive-stage disease is controversial as it has not shown OS benefit.[14]

The median PFS of the study population was 9.3 months which was more than published by Malik *et al*., which was 6 months.[15] However, it was less than that published by Julka *et al*. which was 11.4 months.[11] This difference can be attributed to the fact that there were more representation of localized disease in their study. We have reported a higher median OS of the study cohort (13.1 vs. 9.1 vs. 7.2 months) compared to those available from India.[8,15] We did not find any difference between cis-eto and carbo+eto in terms of PFS and OS as was also shown in the meta-analysis.[16]

Our study has some limitations. It was a retrospective study. Compliance is a big issue and because of that response assessments were not done in many and also many patients did not complete the treatment. Poor compliance is multifactorial which can be due to cost, logistic, family support, deterioration of the general condition, and adverse effect of the treatment.

However, our study does have some strong points. This is one of the few published clinical data regarding patients with SCLC from resource-poor setting like India. In terms of numbers, this is by far the largest experience of SCLC compared to those available from India and also many countries, as shown in Table 3. All the patients were treated with standard chemotherapeutic regimes. Only those patients who received at least one cycle of chemotherapy were included for modified intent to treat survival analysis thus making an honest attempt to avoid censoring. It has also given importance to the issue of compliance which is a serious issue in India.

CONCLUSIONS

Our study reports the largest experience of clinical profile and treatment outcome of patients with SCLC from India. Future studies are required regarding role of maintenance and genomic profiling to see any targets or prognosticate patients with SCLC.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Shi Y, Xing P, Fan Y, Zhang X, Hu C, Wang C, *et al*. Current small cell lung cancer treatment in China. Thorac Cancer 2015;6:233-8.
3. Simon GR, Turrisi A; American College of Chest Physicians. Management of small cell lung cancer: ACCP evidence-based clinical practice guidelines (2nd ed). Chest 2007;132:324S-39S.
4. CTCAE 4.0. Available from: https://www.ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm. [Last accessed on 2019 Aug 12].
5. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al*. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
6. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP; 2009.
7. Benna HL, Gabsi A, Mejri N, Labidi S, Daoud N, Afrit M, *et al*. Small cell lung cancer in good performance status: A mono-center Tunisian study. Int J Cancer Manag 2018;11:e9355.
8. Murali AN, Radhakrishnan V, Ganesan TS, Rajendranath R, Ganesan P, Selvaluxmy G, *et al*. Outcomes in Lung Cancer: 9-year experience from a tertiary cancer center in India. J Glob Oncol 2017;3:459-68.
9. Furrukh M. Tobacco smoking and lung cancer: Perception-changing facts. Sultan Qaboos Univ Med J 2013;13:345-58.
10. Olak J, Colson Y. Gender differences in lung cancer: Have we really come a long way, baby? J Thorac Cardiovasc Surg 2004;128:346-51.
11. Julka PK, Sharma DN, Madan R, Mallick S, Benson R, Kunhi PH, *et al*. Patterns of care and survival among small cell lung cancer patients: Experience from a tertiary center in India. J Egypt Natl Canc Inst 2017;29:47-51.
12. Rowell NP, Gleeson FV. Steroids, radiotherapy, chemotherapy and stents for superior vena caval obstruction in carcinoma of the bronchus: A systematic review. Clin Oncol (R Coll Radiol) 2002;14:338-51.
13. Hermes A, Waschki B, Gatzemeier U, Reck M. Characteristics, treatment patterns and outcomes of patients with small cell lung cancer – A retrospective single institution analysis. Lung Cancer 2011;71:363-6.
14. Yin X, Yan D, Qiu M, Huang L, Yan SX. Prophylactic cranial irradiation in small cell lung cancer: A systematic review and meta-analysis. BMC Cancer 2019;19:95.
15. Malik PS, Sharma MC, Mohanti BK, Shukla NK, Deo S, Mohan A, *et al*. Clinico-pathological profile of lung cancer at AIIMS: A changing paradigm in India. Asian Pac J Cancer Prev 2013;14:489-94.
16. Rossi A, Di Maio M, Chiodini P, Rudd RM, Okamoto H, Skarlos DV, *et al*. Carboplatin-or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: The COCIS meta-analysis of individual patient data. J Clin Oncol 2012;30:1692-8.