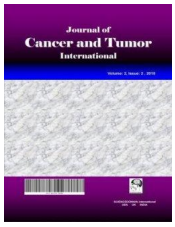

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Patterns of Care and Factors Affecting it in Small Cell Lung Cancer – Analysis of 3 Years Data from a Tertiary Care Hospital in India

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Authors' contributions

This work was carried out in collaboration between all authors. Author AB designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors BM and DG managed the analyses of the study. Author AM managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Objective: In India, 75,000 new cases of lung cancer are diagnosed every year, with approximately 35% of them being locally advanced at presentation. Despite numerous advances in recent years in terms of diagnostic methods, molecular changes, and therapeutic interventions, the outcomes of the small cell lung cancer (SCLC) patients remain poor. There is a dearth in our current understanding of the changing epidemiological trends of small cell lung cancer among Indian patients.

Aim of this study is to evaluate the safety and efficacy of standard chemotherapy or chemo radio therapy in elderly patients with SCLC and their outcome and analysis of prognostic factors.

Methods and Materials: 36 cases of SCLC diagnosed either by histopathology or cytology were accrued for the single Institutional retrospective audit and were analysed. Patients with extensive stage disease are planned for six cycles of platinum doublet based chemotherapy and those with limited stage disease are planned for concomitant or sequential chemo radiation depending on various patient related factors. Patients received 4-6 cycles of chemotherapy (cisplatin 80 mg/M2 Day 1, etoposide 120 mg/m2 Day 1-3), following which based on their initial stage & response after

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Chemotherapy, Thoracic Radiation and PCI (Prophylactic Cranial Irradiation) were given to the suitable candidates.
Statistical analysis was done by bivariate analysis, cox regression analysis, Chi square test, Kaplan Meier survival analysis using IBM SPSS software v.23.
Results: There was a median diagnostic delay of 3 months, about 60% patients presented with extensive stage disease, among which 25% were brain metastasis & 8.2% were having bone mets. Response rate of patients above or below 60yrs were not statistically significant (66% v/s 69%). Median survival were 14 months & 7months for limited & extensive stage.
Conclusion: Elderly Patients can benefit from the EP (Etoposide, Platin) regimen with or without thoracic RT (Radio therapy). Stage, PS (Performance status), Treatment type were notable prognostic factors of median survival. More Prospective, randomised trials are warranted.

Keywords: SCLC; patterns of care; prognosis; Medical College Kolkata, India.

1. INTRODUCTION

Lung cancer is one of the most common cancer diagnosed worldwide. It is also the foremost contributor to cancer-related mortality, resulting in 1.38 million cancer deaths per year worldwide [1]. Several epidemiological observations performed across varied demographic cohorts in India confirm the significant burden of lung cancer in India, contributing significantly toward the cancer morbidity and mortality [2].

In India around 75,000 new cases of lung cancer are diagnosed every year, with approximately 35% of them being locally advanced at presentation. Though lung cancer is one of the most common cancers in the Indian Subcontinent, majority of them are the Non small cell cancer variants and small-cell lung cancer (SCLC) accounts for about 10% of 20% of all lung cancer cases diagnosed in this region [3]. According to the GLOBOCAN 2012 report, the estimated incidence of lung cancer in India was 70,275 in all ages and both sexes; the crude incidence rate per 100,000 was 5.6, the age-standardized rate per 100,000 (world), i.e. ASR (W) was 6.9, and the cumulative risk was 0.85 [4]. Despite numerous advances in recent years in terms of diagnostic methods, molecular changes, and therapeutic interventions, the outcomes of the small cell lung cancer patients remain poor [3]. Moreover concurrent chemo radiation with thoracic radiation and platinum based chemo therapy is at times difficult to administer for localised stage small cell lung cancer. There is a dearth in our current understanding of the changing epidemiological trends of small cell lung cancer among Indian patients.

The current study is an audit of all the small cell lung cancer presenting to our institution in the given period of time and that were treated with chemotherapy and radiation to understand the toxicity, response, and compliance to these and finally their effect on survival.

1.1 Aim and Objective

The aim of this study is to evaluate the patterns of care of small cell lung cancer patients, analysis of prognostic factors and treatment outcome on survival.

2. MATERIALS AND METHODS

Between January 2013 to December 2016, about 47 cases of small cell lung cancers were registered in our department, of which 5 did not receive any therapy, and six patients were started on treatment but defaulted before treatment completion. Rest 36 cases of SCLC diagnosed either by histopathology or cytology were accrued for the retrospective audit and were analysed. Patients with extensive stage disease are planned for six cycles of platinum doublet based for chemotherapy and those with limited stage disease are planned for concomitant or sequential chemo radiation depending on various patient related factors. Patients received 4-6 cycles of chemotherapy (cisplatin 80 mg/M2 Day 1, etoposide 120 mg/m2 Day 1-3), following which based on their initial stage & response after CT, thoracic RT and PCI (Prophylactic cranial Irradiation) were given to the suitable candidates.

ECOG (Eastern Cooperative Oncology Group) Performance Status [5] and the following symptoms were recorded-shortness of breath, cough, chest pain, hemoptysis, significant weight loss (>10% of premorbid body weight in 6 months), anorexia, hoarseness of voice, fever, neurological symptoms (focal weakness, seizures), superior vena cava (SVC) obstruction

(defined as puffiness of face, facial swelling or flushing of face) and other symptoms that the patient complained of at presentation. Cumulative symptom burden was defined as the numerical sum of affirmative symptoms at initial presentation.

Relevant investigations were done to evaluate local extent and metastases. These included CT scans (chest, abdomen and brain), bone marrow examination and bone scan. Limited disease was defined as tumor confined to one hemithorax, but including mediastinum, ipsilateral supraclavicular lymph nodes and ipsilateral pleural effusions.

Diseases beyond this stage was classified as extensive [6].

The baseline laboratory parameters recorded were- total serum protein, serum albumin, serum globulin, serum alkaline phosphatase (SAP), calcium, phosphorus, bilirubin, transaminases (AST/ALT), urea, creatinine, sodium, potassium, hemoglobin, total leukocyte count (TLC) and platelet count.

Records of the above cohort were tabulated using a structured checklist and data regarding patient's demographic characteristics, clinical information, disease status, radiological information, treatment details, toxicity, response and follow up details were entered. Follow up time is Date of treatment completion to date of last contact, local recurrence, distant metastasis or death. All the patients were contacted by mail/telephone and additional data were taken from individual registration files of the patients. Files with inadequate data or patients who could not be contacted were excluded from the study.

Statistical analysis was done by bivariate analysis, Cox Regression analysis, Chi square test, Kaplan Meier [7] for survival & log Rank test [8] for comparison. All analysis were done by IBM SPSS software v.23.

3. RESULTS

In analysis of three years data, keeping the exclusion criteria in mind, our study found the following details.

Mean age of presentation was 63 yr with a male preponderance (M:F – 2:1). 91% patients had an addiction history of tobacco. Most common presenting symptoms were cough followed by respiratory distress & chest pain. There was a median diagnostic delay of 3 months, about 60% patients presented with extensive stage disease, among which 25% were brain metastasis & 8.2% were having bone metastasis. Response rate of patients above or below 60yrs were not statistically significant (66% v/s 69%).

Median Survival were 14 months & 7months for limited & extensive stage .There was a correlation between diagnostic delay & stage of presentation. Patients who were unable to complete 6 cycles of chemotherapy and started PCI more than 2 weeks after Thoracic radiation , showed poor control of disease (P = 0.45). Patients with poor Performance Status (ECOG >2), brain metastasis at presentation, & with more disease burden (symptoms >4) had poor response and survival which were statistically significant. [Table 1, Figs. (1),(2),(3),(4)]. Concurrent chemo radiation was associated with slightly greater Haematological & GI toxicity. Grade 3,4 Haematological toxicity was greater in elderly people (>60yrs) (P= 0.04).

4. DISCUSSION

The patients in the present study were on an average 5 years younger as compared to patients in most other studies and was comparable to other Indian studies [9,10]. The prognostic value of age has been advocated by some, but not other studies, so as ours [11,12,13,14].

Table 1. Multivariate analysis of prognostic factors in SCLC, hazard ratios, 95% CI

Variable	Adjusted HR	95% confidence interval	P value
1. Stage (Limited V/s Extensive)	3.767	1.186 – 11.801	0.027
2. Disease burden (symptoms less than 4/ > 4)	1.434	0.784 – 2.374	0.048
3. ECOG PS(<3,>3)	1.84	0.974- 4.692	0.078
4. Diagnostic delay(<3 month,>3 month)	1.59	0.649- 3.482	0.115
5.Pre treatment Hb(<12 gm%,>12 gm%)	1.02	0.38- 3.879	0.768
6.Brain Mets at presentation	5.72	0.987 – 27.58	0.015

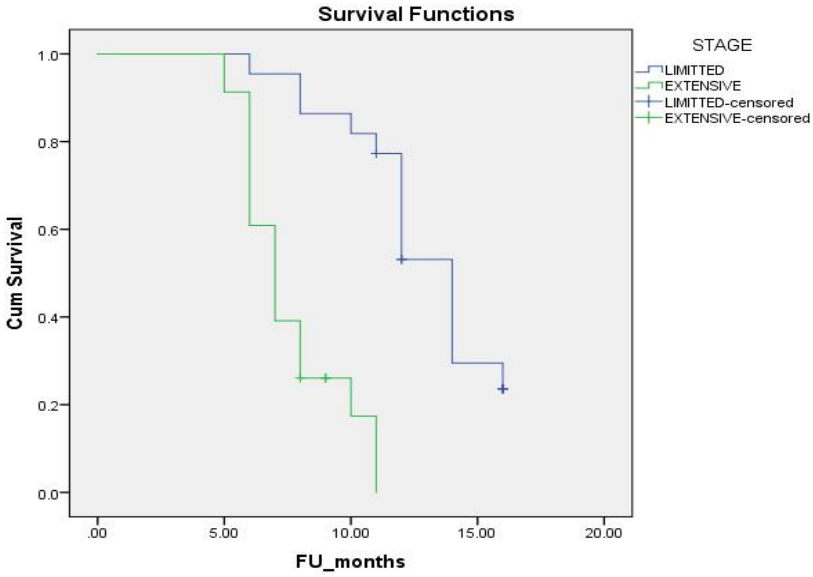

Fig. 1. Survival related to stage [P< 0.001]

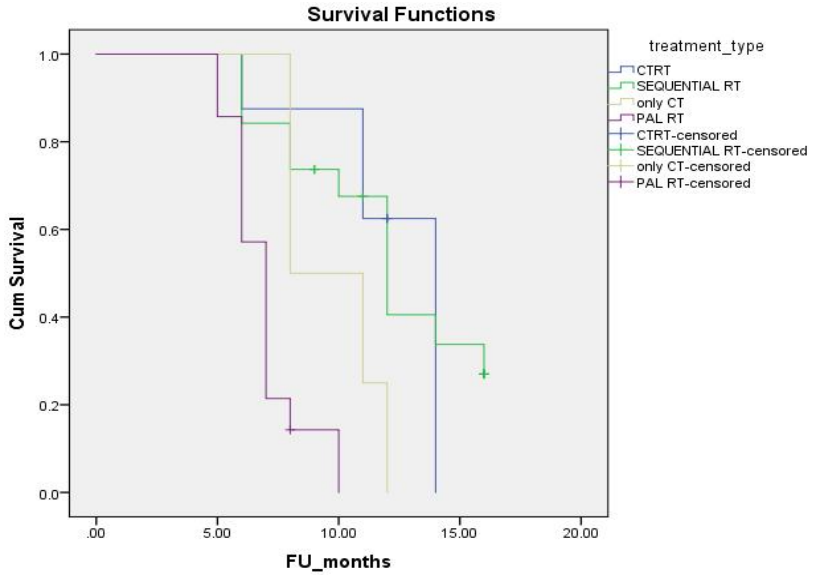

Fig. 2. Survival related to treatment type [P < 0.001]

In spite of the overall lower mean age, the proportion of patients presenting with extensive disease was higher than that reported in previous trials [15,16]. This could be attributed to (a) patient delay with a long interval between onset of the first symptom and seeking medical care due to ignorance about the disease, presence of other background symptoms, poor socio-economic status and lack of access to qualified health care professionals and specialized facilities (especially in far-flung geographical locales), (b) delay in diagnosis with a long interval between first presentation and confirmation of diagnosis due to high prevalence of other diseases, notably tuberculosis, which presents with similar symptoms (hence considerably diluting the clinical suspicion of malignancy) and (c) delay in treatment initiation (possibly due to high patient burden, limited centres offering oncology care and patient's inability to afford chemotherapy), allowing a considerably time for stage migration due to exponential growth of tumours.

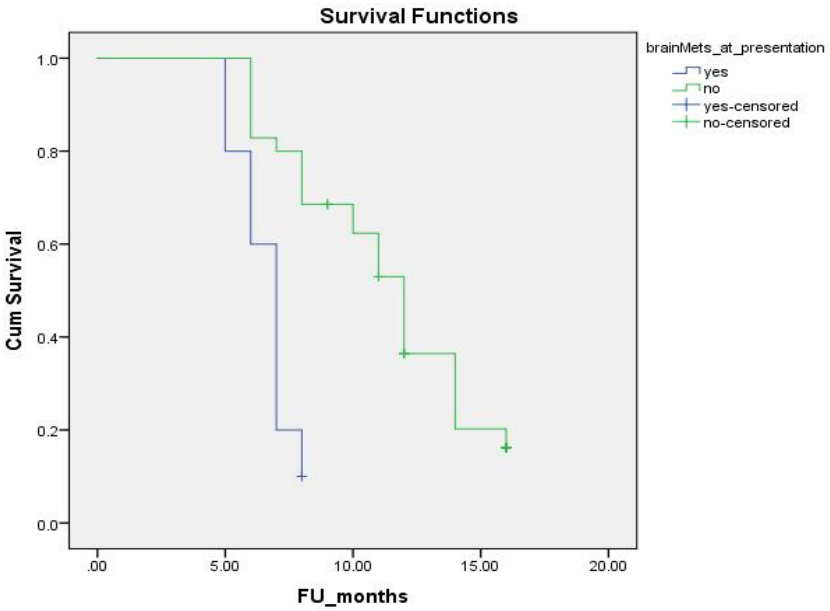

Fig. 3. Survival related to brain metastasis at presentation [P < 0.001]

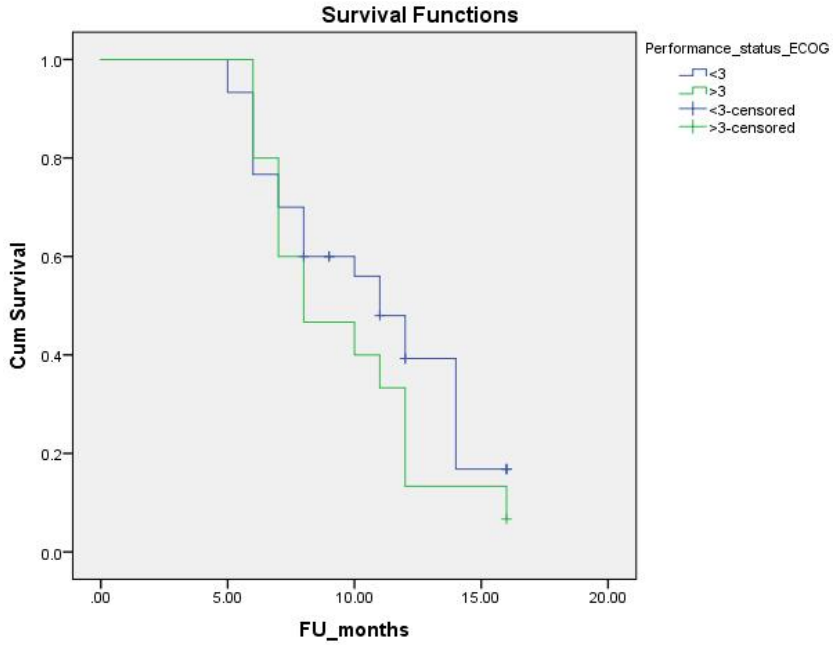

Fig. 4. Survival related to performance status [P = 0.08]

Western literature estimates that the median delay time in non-small cell lung cancer from onset of symptoms to initiation of treatment, is 4.6 months (3.4 months for advanced stage IV), whereas the median in-hospital delay (time of first hospital visit to start of treatment), is 1.6 month [17].

Lung cancer is more successfully treated in its early stages, which has raised interest in screening people for lung cancer before it causes symptoms. Advances in imaging techniques, such as low-dose, helical CT scanning, are currently being researched, and may help find better ways to diagnose lung cancer early. In the future, molecular features in the blood or sputum

may suggest lung cancer is present before it can be seen on a CT scan. Genetic testing to learn which people have a higher risk of lung cancer is also being researched [18].

Radzikowska E et al. (2013) showed that the delay in the diagnosis and treatment had no effect on survival. Interestingly, patients who were diagnosed faster (below 42 days) actually had a worse prognosis than those diagnosed later. The median delay was 30 days (mean 47 days) and the median referral delay to a specialist was 19 days (mean 36 days). Half of SCLC patients were diagnosed during 34 days (mean 55 days). The mean time elapse from the diagnosis to the onset of therapy was 30 days (median 6 days). The multivariate analysis revealed that male gender-HR (hazard ratio = 1.2), ECOG Performance Status of 2 (HR = 1.5) and 3 + 4 (HR = 2.4), and clinical stage III (HR = 1.3) and IV (HR = 1.9) of the disease were independent negative predictors of survival [19].

However, in this study, this delay did not affect survival significantly.

We found a significant correlation between symptom burden and survival, although individual symptoms per se were not significant prognostic indicators. Coy et al., (1981) studied 1839 unresected lung cancer patients and reported that fewer number of symptoms at the time of diagnosis and a longer time interval between the first symptom and diagnosis, were associated with better survival [20].

Poor Performance status and presence of Brain metastasis was associated with poor survival & it was compatible with previous data [21,22,23].

Caveats of our study were non randomisation, retrospective and single Institutional study design, and small sample size. Further investigations are needed to focus on ways of decrease toxicity, especially in the elderly.

5. CONCLUSION

In spite of having more grade 2 and 3 Hematological & GI toxicity, elderly SCLC patients 60 years or older can benefit from the EP regimen with or without thoracic RT. Stage at presentation , PS, and treatment type were related to median survival. More prospective, randomised control trials are needed to understand the radiobiological behaviour of Small cell lung carcinoma in Indian Population in near future.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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