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SHORT COMMUNICATION

Timing of treatment in small-cell lung cancer

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Abstract

Small-cell lung cancer (SCLC) is an aggressive disease with poor survival and rapid doubling time. Current practice is to treat SCLC as soon as possible but evidence on appropriate timing of treatment from diagnosis (TTD) is lacking. This is a retrospective analysis of SCLC patients from the 2012 to 2015 Kentucky Cancer Registry. Data collected included age at diagnosis, stage, gender, race, insurance and treatment. Factors and survival associated with TTD were identified with logistic regression analyses and Cox proportional hazards models. Among the 2992 SCLC patients, 2371 (79%) of SCLC patients were treated with one or more treatment modalities. Among treated patients, 93% received chemotherapy ± radiation with the mean TTD of 18 days. Most patients (80%) have TTD of ≤ 4 weeks with 33% treated within 1 week, 20% 1–2 weeks, and 27% 2–4 weeks from diagnosis. Delay in treatment (TTD > 4 weeks) was less in stage III and IV disease (odds ratio: 0.33 and 0.27 respectively, $p < 0.01$) but not significantly associated with age, race, gender, and insurance. One and two-year survival of patients with TTD ≤ 4 weeks was significantly worse when compared to > 4 weeks (hazard ratio = 1.43, 95% CI 1.2–1.6, $p < 0.01$; HR = 1.45, 95% CI 1.3–1.6, $p < 0.01$ respectively). These results show a trend toward better survival with late treatment of SCLC. Therefore, a general urgency to treat SCLC needs to be re-evaluated with consideration of patients needing more optimization before treatment. Further studies are needed to better clarify the appropriate timing of treatment from diagnosis in SCLC and who will benefit from early versus late treatment.

Keywords SCLC · Timing of treatment · Small-cell lung cancer

Abbreviations

SCLC	Small-cell lung cancer
TTD	Timing of treatment from diagnosis
OR	Odds ratio
HR	Hazard ratio
OS	Overall survival
KCR	Kentucky cancer registry

Introduction

Small-cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers. It is a highly aggressive disease with high doubling time and most (> 70%) diagnosed at distant stage leading to poor survival [1]. There is an urgency to treat SCLC mainly based on expert opinion due to its aggressive nature. Current practice is to refer and treat as soon as possible with NCCN guideline recommendations not to delay the onset of treatment for more than 1 week [2–4]. Scarce evidence exists on appropriate timing of treatment from diagnosis (TTD). Few previous retrospective studies have shown a trend towards worse survival with faster diagnosis [5] and shorter interval between diagnosis and treatment [4].

In this study, we have analyzed the timing of initial treatment from diagnosis of patients with SCLC and determined association with survival, with the initial hypothesis that delay in treatment can adversely affect survival. Kentucky was chosen due to its highest age-adjusted lung cancer incidence rate and has the second highest smoking prevalence in the United States [6].

Preliminary data from this study was presented in abstract form and poster presentation at ESMO congress 2018 on October 20th, 2018 in Munich, Germany.

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Patients and methods

The Kentucky Cancer Registry (KCR) is the official population-based central cancer registry for the Commonwealth of Kentucky. KCR is currently a part of both the National Cancer Institute's Surveillance Epidemiology and End Results program and the Centers for Disease Control and Prevention's National Program of Cancer Registries. This study received an expedited Institutional Review Board approval at the University of Louisville, Kentucky. Data used are derived from de-identified KCR file not subject to the requirement for informed consent.

Adult patients (≥ 18 years of age) with diagnosed SCLC from 2012 through 2015 were abstracted from KCR as part of the Lung Cancer Education Awareness Detection Survival (LEADS) Collaborative and included 2992 eligible patients from a base of 3052 SCLC cases. Patients with missing staging data entries were excluded ($n = 60$ [2%]). Data collected included age at diagnosis, stage, gender, race, insurance, comorbidities, treatment, and vital status. Factors associated with TTD were identified with logistic regression analyses adjusted for age, gender, race, stage, and insurance status. Delay in treatment is defined as ≥ 4 weeks from diagnosis. Multivariable analysis was conducted using Cox proportional hazard and binary logistic regression models. Hazard ratios (HR) and 95% confidence interval (CI) were reported. Survival curves were generated using the Kaplan–Meier method. Statistical significance was considered for $p < 0.05$. Data analysis was performed by means of SAS v9.4 software (SAS Institute, Cary, NC, USA).

Results

Overall, from 2012 through 2015, 2992 eligible cases of SCLC were included in the study. Patient demographics and clinical characteristics are summarized in Table 1, with a mean age of 66.4 years (standard deviation, SD = 9.7) and 53.3% females. Initial treatment received was 56% chemotherapy and radiation, 37% chemotherapy alone, 6.3% radiation alone, 0.8% surgery alone and 21% received no treatment. Among treated patients, mean TTD was 18 days (SD = 21).

Most patients (80%) received treatment within 4 weeks of diagnosis with 33% treated within 1 week, 20% 1–2 weeks, and 27% 2–4 weeks from diagnosis. Delay in treatment was significantly less in stage III (OR 0.33; 95% CI 0.23–0.48; $p < 0.001$) and IV disease (OR 0.27; 95% CI 0.20–0.38; $p < 0.001$) but not significantly associated with age, race, gender, and insurance. Number of comorbidities was significantly associated with TTD and patients with higher number were treated earlier (OR 0.94; 95% CI 0.91–0.97; $p < 0.001$). With a median follow-up of 7.5 months, survival was compared between the groups (Fig. 1). One and two-year survival of patients with TTD ≤ 4 weeks was significantly worse when compared to > 4 weeks (HR = 1.43, 95% CI 1.2–1.6, $p < 0.01$; HR = 1.45, 95% CI 1.3–1.6, $p < 0.01$ respectively).

Discussion

This KCR analysis provides population-based documentation of factors associated with treatment and timing of treatment in SCLC. A key finding in this study is the association between TTD and survival, favoring late treatment (> 4 weeks from diagnosis). Based on our results, the reason for this trend towards better survival with later treatment is unclear. None of the evaluated factors (age, gender, insurance, stage) explain this trend.

One previous study [7] showed that patients with longer waiting times have less advanced disease and better survival, and suggested that patients with advanced disease are probably being "fast-tracked". Survival analysis in our study favoring late treatment is adjusted for stage. Another explanation for poor survival with early treatment could be malnutrition and poor respiratory status [8].

Standard treatment for SCLC was established 1980s with no significant treatment advances since then [9]. Recommended urgency to treat SCLC lacks evidence, is based on expert opinion and has never been formally evaluated. As such, based on our study, we suggest there may not be as great of an urgency to start immediate treatment for SCLC patients, particularly in advance stage SCLC. Because advanced stages were likely to be treated sooner based on the results, it can be speculated that these patients were likely more symptomatic at presentation necessitating faster treatment. Even given the survival advantage of treatment delay (> 4 weeks) seen in our study, we do not suggest delaying treatment when significant symptomatic burden needs to be palliated immediately. One should instead tailor treatment individually and consider secondary factors such as optimizing nutritional and respiratory status before immediately hurrying to treatment. Furthermore, there should be a larger emphasis for treating early stage SCLC sooner to prevent stage shift, which has a much greater impact on survival.

Limitations

There are limitations to this study. Our patient population was limited to patients with SCLC diagnosed and treated in Kentucky which limits generalizability. Data was retrospectively collected from a cancer registry and like with any database,

Table 1 Demographics and clinical characteristics of SCLC patients from KCR, 2012–2015

	Total	Treated		*p*-Value
	N = 2992	*N* = 2371		
		≤ 4 weeks	> 4 weeks	
		N = 1894	*N* = 477	
	Mean (SD)	Mean (SD)	Mean (SD)	
Age at diagnosis	66.4 (9.7)	64.8 (9.2)	66.2 (8.9)	0.006
Number of comorbidities	4.4 (3.4)	4.5 (3.3)	3.8 (3.1)	0.0001
Person days	326 (350)	361 (331)	511 (426)	< 0.0001
	N (%)	*N* (%)	*N* (%)	
Race				0.69
White	2865 (95.8)	1822 (96.0)	457 (95.8)	
Other	127 (4.2)	72 (3.8)	20 (4.2)	
Gender				0.38
Male	1396 (46.7)	886 (46.8)	212 (44.4)	
Female	1596 (53.3)	1008 (53.2)	265 (55.6)	
Primary payer				0.06
Uninsured	90 (3.0)	56 (3.0)	10 (2.1)	
Insured	618 (20.7)	448 (23.7)	95 (19.9)	
Medicaid	335 (11.2)	239 (12.6)	46 (9.6)	
Medicare	1890 (63.2)	1117 (59.0)	313 (65.6)	
Military	44 (1.5)	27 (1.4)	11 (2.3)	
Other	15 (0.5)	7 (0.37)	2 (0.42)	
Stage of disease				< 0.0001
I	136 (4.5)	62 (3.3)	50 (10.5)	
II	62 (2.1)	36 (1.9)	20 (4.2)	
III	798 (26.7)	538 (28.4)	141 (29.6)	
IV	1996 (66.7)	1258 (66.4)	266 (55.8)	
Treatment				0.65
Chemotherapy + radiation		1062 (56.1)	269 (56.4)	
Chemotherapy only		695 (36.7)	175 (36.7)	
Radiation only		123 (6.5)	27 (5.7)	
Surgery only		14 (0.7)	6 (1.3)	
Timing of treatment from diagnosis				
< 1 week		773 (32.6)		
1 to < 2 weeks		467 (19.7)		
2 to 4 weeks		648 (27.3)		
> 4 weeks			477 (20.1)	

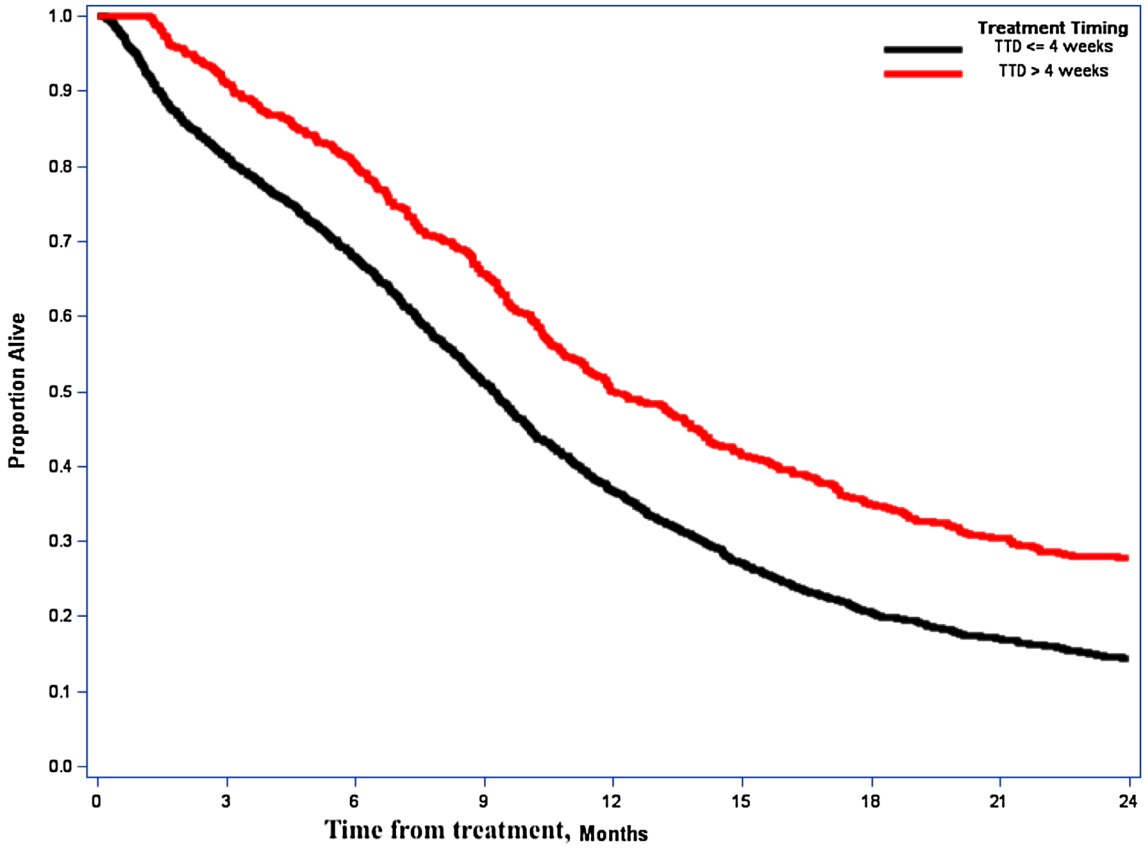

Fig. 1 Kaplan–Meier curve: survival of patients with small-cell lung cancer captured in the Kentucky cancer registry from 2012 to 2015. *TTD* Timing of treatment from diagnosis

there were small proportion of cases with insufficient data and conclusions of the analysis are predicated on the accuracy of initial data input.

Conclusions

Urgency of treating patients with SCLC within a week should be re-evaluated as delay in treatment might not be associated with worse survival. Oncologists should individualize treatment for all SCLC and consider limiting early expedition of treatment to patients' early stage disease or those with significant symptomatic burden in advance stages. A survival advantage otherwise may be seen in delay of treatment who do not require immediate palliation. More prospective studies are needed to understand the appropriate timing of treatment in SCLC and the patient population that would benefit from early vs delayed treatment.

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Compliance with ethical standards

Conflict of interests All the authors declare that they do not have any conflicts of interest in this work.

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