

RESEARCH ARTICLE

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Comparison of demographics, treatment patterns, health care utilization, and costs among elderly patients with extensive-stage small cell and metastatic non-small cell lung cancers

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Abstract

Background: Limited data exist regarding real-world treatment patterns, resource utilization, and costs of extensive-stage small cell lung cancer (esSCLC) among elderly patients in the United States. While abundant data are available on treatment patterns in metastatic non-small cell lung cancer (mNSCLC), to our knowledge no data exist comparing costs and resource use between patients with esSCLC or mNSCLC.

Methods: We retrospectively analyzed administrative claims data (2000–2008) of patients aged ≥ 65 years from the linked Surveillance, Epidemiology and End Results (SEER)-Medicare database. Patients were selected on the basis of having newly diagnosed esSCLC ($n=5,855$) or mNSCLC ($n=24,090$) during 1/1/2000–12/31/2005, and were required to have received cancer-directed therapy. Survival and other measures were compared between esSCLC and mNSCLC patients using Kaplan-Meier log-rank and univariate chi-square and t-tests. Study measures were followed from first diagnosis date of either esSCLC or mNSCLC until the earlier of death or end of the database.

Results: Survival between the cohorts did not differ significantly: mean of 10.4 months for esSCLC patients versus 11.1 months for mNSCLC; median survival was 7.4 months versus 5.9 months. A higher percentage of mNSCLC patients (vs. esSCLC) received radiation therapy (75.6% vs. 65.4%; $P < 0.001$) and surgery (13.6% vs. 7.8%; $P < 0.001$) during the metastatic disease period. Conversely, a higher percentage of esSCLC patients than mNSCLC patients received chemotherapy (85.5% vs. 60.3%; $P < 0.001$), red blood-cell transfusion (20.7% vs. 10.9%; $P < 0.001$), platelet transfusion (5.6% vs. 1.8%; $P < 0.001$), and growth-factor support (59.0% vs. 39.5%; $P < 0.001$). esSCLC patients incurred higher lifetime disease-related costs (\$44,167 vs. \$37,932; $P < 0.001$) and all-cause costs (\$70,549 vs. \$67,176; $P < 0.001$) than mNSCLC patients.

Conclusions: Lifetime total and disease-related costs per patient were high. Increased use of chemotherapy, supportive care therapies (including growth factors), and disease-related hospitalizations were observed in esSCLC patients as compared with mNSCLC patients. Disease-related and all-cause costs for esSCLC also exceeded those of mNSCLC, except for hospice and skilled nursing services. Survival and per-patient costs for both groups underscore the unmet medical need for more effective therapies in patients with esSCLC or mNSCLC.

Keywords: Metastatic lung cancer, Health care utilization, Health care costs, SEER-medicare

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Background

Lung cancer remains the second most commonly diagnosed cancer in the United States (US), with approximately 225,000 new cases and 160,000 deaths expected in 2014 [1]. Approximately 14% of new diagnoses are classified as having small cell lung cancer (SCLC), while the remaining 85% of cases are non-small cell lung cancer (NSCLC) [2]. Nearly two-thirds of these patients are diagnosed at age 65 years or older, with an estimated median age at diagnosis of 70 years [2]. Approximately 70% of SCLC and 54% of NSCLC cases have metastasized to other organs at initial diagnosis; this higher percentage of SCLC patients diagnosed with extensive-stage disease (esSCLC) likely contributes to its lower overall 5-year survival rate (6.2%) versus that of mNSCLC (18.0%) [2].

For patients with mNSCLC, current and previous guidelines recommend platinum-doublet chemotherapy as first-line systemic treatment, although recommendations of specific agents and/or combinations of agents have evolved over time depending on disease histology (squamous or non-squamous) and, more recently, presence of epidermal growth factor receptor (EGFR) and/or anaplastic lymphoma kinase (ALK) gene mutations [3]. For patients with esSCLC, etoposide plus a platinum agent (cisplatin or carboplatin) is the recommended first-line systemic therapy [4]. For both lung cancer types, radiotherapy may also be indicated either in sequential or concurrent use with chemotherapy [3,4].

Lung cancer exerts a significant economic burden on the US health care system. A recent study estimated that in 2010, medical costs related to lung cancer were \$12.1 billion and were expected to increase to \$15.2 billion by 2020 [5]. Because the median age at diagnosis in lung-cancer patients is high (71 years) [2], this cost burden is largely incurred by the US Medicare system. Despite this burden and its expected future trend, limited data exist comparing health care resource use and costs in elderly patients with either esSCLC or mNSCLC [6,7]. Additionally, to our knowledge, there are no data describing treatment patterns for esSCLC.

Most existing cost studies focus on mNSCLC alone [8-10] or on all lung cancers combined [11-13]. Existing cost studies have primarily focused on estimations of chemotherapy use and costs [14-17], with little information presented regarding broader treatment patterns, resource utilization, and costs for other service categories. Only one recently published US study addressed these knowledge gaps, although the authors used data drawn from 1992 to 2003 [18].

To help meet these information needs, we conducted a retrospective analysis of the linked Surveillance, Epidemiology and End Results (SEER)-Medicare database to provide a summary of trends in treatment patterns, and a comparison of health care resource utilization and direct

health care costs among elderly Medicare enrollees with esSCLC and mNSCLC.

Methods

Data source

The SEER program, initiated by the National Cancer Institute in 1973, collects cancer incidence and survival data from population-based registries covering approximately 28% of the US population [19]. In this retrospective longitudinal cohort study, we analyzed the SEER-Medicare linked database from 2000 through 2008. At the time this study was conducted, the SEER-Medicare database included new cancer cases first diagnosed through 2005, with linked claims data available on these subjects through 2008.

The data files utilized for this analysis were those included in the standard SEER-Medicare file set available from the NCI: Patient Entitlement and Diagnosis Summary File (PEDSF); Medicare Provider Analysis and Review (MEDPAR) hospital file; Carrier Claims (physician office visits) file; Outpatient (other ambulatory care) file; Home Health Agency (home health services) file; Hospice file; and Durable Medical Equipment file.

The conduct of this study was approved by an authorized institutional review board: the Research Triangle Institute (RTI) Committee on the Protection of Human Subjects (Federal-Wide Assurance [FWA] #3331) is registered with the US Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP).

Patient selection

Patients with a new lung cancer diagnosis (*International Classification of Diseases for Oncology, Third Edition* [ICD-O-3] topography codes: C34.0-C34.9) between January 1, 2000, and December 31, 2005, were selected for initial inclusion. These patients were classified as SCLC or NSCLC, using ICD-O-3 histology codes 8041-8045 for SCLC and 8046 for NSCLC [20]. We further restricted the sample to patients with extensive-stage and metastatic disease (esSCLC or mNSCLC) at diagnosis, using tumor staging information provided in the SEER data. Details on SEER cancer staging classifications are provided elsewhere [21]. For all selected patients, the study index date was defined as the date of the first SEER-reported diagnosis of esSCLC or mNSCLC. Furthermore, the study cohort was limited to patients who received cancer-directed therapy (surgery, radiation, chemotherapy, biologic therapy) at some point on or after their index date. All patients were required to be 65 years of age or older at first diagnosis and to have age as their reason for Medicare eligibility. Patients also were required to have at least 6 months of continuous Medicare enrollment prior to their study index date.

Patients were followed from the index date until the earlier of death or end of the database. A minimum post-index follow-up duration was not required for study inclusion. Patients enrolled in a health maintenance organization during the 6-month pre-index period or at any time during post-index follow-up were excluded [22,23]. Finally, we excluded patients with evidence of other malignancies at any point pre- or post-index, except for basal and squamous cell carcinomas of the skin which are not reportable to SEER.

Study measures

Patient characteristics

Background characteristics of age, sex, race, US Census region of residence, urban versus rural location of residence, and tumor histology were evaluated. Underlying comorbidity burden was assessed using the Charlson Comorbidity Index score (excluding diagnosis codes for lung cancer) with the Deyo adaptation for claims data [24].

Treatment patterns

Treatment patterns associated with esSCLC and mNSCLC, including supportive and palliative therapies, were defined by the relevant Health Care Financing Administration Common Procedure Coding System (HCPCS), *International Classification of Diseases, Ninth Revision, Clinical Modifications* (ICD-9-CM) procedure codes, and certain ICD-9-CM diagnostic codes and administrative revenue codes (see Additional file 1) recorded in the linked Medicare claims data.

We documented detailed usage patterns of chemotherapy including the most frequently observed first-, second-, and third-line chemotherapy regimens. Specific regimen compositions were defined by using algorithms developed in previous claims-based studies of chemotherapy utilization [9,14]. For first-, second-, and third-line chemotherapy regimens, we assessed the number of treatment cycles that were administered to each patient by using methods presented in recent claims-based cancer studies by Ramsey et al. [13] and Weycker et al. [25].

Health care utilization and costs

Total all-cause and disease-related health care utilization as well as costs were aggregated for each patient across the entire available follow-up period and stratified by major care settings: inpatient, outpatient, emergency department, physician office, skilled nursing facility, hospice, and other ancillary care. Disease-related health care utilization and associated costs were defined as claims for cancer-directed treatment or medical encounters or discharge records for inpatient admission carrying a lung cancer ICD-9-CM diagnosis code [16,26].

Medicare-reimbursed amounts provided on each unique claim in the database were used to assess all-cause and

disease-related costs. To approximate total lifetime costs, all cost data associated with the selected service categories were aggregated and reported as per-patient total costs across all available follow-up, from study index date until the earlier death or end of the database (December 31, 2008). Costs were inflated at the claim level to 2010 US dollars using the medical component of the US Consumer Price Index.

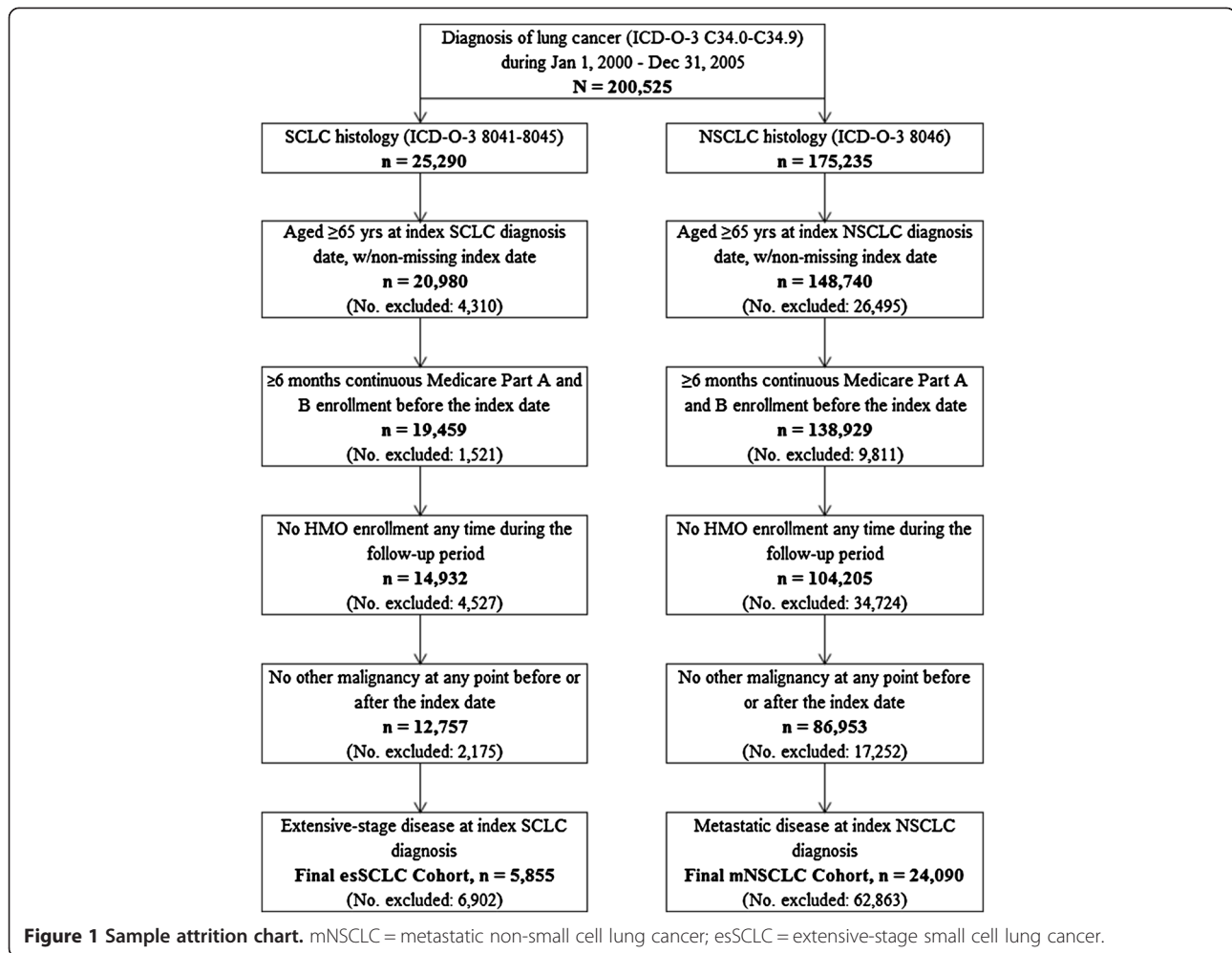
Statistical analyses

Descriptive statistics that were generated for all analysis variables included frequency distributions for categorical variables, and mean values and standard deviations (SDs) for continuous variables. The statistical significance of unadjusted differences in the outcomes of interest between patient cohorts (esSCLC vs. mNSCLC) was measured using Student t-tests and chi-square tests, as appropriate. Kaplan-Meier survival curves and corresponding log-rank tests were used to compare differences in survival time by cancer type. Among patients who died during follow-up, survival time was defined as the number of months between the study index date and the date of death. Among patients who did not die during follow-up, survival time was censored at the end of the database.

Results

Patient characteristics

A total of 29,945 patients met all study inclusion criteria: 5,855 (19.6%) of whom had esSCLC and 24,090 (80.4%) had mNSCLC (Figure 1). Patients differed statistically ($P < 0.001$) across all demographic characteristics between the two lung-cancer types (Table 1). The majority of patients in both cohorts were between the ages of 65 and 74 years; esSCLC patients on average were slightly younger than those with mNSCLC (73.5 vs. 74.4; $p < 0.001$). A greater number of patients in both cohorts were male, white, and were more likely to be located in the western part of the US in large metropolitan areas. Approximately 20% of patients with mNSCLC had tumors of squamous histology, while 41% had adenocarcinomas. While there were statistical differences, the co-morbidity status (measured by mean Charlson score) of both groups were comparable (esSCLC: 1.6 [SD: 1.9] vs mNSCLC: 1.4 [SD 1.9]). Nearly all patients (approximately 99%) from both study groups died during the follow-up period. Survival time between the cohorts did not differ significantly (log-rank: $P = 0.424$): mean [standard error] survival was 10.4 [0.2] months for esSCLC patients versus 11.1 [0.1] months for mNSCLC patients; median survival was 7.4 months (interquartile range [IQR]: 3 – 12.5) versus 5.9 months (IQR: 2.9 – 12.5), respectively (Figure 2).



Treatment patterns

Chemotherapy use was significantly more prevalent in esSCLC patients than in mNSCLC patients (85.4% vs. 60.3%; $P < 0.001$) (Table 2), and fewer esSCLC patients received surgery (7.8% vs. 13.6%; $P < 0.001$) and radiation therapy (65.4% vs. 75.6%; $P < 0.001$). Approximately 46.7% of esSCLC patients and 32.4% of mNSCLC patients received both radiation and chemotherapy during the follow-up period ($P < 0.001$). Radiation plus chemotherapy was the only combination treatment approach seen with substantial frequency in either cohort. Overall, the proportion of patients receiving biologic therapy, which included interleukin and interferon, was low in both the esSCLC (1.8%) and mNSCLC (1.2%) cohorts.

Among esSCLC patients initiating chemotherapy, etoposide plus either carboplatin or cisplatin was the most frequently observed first-line regimen, with a mean of 3.7 (carboplatin plus etoposide) and 3.4 (cisplatin plus etoposide) total cycles administered (Figure 3). Of all esSCLC patients receiving first-line chemotherapy, 43.2% received a second-line regimen and 18.0% received a

third-line regimen. Monotherapy with intravenous topotecan was the most common regimen seen in second-line (26.3%) and third-line initiators (20.8%) with esSCLC.

A carboplatin-based regimen was the most common first-line therapy initiated in mNSCLC patients (65.6%) with carboplatin plus paclitaxel being the most frequently used (44.0%) combination, with a mean of 3.3 cycles administered. Among mNSCLC patients initiating a first-line regimen, 22.6% subsequently received second-line therapy and 8.8% received third-line therapy. The most commonly used second- and third-line regimens included docetaxel (20.2%) and vinorelbine monotherapy (16.1%). Utilization of supportive and other palliative therapies during the follow-up period are presented in Table 2. A significantly higher proportion of esSCLC patients received growth-factor therapy than did mNSCLC patients (59.0% vs. 39.5%; $P < 0.001$). Among patients who required growth-factor support, erythropoietin (40.1%), filgrastim (25.1%), and pegfilgrastim (21.6%) were the most commonly used agents for esSCLC patients. For mNSCLC patients, erythropoietin (28.4%), darbepoetin

Table 1 Baseline esSCLC and mNSCLC patient characteristics

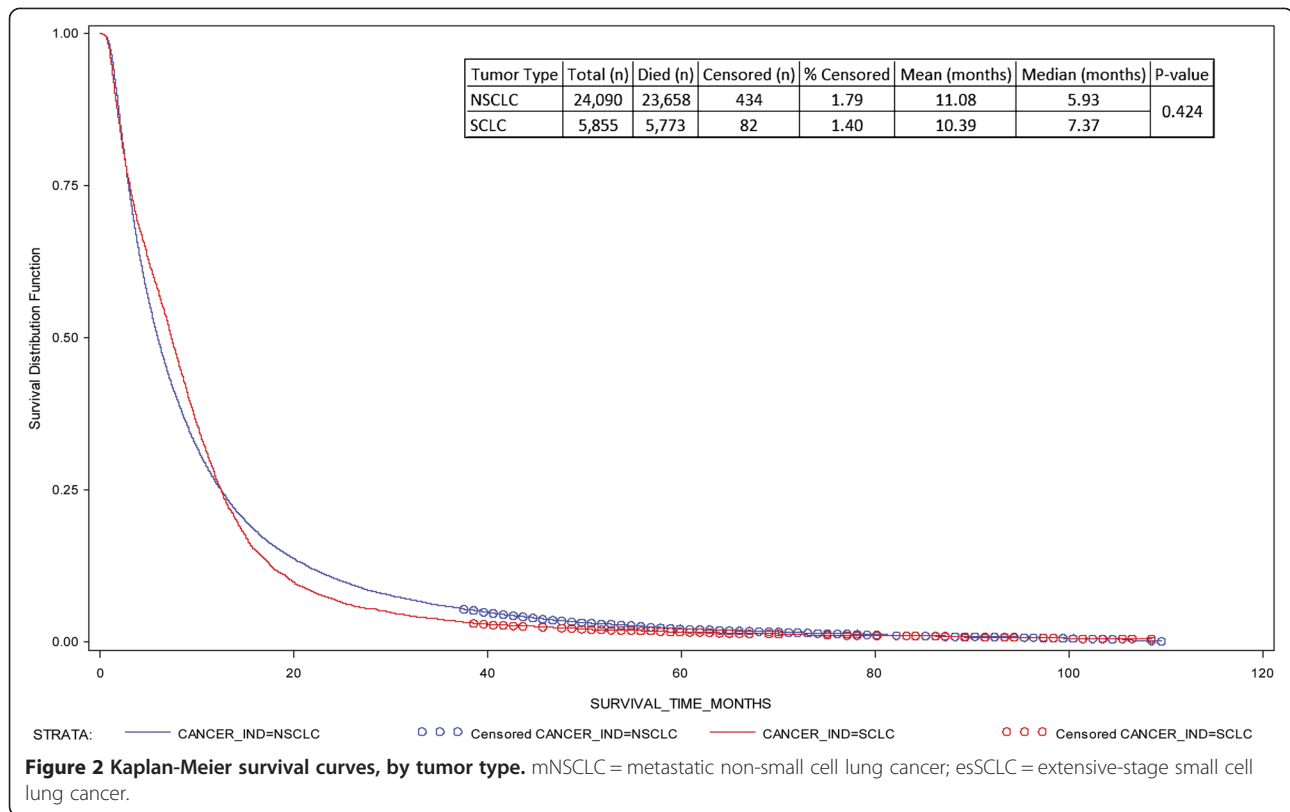
	Study groups		P value
	esSCLC	mNSCLC	
Overall, (n, %)	5,855 (100.0)	24,090 (100.0)	—
Age			
Mean (SD)	73.5 (5.6)	74.4 (6.0)	< 0.001
Age group, n (%)			
65-74 years	3,474 (59.3)	12,911 (53.6)	< 0.001
75-84 years	2,170 (37.1)	9,749 (40.5)	
≥ 85 years	211 (3.6)	1,430 (5.9)	
Gender, n (%)			
Male	2,998 (51.2)	13,535 (56.2)	< 0.001
Female	2,857 (48.8)	10,555 (43.8)	
Race, n (%)			
White	5,243 (89.6)	20,519 (85.2)	< 0.001
Black	376 (6.4)	2,102 (8.7)	
Other/unknown	236 (4.0)	1,469 (6.1)	
Census region, n (%)			
Northeast	1,303 (22.3)	5,620 (23.3)	< 0.001
Midwest	941 (16.1)	3,521 (14.6)	
South	1,482 (25.3)	5,397 (22.4)	
West	2,129 (36.4)	9,552 (39.7)	
Urban/rural status of residency, n (%) ^a			
Big metro	3,029 (51.7)	13,331 (55.3)	< 0.001
Metro	1,708 (29.2)	6,905 (28.7)	
Urban	409 (7.0)	1,568 (6.5)	
Less urban	566 (9.7)	1,865 (7.7)	
Rural	143 (2.4)	421 (1.8)	
Tumor histology, n (%)			
esSCLC cases			
Small cell carcinoma	5,855 (100.0)	—	—
mNSCLC cases			
Squamous cell	—	4,865 (20.2)	—
Adenocarcinoma	—	9,816 (40.7)	—
Large Cell	—	1,363 (5.7)	—
Other specified carcinomas	—	316 (1.3)	—
Carcinomas unspecified	—	7,730 (32.1)	—
Charlson comorbidity index score			
Mean (SD)	1.6 (1.9)	1.4 (1.9)	< 0.001

mNSCLC = metastatic non-small cell lung cancer; esSCLC = extensive-stage small cell lung cancer; SD = standard deviation.

^aUrban/rural definitions per SEER registry: Big Metro = counties in metro areas of >1 million population; Metro = counties in metro areas of ≤1 million population; Urban = areas of ≥20,000 population adjacent/non-adjacent to (but not in) a metro area; Less Urban = areas of <20,000 population adjacent/non-adjacent to (but not in) a metro area; Rural = completely rural or urban population <2,500 adjacent/non-adjacent to (but not in) a metro area.

(11.9%), and filgrastim (11.4%) were most commonly used. Among esSCLC patients who received either carboplatin or etoposide chemotherapy, approximately 53% received epoetin alfa and approximately 34% received filgrastim

during the follow-up period. Among esSCLC patients who received topotecan, approximately 68% received epoetin alfa and 44% received filgrastim. Among mNSCLC patients who received either carboplatin or paclitaxel chemotherapy,



over 47% received epoetin alfa and approximately 22% received filgrastim during follow-up (tabular data available upon request).

A significantly higher proportion of esSCLC patients received other supportive therapies than did mNSCLC patients (Table 2): megestrol (38.9% vs. 25.2%; $P < 0.001$), antiemetics (69.9% vs. 53.7%; $P < 0.001$), and red blood-cell (20.7% vs. 10.9%; $P < 0.001$) and platelet transfusions (5.6% vs. 1.8%; $P < 0.001$). mNSCLC patients received bisphosphonates with significantly greater frequency than patients with esSCLC (9.4% vs 6.4% $P < 0.001$). The frequency in esSCLC and mNSCLC, respectively, of antibiotics (10.5% vs 9.7%; $p = 0.063$), pain medications (23.3% vs 24.0%; $P = 0.280$), and oxygen (29.0% vs 28.5%; $P = 0.118$) utilization was similar between the two groups.

Health care utilization and costs

The percentage of patients with at least one hospitalization for any cause was high for both cohorts (esSCLC vs. mNSCLC: 91.4% vs. 88.6%; $P < 0.001$) (Table 3). Examining lung-cancer-specific hospitalizations, the frequency of post-index hospitalization was significantly higher in esSCLC patients than in mNSCLC patients (55.9% vs. 44.9%; $P < 0.001$), as was average total inpatient days (mean [SD]: 7.5 [11.1] vs. 5.4 [9.3] days; $P < 0.001$). For all other categories evaluated, disease-related health care resource utilization occurred with greater frequency for

mNSCLC patients while all-cause health care utilization was comparable between the two groups.

Per-patient total all-cause health care costs over all available follow-up among esSCLC patients exceeded those of mNSCLC patients (\$70,549 vs. \$67,176; $P < 0.001$) (Table 4). In both cohorts, hospitalization was the predominant cost driver, followed by office visits, the typical setting in which outpatient chemotherapy is administered. The mean numbers of all-cause inpatient visits (2.6 vs. 2.3; $P = 0.001$) and office visits (44.3 vs. 39.2; $P < 0.001$) were higher for esSCLC patients than for mNSCLC patients. In examining disease-related costs, office visits were proportionately the largest cost driver, accounting for 43% of all disease-related costs to esSCLC patients and approximately 41% of disease-related costs to mNSCLC patients. Among esSCLC patients, total disease-related per-patient costs for all available follow-up were 16.4% higher than for mNSCLC patients (\$44,167 vs. \$37,932; $P < 0.001$). Per-month costs for esSCLC patients were 17.2% higher (\$6,702 vs. \$5,721; $P < 0.001$) than for mNSCLC patients.

Discussion

Our study confirms the substantial economic burden presented by patients with esSCLC and mNSCLC who were enrolled in the US Medicare system and who received cancer-directed treatment during 2000–2008.

Table 2 Treatment utilization among esSCLC and mNSCLC patients, by tumor type

	Study groups		P value
	esSCLC (N = 5,855)	mNSCLC (N = 24,090)	
Post-index prevalence of cancer-directed therapies			
Overall, n (%) ^a			
Surgery	458 (7.8)	3,278 (13.6)	< 0.001
Radiation therapy	3,827 (65.4)	18,208 (75.6)	< 0.001
Biologic therapy	103 (1.8)	282 (1.2)	< 0.001
Chemotherapy	5,003 (85.4)	14,527 (60.3)	< 0.001
No. cycles received in first-line treatment, mean (SD)	3.4 (2.1)	3.2 (2.3)	
Post-index prevalence of supportive or palliative therapies			
Growth factors, n (%) ^a			
Filgrastim/pegfilgrastim/sargramostim	2,483 (42.4)	4,275 (17.8)	< 0.001
Darbepoetin/erythropoietin	2,926 (50.0)	8,640 (35.9)	< 0.001
Any growth factor	3,453 (59.0)	9,506 (39.5)	< 0.001
Other supportive or palliative therapies, n (%) ^a			
Iron supplements	39 (0.7)	249 (1.0)	0.012
Antibiotics	613 (10.5)	2,328 (9.7)	0.063
Antiemetics	4,095 (69.9)	12,947 (53.7)	< 0.001
Antifungals ^b		21 (0.1)	
Pain medications	1,366 (23.3)	5,782 (24.0)	0.280
Bisphosphonates	373 (6.4)	2,271 (9.4)	< 0.001
Megestrol acetate	2,276 (38.9)	6,078 (25.2)	< 0.001
Oxygen	1,696 (29.0)	6,861 (28.5)	0.118
Red blood-cell transfusion	1,212 (20.7)	2,629 (10.9)	< 0.001
Platelet transfusion	330 (5.6)	426 (1.8)	< 0.001

mNSCLC = non-small cell lung cancer; esSCLC = small cell lung cancer.

^aCategories are not mutually exclusive.

^bPer National Cancer Institute protocol, data suppressed due to cell size <11.

All-cause and disease-related costs for esSCLC across all cost categories were at least as high and in most instances higher than for the mNSCLC cohort, with the exception of hospice and skilled nursing facility services. The primary drivers of costs for the esSCLC and mNSCLC cohorts were hospitalizations, office visits, and hospital outpatient visits.

Despite statistically significant differences between clinical and demographic characteristics, the distribution of patients in the esSCLC and mNSCLC cohorts by age, gender, race, census region, and urban versus rural status of residency at baseline were comparable. The mean age and Charlson Comorbidity Index scores were also similar. In our study, approximately 71% of patients with esSCLC initiated a first-line chemotherapy regimen of etoposide with cisplatin or carboplatin, which was considered the recommended standard regimen for esSCLC during the period studied [27-30]. A clinical trial published in 2002

reported improved survival among esSCLC patients using irinotecan plus cisplatin when compared with patients using etoposide with cisplatin [31]. However, more recent studies reported no additional survival benefit from using irinotecan-plus-cisplatin combination therapy versus etoposide-plus-cisplatin. Therefore, it was expected that utilization data from 2008 to the present may reflect different patterns compared with our data from 2000–2008 [32,33]. Overall, in our study, irinotecan in combination with cisplatin was the third most commonly used first-line chemotherapy regimen among esSCLC patients.

There was significant heterogeneity with esSCLC regimens used in second- and third-line therapy, reflecting the lack of standard treatment options for these settings. In our study, intravenous topotecan was the predominant regimen in both the second line (26.3%) and the third line (20.8%) for esSCLC patients, followed by carboplatin plus etoposide (18.1% of second-line initiators, 11.7% of third-

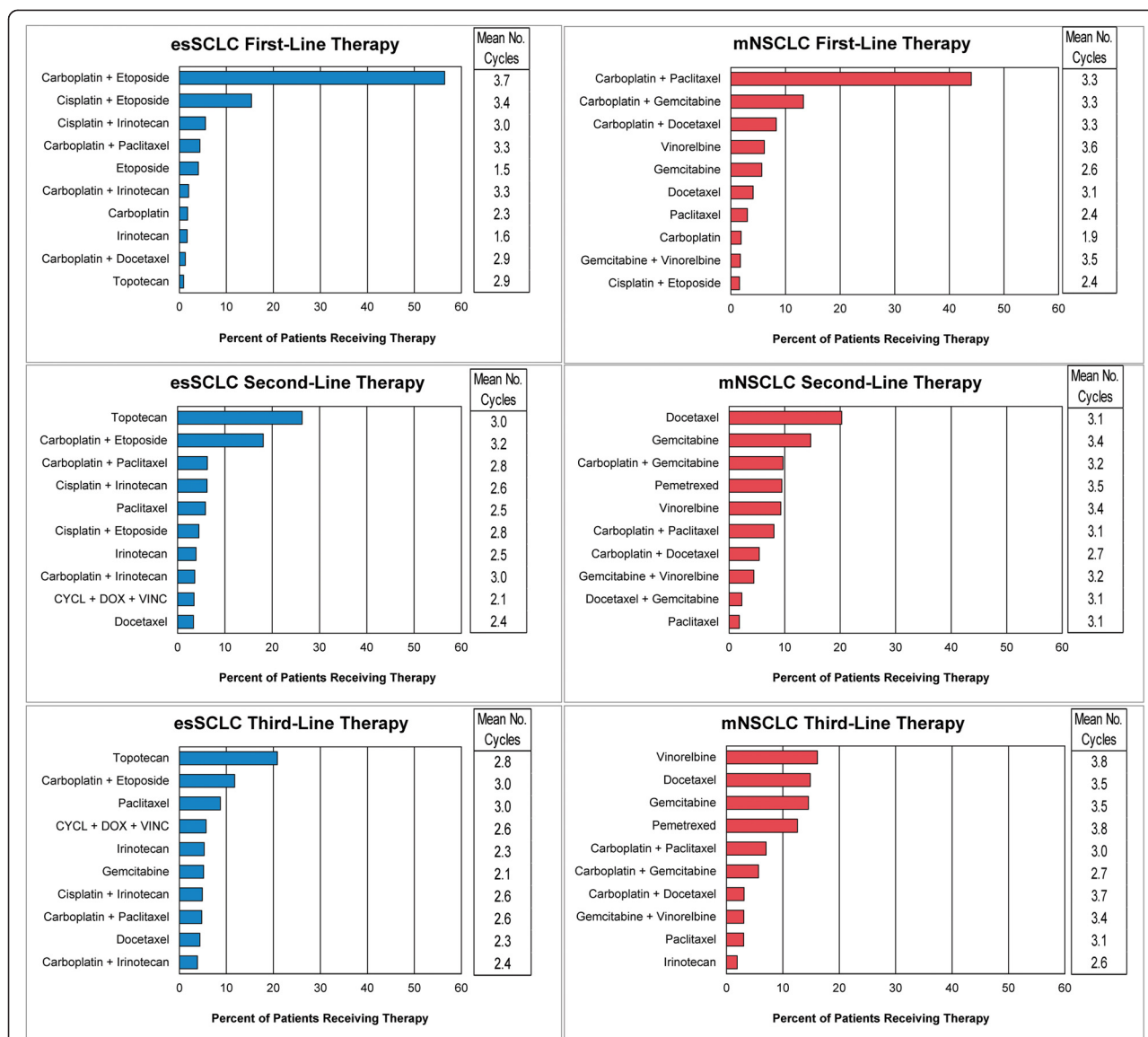


Figure 3 Chemotherapy utilization patterns, by tumor type. CYCL + DOX + VINC = cyclophosphamide + doxorubicin + vincristine; HCPCS = Healthcare Common Procedure Coding System; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer. Notes: Top 10 most frequently used regimens. Real-world data may show both approved and non-approved single agent and/or combination therapies (e.g. gemcitabine is indicated in combination with cisplatin for the first-line treatment of mNSCLC). Denominator for the estimated frequency distribution includes only patients initiating a HCPCS-identifiable first-, second-, or third-line chemotherapy regimen. For the esSCLC cohort, there were 4,256 patients initiating an HCPCS-identifiable first-line chemotherapy regimen, 1,824 patients initiating an HCPCS-identifiable second-line chemotherapy regimen, and 758 patients initiating an HCPCS-identifiable third-line chemotherapy regimen. For the mNSCLC cohort, there were 13,298 patients initiating an HCPCS-identifiable first-line chemotherapy regimen, 5,485 patients initiating an HCPCS-identifiable second-line chemotherapy regimen, and 2,108 patients initiating an HCPCS-identifiable third-line chemotherapy regimen.

line initiators). Intravenous topotecan is the only therapy approved by the US Food and Drug Administration (FDA) for platinum-sensitive esSCLC patients after failure of first-line therapy, despite demonstrating nonsignificant differences in efficacy outcomes when compared with cyclophosphamide, doxorubicin, and vincristine [34]. The relatively high usage of these therapies, with lack of improved survival outcomes from the registration trial,

may reflect the greater need for and lack of impactful treatment alternatives for esSCLC patients. The US FDA also approved oral topotecan for patients with relapsed esSCLC on the basis of significantly improved differences in overall survival versus best supportive care (log-rank: $P = 0.0104$) [35]. Because of limited claims data from the Medicare Part D program, we were not able to capture the use of oral topotecan, but this information has

Table 3 Overall health care utilization among esSCLC and mNSCLC patients, by tumor type

	Study groups		P value
	esSCLC (N = 5,855)	mNSCLC (N = 24,090)	
Hospitalizations			
All cause			
Had ≥1 admission, n (%)	5,349 (91.36)	21,351 (88.63)	< 0.001
Mean (SD) number of admissions	2.56 (2.16)	2.28 (1.96)	0.001
Mean (SD) total days in hospital	17.79 (17.37)	16.40 (17.34)	< 0.001
Disease related			
Had ≥1 admission, n (%)	3,272 (55.88)	10,825 (44.94)	< 0.001
Mean (SD) number of admissions	0.91 (1.25)	0.61 (0.86)	< 0.001
Mean (SD) total days in hospital	7.47 (11.09)	5.40 (9.31)	< 0.001
ER visits			
All cause			
Had ≥1 visit, n (%)	4,850 (82.84)	19,393 (80.50)	< 0.001
Mean (SD) number of visits	2.32 (2.38)	2.20 (2.36)	< 0.001
Disease related			
Had ≥1 visit, n (%)	2,295 (39.20)	9,145 (37.96)	0.081
Mean (SD) number of visits	0.54 (1.05)	0.66 (1.17)	0.003
Office visits			
All cause			
Had ≥1 visit, n (%)	5,789 (98.87)	23,764 (98.65)	0.172
Mean (SD) number of visits	44.27 (43.57)	39.18 (43.79)	< 0.001
Disease-related			
Had ≥1 visit, n (%)	5,527 (94.40)	22,915 (95.12)	0.023
Mean (SD) number of visits	22.93 (31.00)	31.82 (32.93)	< 0.001
Hospital outpatient visits			
All cause			
Had ≥1 visit, n (%)	5,320 (90.86)	22,018 (91.40)	0.192
Mean (SD) number of visits	13.05 (16.69)	12.18 (16.78)	< 0.001
Disease related			
Had ≥1 visit, n (%)	4,846 (82.77)	19,881 (82.53)	0.666
Mean (SD) number of visits	6.47 (11.35)	8.97 (12.65)	< 0.001
Hospice visits			
All cause			
Had ≥1 visit, n (%)	3,091 (52.79)	12,982 (53.89)	0.131
Mean (SD) number of visits	1.17 (2.12)	1.30 (2.57)	< 0.001
Disease related			
Had ≥1 visit, n (%)	2,927 (49.99)	12,104 (50.24)	0.728
Mean (SD) number of visits	1.04 (2.22)	1.10 (2.05)	< 0.001
Skilled nursing facility care			
All cause			
Had ≥1 visit, n (%)	1,497 (25.57)	6,171 (25.62)	0.939
Mean (SD) number of visits	0.37 (0.79)	0.37 (0.77)	0.652

Table 3 Overall health care utilization among esSCLC and mNSCLC patients, by tumor type (Continued)

Disease related			
Had ≥1 visit, n (%)	1,211 (20.68)	4,829 (20.05)	0.276
Mean (SD) number of visits	0.24 (0.60)	0.28 (0.66)	0.026
Ancillary care			
All cause			
Had ≥1 visit, n (%)	4,070 (69.51)	16,455 (68.31)	0.075
Mean (SD) number of visits	5.94 (10.07)	5.62 (11.14)	0.049
Disease related			
Had ≥1 visit, n (%)	3,035 (51.84)	11,793 (48.95)	< 0.001
Mean (SD) number of visits	1.96 (4.58)	2.65 (5.25)	< 0.001

ER = emergency department; mNSCLC = metastatic non-small cell lung cancer; esSCLC = extensive-stage small cell lung cancer; SD = standard deviation.

recently become available via the SEER-Medicare data program.

Approximately 40% of patients in the mNSCLC cohort and 60% of patients in the esSCLC cohort received either an erythropoietic therapy (ESA) or myeloid growth factor during the follow-up period. Pegfilgrastim, filgrastim, and sargramostim use was 42.4% across lines of therapy among esSCLC patients, and use was significantly greater than patients with mNSCLC (17.8%). Darbepoetin/erythropoietin use was also fairly high across both esSCLC (50%) and mNSCLC (35.9%) cohorts. A high rate of growth-factor use (>50%) in the real-world setting has been reported previously, despite low support of its use by the American Society of Clinical Oncology [36]. According to current guidelines by the National Comprehensive Cancer Network (NCCN), use of myeloid growth factor is not routinely recommended for primary prophylaxis in esSCLC or mNSCLC patients receiving chemotherapy. However, such therapy is recommended and should be considered after risk factor assessment in patients who are at high (>20%) or intermediate (10%-20%) risk for developing febrile neutropenia. NCCN strongly prefers that a less myelosuppressive therapy be used or dose reductions be considered so long as efficacy

outcomes are not compromised [37]. NCCN guidelines that were in place during the observation period of our study reflect these same considerations [38].

Guidelines for ESA use evolved from 2002 to 2008 due to the increasing knowledge over time regarding safety of these agents. Prior to 2007, the guidelines recommended ESAs in an effort to avoid transfusions and improve patient quality of life. However, since that time an increasing amount of data became available outlining the thrombosis risk and potential negative impact on patient survival. This not only prompted black box warnings by FDA for these agents, but changed the guideline recommendation in 2008 to exclude use in patients who could be cured of their disease. Additionally, the hemoglobin target was lowered from twelve to ten grams per deciliter. The 2008 guideline also communicated the thrombosis and mortality risk associated with blood transfusions, and urged patients to thoroughly discuss the risks and benefits of both ESA use and/or blood transfusions with their physician [39].

The availability of data outlining concerns associated with ESA use, black box warnings, and changes in treatment recommendations all occurred during the latter portion of our study period. We did not conduct a trend

Table 4 Mean all-cause and disease-related health care costs among esSCLC and mNSCLC patients, by tumor type

	All cause		Disease-related		esSCLC vs. mNSCLC	
	esSCLC (\$)	mNSCLC (\$)	esSCLC (\$)	mNSCLC (\$)	P value (All-cause costs)	P value (Disease-related costs)
Hospitalizations	32,456	32,027	12,498	9,778	0.403	< 0.001
Office Visits	22,340	18,995	19,168	15,622	< 0.001	< 0.001
Hospital OP Visits	7,253	7,040	6,044	5,767	0.270	0.116
Hospice	3,099	3,693	2,933	3,419	< 0.001	< 0.001
Other Ancillary Care	2,624	2,502	1,656	1,495	0.086	0.001
Skilled Nursing Facility	2,453	2,607	1,790	1,775	0.111	0.846
ER Visits	324	312	78	76	0.022	0.389
Total	70,549	67,176	44,167	37,932	< 0.001	< 0.001

ER = emergency department; mNSCLC = metastatic non-small cell lung cancer; OP = outpatient; esSCLC = extensive-stage small cell lung cancer.

analysis evaluating use over time of either myeloid factors or ESAs given that our observation period ended in 2008; this did not allow enough time to observe a meaningful trend. Further research is warranted in the esSCLC and mNSCLC populations to characterize the trajectory of this information over time. These data suggest that use of ESAs did indeed decrease over time due to changing guidelines as well as subsequent reimbursement stipulations [40]. While the assessment of side effects associated with chemotherapy was beyond the scope of this project, the higher use of chemotherapy among esSCLC patients (85.5%) than mNSCLC patients (60.3%) could have contributed to a higher rate of side effects (e.g., chemotherapy-induced nausea and vomiting), resulting in greater use of supportive care therapies, greater health care utilization, and associated costs [41,42]. In addition to growth factor use, there was significantly greater use of antiemetics and megesterol acetate; as well as RBC and platelet transfusions in patients with esSCLC. Additionally, a greater proportion of esSCLC patients had at least one hospitalization and spent on average 1.5 days longer in the hospital. These findings may be a reflection of the negative sequelae that can be associated with chemotherapy use (and its more significant use among esSCLC patients) and may also reflect the aggressiveness of esSCLC. Further research is necessary to assess the costs associated with chemotherapy-related side effects for esSCLC and mNSCLC patients [43].

Among mNSCLC patients, we found that 75.6% received radiation which is recommended as palliation according to NCCN [44], and to help prevent symptoms due to primary or metastatic tumors. In our study, approximately two-thirds of mNSCLC patients initiating chemotherapy received carboplatin in combination with paclitaxel, docetaxel, or gemcitabine; this is consistent with prior research and recommendations during the time period of our study [45-48], but may not always match the product labels. It is important to note that more recent advancements in mNSCLC are not fully captured in our data, either because there was minimal time from the availability of a new therapy to the end of our observation period or because therapies were approved after the end of our study period. This includes the US FDA approvals for bevacizumab, erlotinib, pemetrexed, nab-paclitaxel, afatinib, gefitinib, crizotinib, and ceritinib. This is a significant limitation of the generalizability of mNSCLC treatment pattern data in our study to current practice.

The lack of oral prescription drug data (i.e., Medicare Part D) in our study further contributed to the conservative nature of our cost estimates and limited our ability to gain information relative to erlotinib and topotecan use in mNSCLC patients and esSCLC patients, respectively. We recommend that these analyses be updated now that these claim data are available.

A few additional limitations must be considered when interpreting these study findings. First, our analysis did not include clinical trial participants or patients receiving only supportive care; this likely underestimated the total economic burden of esSCLC and mNSCLC. Second, our definition of lung-cancer-specific treatment (chemotherapy, radiation) was based on HCPCS and ICD-9-CM diagnosis and procedure codes; any coding inaccuracies could lead to misclassification of these treatments. Third, our method of estimating disease-related costs accounted only for adjudicated medical claims carrying a lung-cancer diagnosis code or claim for treatments and procedures (chemotherapy, surgery, radiation) that were likely to be cancer related. This microcosting approach likely understates the true direct costs to Medicare of lung-cancer management because other treatments and other medical services not considered in the definition are likely to be utilized in the management of the disease. We therefore also assessed all-cause resource utilization, which likely overstated actual costs. Fourth, this analysis was limited to elderly Medicare enrollees with distant-stage lung cancer. While this is the subpopulation in which lung cancer occurs most often, our results may not be generalizable to younger adults, individuals enrolled in other federal or commercial health plans, individuals without health coverage, or individuals with localized- or regional-stage lung cancer. Finally, while this study was conducted using the most up-to-date SEER-Medicare data at the time, more recent data are now available. As noted above, while this is a significant limitation in terms of the mNSCLC treatment pattern data, it is not believed to be a limitation to the accuracy of the cost and HCRU data. Since there have been no recent advancements in the treatment of esSCLC, the data used in this study remain representative and informative with regard to real-world treatment patterns, costs, and survival in these patients.

Conclusion

In conclusion, our study demonstrated that the direct medical costs of both esSCLC and mNSCLC are substantial and comparable; with a growing elderly population, this cost burden to the Medicare system will increase in the future. Additionally, therapies that provide clinically meaningful improvements in efficacy, safety, and less frequent dosing may help lower treatment-specific and future downstream costs. In contrast to mNSCLC, distant-stage esSCLC has had few therapies introduced that have advanced overall survival, thus underscoring the unmet need in this particular population of patients with lung cancer. Overall, the similar survival estimates and the significant per-patient lifetime costs for esSCLC and metastatic mNSCLC underscore the unmet medical need for patients with these tumor types. Our study findings complement existing literature and may help

researchers and policy makers by providing support and model inputs to Medicare-based cost-effectiveness studies of interventions focused on prevention of lung cancer or prevention of progression to the advanced-disease stage.

Additional file

Additional file 1: Procedure and diagnosis codes used to identify cancer-directed and supportive therapies.

Competing interests

Keith Davis is an employee and Sudeep Karve is a former employee of RTI Health Solutions, an independent contract research organization that has received research funding from Eli Lilly and Company (Lilly) for this study. Greg Price, Gerhardt Pohl, Emily Nash Smyth, and Lee Bowman are employees of Lilly. The manuscript underwent scientific quality and legal review by Lilly prior to submission. Final decisions regarding manuscript content were made jointly by the authors.

Authors information

SJ Karve was an employee of RTI Health Solutions at the time this study was conducted.

Authors' contributions

KD, SK, GP, and GP were the primary developers of the study design. As principal investigator, Sudeep Karve had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. KD and SK led all statistical analyses. SK also served as the primary writer in drafting the manuscript text and in interpreting the findings. GP, GP, ENS and LB assisted in interpreting the study findings and drafting the manuscript text; they also served as the primary reviewers of the manuscript text. All authors were responsible for approving the manuscript and its contents.

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Received: 29 August 2013 Accepted: 24 October 2014

Published online: 13 November 2014

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doi:10.1186/s12913-014-0555-8

Cite this article as: Karve et al.: Comparison of demographics, treatment patterns, health care utilization, and costs among elderly patients with extensive-stage small cell and metastatic non-small cell lung cancers. *BMC Health Services Research* 2014 **14**:555.

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