Lung Cancer (2005) **50**, 143—154

ELSEVIER

LUNG CANCER

IASLC

www.elsevier.com/locate/lungcan

The economic burden of lung cancer and the associated costs of treatment failure in the United States

Lucie Kutikova[a,*], Lee Bowman[a], Stella Chang[b], Stacey R. Long[b], Coleman Obasaju[a], William H. Crown[c]

[a] *Eli Lilly and Company, Lilly Corporate Center, DC 1833, Indianapolis, IN 46285, USA*
[b] *Medstat Inc., Washington, DC, 20008, USA*
[c] *Medstat Inc., Cambridge, MA, 02140, USA*

Received 24 January 2005; received in revised form 10 June 2005; accepted 14 June 2005

KEYWORDS
Non-small cell lung cancer;
Small cell lung cancer;
Lung cancer;
Treatment failure;
Costs;
Resource use

Summary The economic burden of lung cancer was examined with a retrospective case-control cohort study on a database containing inpatient, outpatient and drug claims for employees, dependents and retirees of multiple large US employers with wide geographic distribution. Patients were followed for maximum of 2 years from first cancer diagnosis until death, health benefits disenrollment or study end (31 December 2000). Compared with controls (subjects without any cancer), patients with lung cancer ($n = 2040$) had greater health care service utilization and costs for hospitalization, emergency room visits, outpatient office visits, radiology procedures, laboratory procedures and pharmacy-dispensed drugs (all $P < 0.05$). Regression-adjusted mean monthly total costs were US$ 6520 for patients versus US$ 339 for controls ($P < 0.0001$), and overall costs across the study period (from diagnosis to death or maximum of 2 years) were US$ 45,897 for patients and US$ 2907 for controls ($P < 0.0001$). The main cost drivers were hospitalization (49.0% of costs) and outpatient office visits (35.2% of costs). Monthly initial treatment phase costs (US$ 11,496 per patient) were higher than costs during the secondary treatment phase (US$ 3733) or terminal care phase (US$ 9399). Failure of initial treatment was associated with markedly increased costs. Compared with patients requiring only initial treatment, patients experiencing treatment failure accrued an additional US$ 10,370 per month in initial treatment phase costs and US$ 8779 more per month after starting the secondary and/or terminal care phase. Over the course of the study period, these patients had total costs of US$ 120,650, compared with US$ 45,953 for those receiving initial treatment only. Thus, the incremental costs associated with treatment

* Corresponding author. Tel.: +1 317 651 2580; fax: +1 317 277 1697.
E-mail address: kutikova_lucie@lilly.com (L. Kutikova).

0169-5002/$ — see front matter
doi:10.1016/j.lungcan.2005.06.005

failure were US$ 19,149 per month and US$ 74,697 across the study period. Other types of clinical and epidemiological analysis are needed to identify risks for treatment failure. The economic burden of lung cancer on the US health care system is significant and increased prevention, new therapies or adjuvant chemotherapy may reduce both resource use and healthcare costs. New strategies for lung cancer that reduce hospitalizations and/or prevent or delay treatment failure could offset some of the economic burden associated with the disease.

1. Introduction

Lung cancer was the third most frequently diagnosed cancer (approximately 172,000 new cases) in the United States in 2002 [1] and is the leading cause of cancer death in the United States and worldwide [1,2]. Relatively few published studies in the United States or globally document the economic burden of lung cancer. For lung cancer cases diagnosed in Canada in 1988, the total costs over 5 years exceeded Cdn$ 328 million [3]. The median overall cost per small cell lung cancer (SCLC) patient in Australia in 1987 was $14,413 [4]. In the United States, annual direct costs of lung cancer were estimated at US$ 5.1 billion in 1990 [5] and at $4.9 billion in 1996 [6]. Per-patient total health care costs were estimated at US$ 47,941 for the 2 years following diagnosis or until death in a commercially insured population in Virginia [7] and at US$ 15,127 per year in a health maintenance organization (HMO) population in Northern California [8]. A study of non-small cell lung cancer (NSCLC) patients enrolled in clinical trials found that the average 1-year cost for inpatient and outpatient visits was US$ 41,734 for trial enrollees and US$ 34,191 for non-enrollees [9].

Much of the available published estimates on costs are limited in that they are derived largely from Medicare claims, single employers or local HMOs. For example, studies of Medicare claims, such as those based on the Continuous Medicare History Sample File (CMHSF) [9] or the Surveillance, Epidemiology, and End Results (SEER)/Medicare database [6], are generally restricted to patients over age 64. Other studies have relied on population samples from single registries [9,10] or from select geographic regions [7,8,12]. These limitations have made it difficult to generalize study findings to the lung cancer population at large. To date, no studies have been published regarding the impact of lung cancer treatment outcomes on cost.

This study estimates the direct costs of lung cancer in populations with private insurance and with Medicare coverage supplemented by private insurance. Using a single longitudinal database of administrative insurance claims of patients distributed widely across the United States, we provide an updated assessment of the direct costs associated with lung cancer for up to 2 years following diagnosis or until death. The data source allows for a large sample population, with no age limitations, and the assessment of costs across the continuum of care. We examine the main drivers of treatment costs and the costs incurred across treatment phases. A demographically matched control population is used to assess the incremental costs resulting from lung cancer. The economic consequences of lung cancer treatment failure, which have not been previously published, are evaluated in this study. Data presented here are part of a larger study that assessed costs associated with a range of other cancers, including non-Hodgkin's lymphoma (aggressive and indolent) and colorectal, pancreatic, ovarian, prostate and brain cancers [11].

2. Methods

This retrospective study used the MarketScan® Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases for the years 1998—2000, which contained the inpatient, outpatient and outpatient pharmacy-dispensed drug claims for over three million individuals (annually) covered through large US employers. Employees and their spouses and dependents with private insurance, as well as retirees and disabled persons with Medicare and supplemental private insurance, were included in the database.

Cases in the study population consisted of patients newly diagnosed with lung cancer (ICD-9-CM code 162.2x, 162.3x, 162.4x, 162.8x or 162.9x) between 1 January 1999 and 30 November 2000, with pharmacy benefits and continuous enrollment in the health plan for at least 12 months prior to the first diagnosis date (index date) and 1 month following the index date. The lung cancer diagnosis

was verified by at least one subsequent diagnosis or treatment claim within 3 months after the index date. Claims and encounters for the 12 months prior to the index date were reviewed to ensure absence of any cancer diagnosis or related treatment during that period. Patients were followed for a maximum of 2 years from the index date until the earliest of enrollment end, death or study period end (31 December 2000). A control group without any treatment for or diagnoses of any cancer (ICD-9-CM codes 140-208, 230-239) between July 1997 and December 2000 was randomly selected matching (3:1) for age, gender, geographic region, type of health plan and length of enrollment. Age and length of enrollment were permitted to vary by 2.5% from cases.

A patient-level analytical file was constructed to summarize the demographic, clinical and economic data for patients in the final study population. Medical services were classified as inpatient, emergency room (ER), outpatient office visit, radiology (therapeutic and diagnostic) laboratory and outpatient pharmacy-dispensed drugs. If not dispensed in an outpatient pharmacy, costs for antineoplastic drug therapy (chemotherapy, hormone and immunotherapy) and other supportive drug therapy were included within costs of the office visits or hospital stays. Because of the variable length of follow-up, mean monthly health care service utilization and costs were calculated. However, to offer a broader look at the data, study-period health care utilization and costs were reported. Cost estimates were based on paid amounts of adjudicated claims. For patients with Medicare coverage, both the Medicare and private-insurance reimbursed amounts are included. To adjust for expected resource consumption associated with major co-morbid health conditions, such as diabetes or heart disease, a Charlson Comorbidity Index (CCI) score was calculated for each patient/control [14].

2.1. Cancer severity

Cancer severity was assigned by using disease staging software [15]. To determine baseline cancer severity, claims were evaluated from 1 year prior to diagnosis to 1 month following diagnosis. In its application to claims data, the software utilized ICD-9 diagnosis codes to identify the primary lung cancer and subsequent diagnoses of secondary neoplasms in the respiratory system, lymph nodes and distant organs. Severity was determined by the extent of the metastasis. Patients coded for NSCLC that did not extend to the regional lymph node or spread to lymph nodes in the peribronchial and/or the ipsilateral hilar region were designated as having mild to moderate disease. Patients whose disease had metastasized to distant sites, or who had SCLC, were identified as having advanced lung cancer. These severity designations correspond to American Joint Committee on Cancer (AJCC) stages I and II (mild to moderate severity) and AJCC stages III and IV (advanced severity) [15].

2.2. Assignment by treatment phase

Fig. 1 outlines the approach in determining treatment phase. Patients' costs were categorized throughout the study period into three treatment phases: initial, secondary and terminal care. Patients' costs started to accrue in either the initial treatment phase or the terminal care phase. During the study period, patients' costs may have accrued during more than one treatment phase. The initial treatment phase included the period from first cancer diagnosis until any shift in treatment, cancer severity, treatment location or in-hospital death that signaled disease progression. These shifts resulted in an advance of treatment phase. The secondary treatment phase was defined as the period after the shift in treatment. The terminal care phase represented either the start of terminal care (hospice, skilled nursing facility) or advanced cancer severity. All care provided in the 12 months preceding an in-hospital death was also assigned to the terminal care phase. However, if patients were still enrolled in the study 12 months after being diagnosed with advanced severity and did not receive terminal care, they were considered to have remained in the secondary treatment phase.

2.3. Designation of treatment failure

Classification by treatment phase helped identify patients who experienced treatment failure. Patients who started the study in the terminal care phase were excluded from the treatment failure analysis. Patients who received only initial treatment during the study were considered to be patients without treatment failure, as they did not experience a shift in their treatment regimen or advance to terminal care. Patients who advanced from the initial treatment phase to the secondary and/or terminal care phase were considered to have experienced treatment failure.

2.4. Study outcomes

Resource utilization and costs were summarized for patient and control groups and stratified by treatment phase. Summary statistics were standardized as the number of services or dollars per

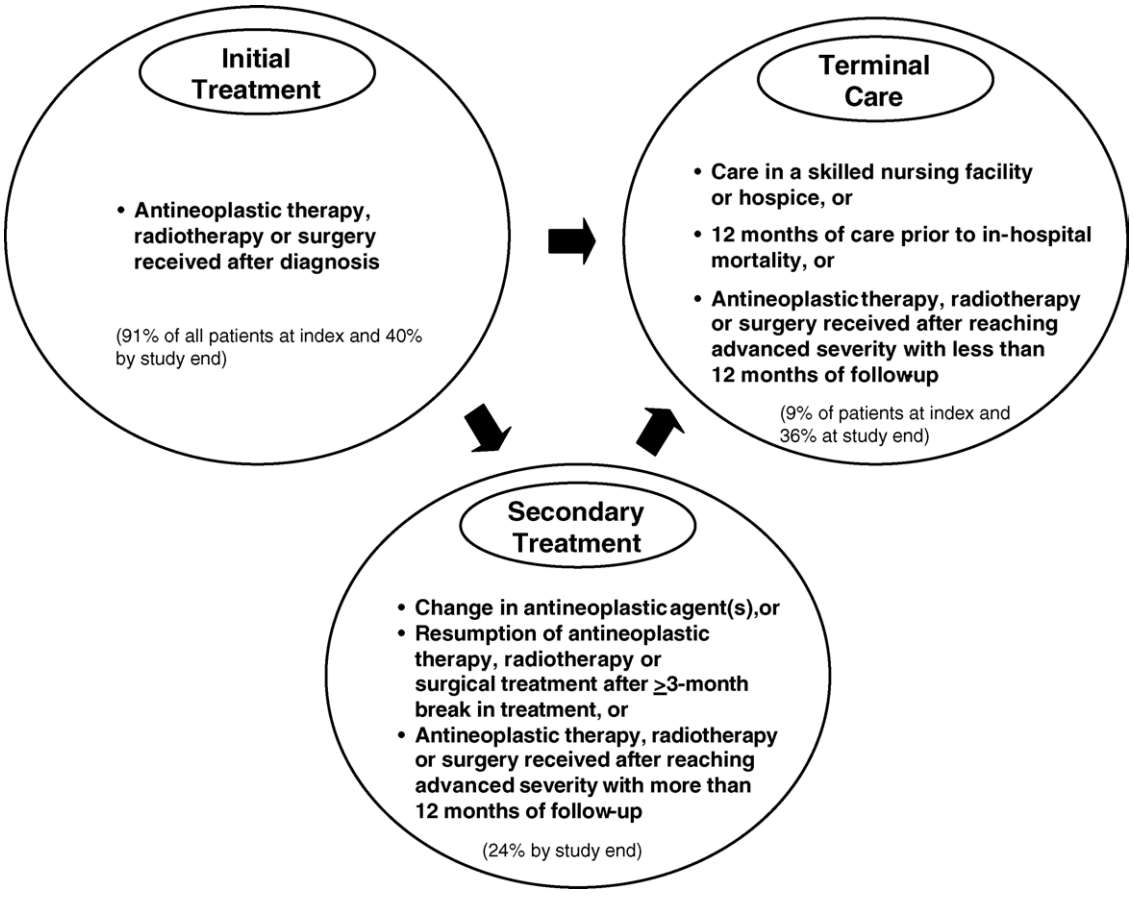


Fig. 1 Criteria for determining shifts among treatment phases. Patients started the study in either the initial treatment or terminal care phase. Secondary treatment began with either a change in antineoplastic agents or any treatment change after a time period greater than 3 months.

month across all patients/controls. The cost of failed treatment was calculated as the difference in costs between lung cancer patients with treatment failure and those without treatment failure, excluding patients starting the study in terminal care phase.

2.5. Statistical analysis

To compare lung cancer patients and controls, and to compare patients by treatment phase, two-sided *t*-tests were used for continuous variables and chi-square tests were used for categorical variables. Regression-adjusted total direct costs per month and across the study period were estimated by using multi-variate modeling that controlled for gender, age, health plan type, geographic region, CCI, length of follow-up and in-hospital mortality in the model. Cost modeling was performed separately for cancer patients and controls, since both populations were matched on the majority of co-variates and since the cost data distributions for the populations were different (as determined by a Wald test of parameter equality). However, the co-variate in both models was the same. Specification testing was conducted to determine the most appropriate functional form for the multi-variate estimations of total costs. An ordinary least squares model with natural logarithmic transformation of the dependent variable (total direct costs) was found to be the best model based on total explained variance in costs for lung cancer patients. Two-part models were used to estimate costs for controls due to left-skewed cost distribution in this group: logistic regression was used to estimate the probability of costs greater than zero, and an ordinary least squares regression was performed on log transformed costs among controls with costs greater than zero. The log-predicted values were transformed into actual costs via exponentiation and application of a smearing estimate [16]. Two patients with outlier monthly costs (>US$ 250,000 per month or US$ 0 per month) were excluded

from multi-variate analysis. For cancer patients, additional models were used to produce regression-adjusted cost estimates by treatment phases. These additional models were also OLS models on log-transformed costs. Because all cancer patients incurred costs, a logistic regression to adjust for a left-skewed cost distribution, due to no incurred costs, was not necessary. The models included as co-variates gender, age, health plan type, geographic region, CCI, length of follow-up, in-hospital mortality, and baseline cancer severity. A Cox proportional hazards model was used to identify factors associated with treatment failure in the lung cancer patients. Co-variates consisted of demographics, insurance type, baseline CCI, baseline cancer severity, and type of initial cancer treatment (surgery, radiotherapy, antineoplastic therapy).

3. Results

The study included 2040 patients newly diagnosed with lung cancer and 6120 matched control subjects. Table 1 presents demographic characteristics of the study population. The majority of patients were male; the median age of cancer patients and controls was 68 and 69 years, respectively. The majority of patients had non-capitated health coverage and resided in the northeastern, north central, and southern United States. More than half of patients and controls had Medicare benefits. Cancer patients had a significantly higher CCI score (1.17 versus 0.58, $P < 0.05$). Mean duration of follow-up was 9.4 months for patients and 9.3 months for controls. In-hospital mortality occurred in 6.5% of cancer patients, compared with 0.1% of controls ($P < 0.05$). At baseline (1 month following the index

Table 1 Demographics and other characteristics

	Lung cancer patients ($n = 2040$)	Controls ($n = 6120$)
Gender, *n* (%)		
Male	1161 (56.9)	3599 (56.8)
Female	879 (43.1)	2521 (41.2)
Age, *n* (%)		
0—17 y	0 (0)	0 (0)
18—34 y	14 (0.7)	9 (0.2)
35—44 y	38 (1.9)	102 (1.7)
45—54 y	227 (11.1)	734 (12.0)
55—64	567 (27.8)	1687 (27.5)
65+ y	1194 (58.5)	3588 (58.6)
Tumor severity, *n* (%)		
Mild/moderate	1570 (77.0)	—
Advanced	470 (23.0)	—
Insurance plan type, *n* (%)		
Non-capitated	1738 (85.2)	5209 (85.1)
Capitated	302 (14.8)	911 (14.9)
Medicare coverage, *n* (%)	1190 (58.3)	3572 (58.4)
US geographic region, *n* (%)		
Northeast	527 (25.8)	1593 (26.0)
North Central	565 (27.7)	1764 (28.9)
South	824 (40.4)	2373 (38.8)
West	99 (4.9)	314 (5.1)
Unknown	25 (1.2)	76 (1.2)
Employee relationship, *n* (%)		
Employee	1432 (70.2)	4316 (70.5)
Spouse	601 (29.5)	1792 (29.3)
Dependent	7 (0.3)	12 (0.2)
Mean CCI score (S.D.)[a]	1.17 (1.8)	0.58 (1.2)
Mean follow-up, months (S.D.)	9.3 (6.3)	9.3 (5.4)
In-hospital mortality,[a] *n* (%)	133 (6.5)	7 (0.1)

CCI: Charlson Comorbity Index; S.D.: standard deviation.

[a] Lung cancer and control cohort values are statistically different from each other ($P < 0.05$).

Table 2 Mean health care utilization and costs: lung cancer patients vs. controls

	Patients ($n = 2040$)	Controls ($n = 6120$)	Incremental costs attributed to lung cancer
Hospital inpatient			
Admissions per month (S.D.)[a]	0.2 (0.3)	0.01 (0.1)	
Length of stay, days (S.D.)[a]	5.1 (6.7)	0.4 (3.2)	
Cost per month (S.D.)[a]	US$ 3232 (US$ 8960)	US$ 87 (US$ 868)	US$ 3145
ER visits			
Visits per month (S.D.)[a]	0.1 (0.3)	0.02 (0.1)	
Cost per month (S.D.)[a]	US$ 43 (US$ 203)	US$ 4 (US$ 35)	US$ 39
Outpatient office visits			
Visits per month (S.D.)[a]	8.6 (9.3)	0.9 (1.8)	
Cost per month (S.D.)[a]	US$ 2315 (US$ 2955)	US$ 118 (US$ 340)	US$ 2197
Outpatient laboratory procedures			
No. per month (S.D.)[a]	2.0 (3.6)	0.2 (0.6)	
Cost per month (S.D.)[a]	US$ 121 (US$ 255)	US$ 11 (US$ 173)	US$ 110
Outpatient radiology procedures			
No. per month (S.D.)[a]	3.0 (3.9)	0.1 (0.4)	
Cost per month (S.D.)[a]	US$ 630 (US$ 1112)	US$ 13 (US$ 53)	US$ 617
Outpatient pharmacy prescriptions			
No. per month (S.D.)[a]	3.6 (3.0)	1.5 (2.3)	
Cost per month (S.D.)[a]	US$ 241 (US$ 399)	US$ 78 (US$ 138)	US$ 163
Total costs per month, unadjusted (S.D.)[a]	US$ 6582 (US$ 10200)	US$ 310 (US$ 1063)	US$ 6272
Total costs per month for Medicare, unadjusted (S.D.)[a]	US$ 4471 (US$ 5785)	US$ 364 (US$ 1156)	US$ 4107
Total costs per month for private insurance only, unadjusted (S.D.)[a]	US$ 9536 (US$ 13713)	US$ 234 (US$ 911)	US$ 9302
Total costs per month, regression-adjusted (S.D.)[a,b]	US$ 6520 (US$ 4511)	US$ 339 (US$ 376)	US$ 6181
Total costs during study, adjusted (S.D.)[a,b]	US$ 45897 (US$ 31099)	US$ 2907 (US$ 4056)	US$ 42990

S.D.: standard deviation.
[a] $P < 0.05$ vs. controls.
[b] Adjusted for gender, age, health coverage type, geographic region, length of follow-up, Charlson Comorbidity Index and in-hospital mortality.

date), 1570 patients (77.0%) had mild to moderate disease, and 470 (23.0%) had advanced disease.

3.1. Direct health care utilization and costs: patients versus controls

Lung cancer patients had higher ER visit and inpatient hospitalization rates and significantly longer hospital stays ($P < 0.05$). The rates of major components of outpatient care, office visits, laboratory tests, radiology services and pharmacy-dispensed drugs, were also higher for lung cancer patients ($P < 0.05$, Table 2). Regression-adjusted mean monthly total costs were US$ 6520 for patients versus US$ 339 for controls ($P < 0.0001$) and overall costs across the study period (from diagnosis to death or up to 2 years) were US$ 45,897 for patients and US$ 2907 for controls ($P < 0.0001$). The difference in these costs reflects the costs associated with lung cancer and comorbid conditions: US$ 6181 per month and US$ 42,990 overall. Fig. 2 presents the distribution of total costs by type of care, illustrating the impact of hospitalizations (49%) and outpatient office visits (35%) as cost drivers. Among lung cancer patients, male gender, younger age, capitated insurance coverage, geographic region, fewer days of follow-up and in-hospital mortality were significantly associated with increasing monthly costs ($P < 0.05$). Total cost estimates were also associated with payer type; Medicare patients with supplemental private insurance were significantly less expensive than the private payer—only patients (US$ 4471 versus US$ 9536, respectively). Hospital costs were also less expensive for these

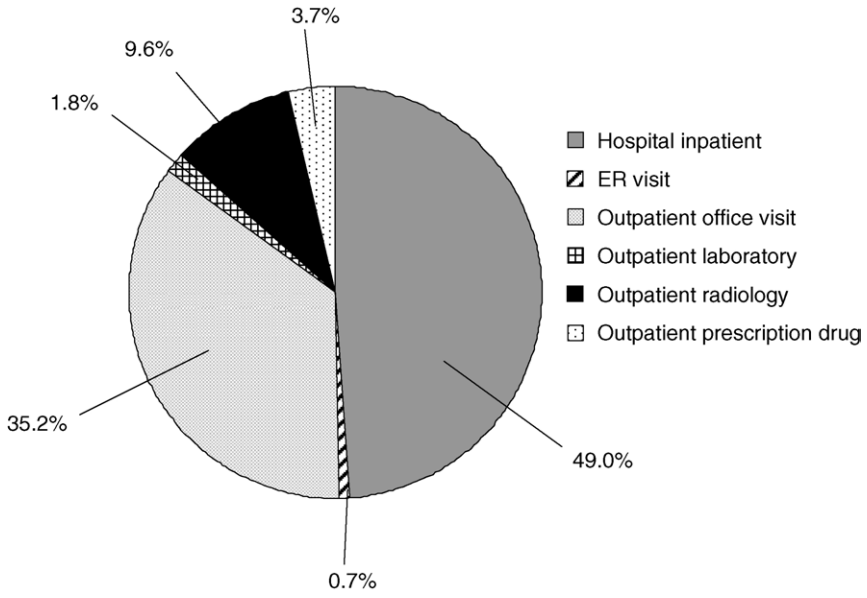


Fig. 2 Distribution of mean monthly total health care costs (unadjusted) by service type per case.

Medicare patients (US$ 2010) versus those insured by private payers only (US$ 4943).

3.2. Costs by treatment phase in lung cancer patients

Among the 2040 lung cancer patients, 177 patients (9%) were considered to have received terminal care immediately after diagnosis based on the algorithm presented in Fig. 1. Of the remaining 1863 patients (91%) who were classified as receiving an initial therapy, 591 (29%) went on to have secondary treatment, and 555 (27%) went on to have terminal care, following initial or secondary treatment. Mean monthly adjusted costs were US$ 11,496 per patient during the initial treatment phase, US$ 3733 during the secondary treatment phase, and US$ 9399 during the terminal care phase, with mean durations of the treatment phases being 5.7, 7.4 and 5.6 months, respectively (Table 3). The highest hospital admission rate and the highest utilization rates for ER visits, outpatient laboratory procedures and outpatient drug prescriptions occurred during the initial treatment phase, which drove the cost differences by phases as depicted in Table 3. Costs were highest for these services during the initial treatment phase, followed by costs incurred during the terminal care phase. Patients in the terminal care phase had the longest hospital stays and the highest rates for outpatient office visits and radiology procedures. Hospitalizations represented the majority of costs across all treatment phases. However, during the initial treatment and terminal care phases, higher proportions of costs were attributable to inpatient hospitalization (67 and 47%, respectively) than during the secondary treatment phase (30%). Radiotherapy was the most costly cancer treatment approach during the initial and terminal care phases, responsible for 6 and 13% of total costs, respectively.

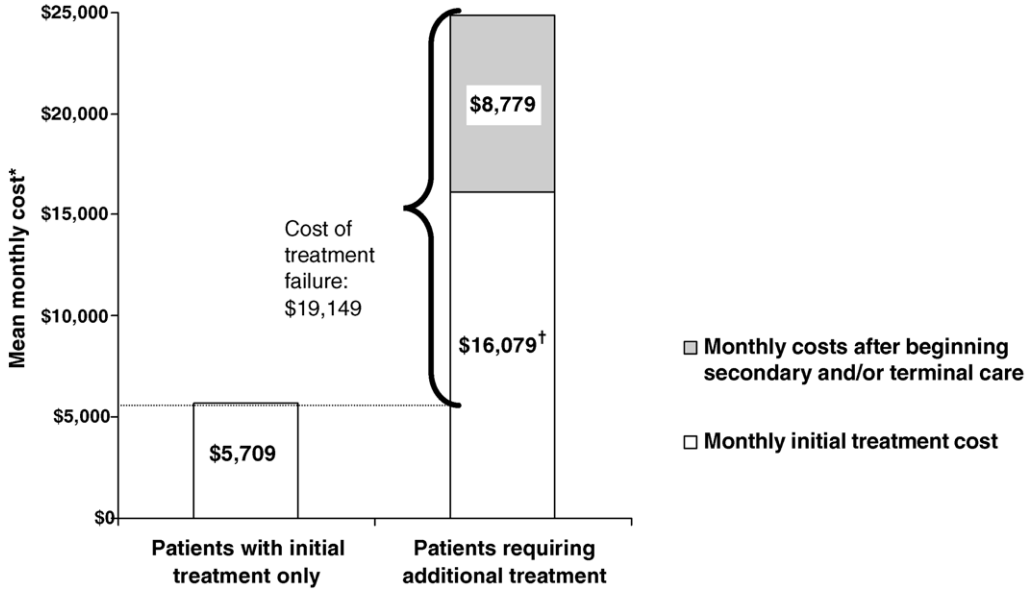
3.3. Costs of treatment failure

Of patients receiving initial treatment for lung cancer, 56% experienced treatment failure. Patients with initial treatment only had adjusted mean monthly costs of US$ 5709. Patients with treatment failure had monthly initial treatment costs of US$ 16,079 and monthly costs of US$ 8779 after beginning secondary and/or terminal care. The costs of treatment failure were US$ 19,149 per month, US$ 10,370 of which was due to additional costs accrued in the initial treatment phase (Fig. 3). For patients with treatment failure, the monthly costs for hospitalizations (US$ 2741) and office visits (US$ 2742) accounted for most of the total costs. During initial treatment, patients who experienced treatment failure had higher costs for hospitalizations (US$ 12,026 versus US$ 3147) and office visits (US$ 3578 versus US$ 1684) compared with patients who had no treatment failure. During secondary and/or terminal care, the additional costs of inpatient care, outpatient care, and services provided in skilled nursing facilities and hospice care resulted in costs that were more than four times higher for patients who experienced treatment failure than costs for patients without treat-

Table 3 Mean monthly costs by treatment phase for lung cancer patients

	Initial treatment phase ($n = 1863$)	Secondary treatment phase ($n = 591$)	Terminal care phase ($n = 732$)
Months in treatment phase (S.D.)[a]	5.7 (5.3)	7.4 (5.5)	5.6 (4.1)
Most common cancer treatment approaches			
Cancer-related surgery (S.D.)[a]	US$ 182 (US$ 1867)	US$ 54 (US$ 282)	US$ 255 (US$ 1555)
Radiotherapy (S.D.)	US$ 773 (US$ 3634)	US$ 173 (US$ 690)	US$ 1081 (US$ 2019)
Outpatient visits for antineoplastic therapy (S.D.)	US$ 496 (US$ 1642)	US$ 421 (US$ 2341)	US$ 742 (US$ 1667)
Outpatient pharmacy for antineoplastic therapy (S.D.)[a]	US$ 7 (US$ 62)	US$ 19 (US$ 123)	US$ 18 (US$ 58)
All care			
Hospital inpatient (S.D.)[a]	US$ 8099 (US$ 48201)	US$ 868 (US$ 3236)	US$ 3903 (US$ 9573)
ER visits (S.D.)	US$ 76 (US$ 912)	US$ 60 (US$ 498)	US$ 52 (US$ 166)
Outpatient office visits (S.D.)	US$ 2740 (US$ 4068)	US$ 1433 (US$ 3581)	US$ 2997 (US$ 3389)
Outpatient laboratory procedures (S.D.)[a]	US$ 213 (US$ 1079)	US$ 61 (US$ 302)	US$ 130 (US$ 298)
Outpatient radiology procedures (S.D.)	US$ 802 (US$ 3113)	US$ 284 (US$ 869)	US$ 920 (US$ 1537)
Outpatient pharmacy (S.D.)[a]	US$ 221 (US$ 424)	US$ 225 (US$ 408)	US$ 304 (US$ 604)
Total costs per month, unadjusted (S.D.)	US$ 12150 (US$ 49219)	US$ 2932 (US$ 5698)	US$ 8306 ($10728)
Total costs per month, regression-adjusted (S.D.)[a,b]	US$ 11496 (US$ 7545)	US$ 3733 (US$ 4351)	US$ 9399 (US$ 7191)

S.D.: standard deviation.
[a] $P < 0.05$: initial phase vs. secondary phase, secondary phase vs. terminal care and terminal care vs. initial phase.
[b] Adjusted for gender, age, health coverage type, geographic region, length of follow-up, Charlson Comorbidity Index, severity, and in-hospital mortality.



*Regression-adjusted for age, gender, geographic region, insurance type, severity, in-hospital mortality and Charlson Comorbidity Index.
†$P < 0.05$, costs compared in the initial treatment phase.

Fig. 3 Cost of failed treatment.

Table 4 Factors associated with decreased time to initial treatment failure on Cox proportional hazards analysis

Variable	Parameter estimate (S.E.)	*P* value	Hazard ratio
Female gender	−0.09 (0.06)	0.18	0.92
Age	0.002 (0.003)	0.53	1.00
Fee-for-service plan type vs. capitated health plan	0.02 (0.10)	0.83	1.02
Region vs. Northeast			
North Central	−0.09 (0.09)	0.30	0.92
South	−0.13 (0.08)	0.11	0.88
West	−0.24 (0.16)	0.14	0.79
CCI score vs. 0			
≥4	−0.02 (0.12)	0.87	0.98
3 to <4	0.02 (0.14)	0.87	1.02
2 to <3	−0.12 (0.10)	0.20	0.88
1 to <2	0.06 (0.09)	0.48	1.06
Baseline cancer severity vs. mild/moderate			
Advanced	1.18 (0.07)	<0.0001	3.25
Initial therapy			
Antineoplastic drug treatment	−0.0004 (0.12)	1.00	1.00
Radiotherapy	0.31 (0.07)	<0.0001	1.36
Surgery	0.17 (0.10)	0.10	1.18

S.E.: standard error; CCI: Charlson Comorbity Index. From Cox proportional hazards model, $N = 1842$ (21 observations were dropped for missing data); % censored = 44.25%; likelihood ratio chi-square = 287.16; $P < 0.0001$.

ment failure. Total study period costs for patients without treatment failure were US$ 45,953. Total study period costs for patients with treatment failure were US$ 55,952 during the initial treatment phase and US$ 64,698 after beginning secondary and/or terminal care. Thus, the cost of treatment failure was US$ 74,697 across the study period. A proportional hazards model was estimated (Table 4) to determine the factors associated with treatment failure. Advanced lung cancer severity at baseline (hazard ratio, 3.25) and use of radiotherapy (hazard ratio, 1.36) were significantly associated with shorter time until treatment failure. Chemotherapy, which comprised most of the antineoplastic therapy group, did not increase risk of treatment failure significantly.

4. Discussion

Costs associated with management of lung cancer have been examined in a limited number of studies and are not well understood. In the current study, we used a single longitudinal data source, which provided a large study population with data on care provided across the spectrum of delivery sites and with a wide geographic distribution. These data also included not only a private-pay population but also a subset with both Medicare coverage and supplemental private insurance, a population that has not been examined before. Given our findings of significantly different cost estimates for those with Medicare coverage and findings from other studies that cancer costs vary by age [17—19], this payer mix and the results are complementary to those previously reported. The use of a control group without cancer provided estimates of costs attributed to lung cancer, discounting the costs associated with routine care that would have been delivered in the absence of lung cancer. A unique contribution of this study is the assessment of direct costs by treatment phase and the estimation of costs due to treatment failure in the lung cancer population.

This study estimated the per-patient health care costs of lung cancer to be US$ 6181 per month and US$ 42,990 across the study period (from diagnosis to death or up to 2 years). Mean monthly costs for lung cancer ranked as the second highest costs among analyzed costs for non-Hodgkin's lymphoma and lung, colorectal, pancreatic, ovarian, prostate and brain cancers [13]. The costliest cancer of this group was pancreatic cancer. Hospitalization accounted for 49% of total costs, followed by outpatient office visits accounting for 35%. The highest costs were incurred during the initial treatment phase, followed by the terminal care phase. Treatment failure was expensive. Compared with patients having initial treatment only, patients for whom initial treatment failed had US$ 10,370 per month in additional initial treatment phase costs and US$ 8779 per month in additional treatment costs after starting secondary or/and termi-

nal care, yielding US$ 19,149 in additional costs per month. Over the study period, patients with treatment failure accrued US$ 74,697 in additional treatment costs versus those receiving initial treatment only. The multivariate analysis indicated a number of factors that were significantly associated with increased costs. Males and younger age significantly increased costs. Fewer days of follow-up also increased costs, suggesting that sicker patients were more likely to be lost to follow-up because of mortality or disenrollment. Capitated insurance coverage was also associated with higher costs. This study suggests that for lung cancer patients, this model may ultimately result in higher utilization and cost. While the goal of the multivariate model was to adjust for factors that may confound costs estimate, this finding suggest that additional research is warranted to investigate the effects of health plan design on cancer costs.

A limited number of studies analyzed total health care costs associated with lung cancer. Hillner et al. [7] reported direct costs of US$ 47,941 per patient for 2 years after diagnosis or until death in a commercially insured population with NSCLC in Virginia, which is similar to the findings in our study. Fireman et al. [8] found long-term direct medical costs (from diagnosis until death or 15 years) of US$ 33,000 per patient among patients in the Kaiser Permanente HMO in Northern California. The slightly lower estimates reported by Fireman may be due to use of data that was older and with limited geographic variability. In a case-control analysis of employees of a single large employer, Barnett et al. [20] found a total incremental cost of US$ 72,465 per case of lung cancer. The study incorporated both direct medical and indirect productivity costs in its determination of costs. The additional costs in Barnett's estimate, compared with those in this study, are likely attributable to the indirect productivity costs not included as part of this analysis.

We found that the major cost drivers between our lung cancer and control populations were due to increased hospitalization and outpatient visit resource use. Hospitalizations may have occurred because of complications associated with the disease or treatment, or for therapy administration. Because the cancer treatment in the United States has become primarily outpatient-based, it is much less likely that patients received chemotherapy in the hospital. The findings are consistent with prior observations in commercially insured patients. Hillner et al. found 54—65% of the mean 2-year costs to be attributable to hospitalizations [7]. Fireman et al. found that inpatient costs accounted for 72% of the total adjusted long-term cost of lung cancer, with outpatient visits comprising the second-highest proportion of costs [8]. The somewhat lower inpatient costs (49%) in this study may be attributable to our sample having a slightly younger age range and a larger proportion diagnosed and treated at the mild/moderate severity of disease. Additionally, the previous studies used older data, when care, particularly cisplatin-based therapy may have been primarily hospital-based. Although there are difficulties in cost comparison of international data [21], it is of interest that the Australian study showed hospitalization to be the major cost driver (42%) for SCLC [4]. Similarly, hospitalization costs exceeded 50% of total costs in NSCLC patients in Canada [3]. Given the high costs associated with hospitalizations worldwide, strategies that help reduce rate and/or duration of hospitalizations should be considered in lung cancer management.

A unique aspect of this study is the approximation of costs by treatment phase and the estimation of the economic burden associated with treatment failure. The mean monthly-adjusted costs in this study were highest during the initial treatment phase, followed by terminal care. The highest costs occurring in the initial treatment phase most likely reflect diagnostic as well as treatment costs, including toxicity management, whereas terminal care includes additional costs associated with skilled nursing and hospice facilities.

Given the rising rates of cancer prevalence and the growing influence of treatment guidelines—such as those from the National Comprehensive Cancer Network [22] that may become standard for clinical policy in oncology and may be used by managed care companies to establish coverage—it is more important than ever to understand the costs associated with treatment patterns and the overall cost and effectiveness of care for lung cancer patients. To date, it has been demonstrated that the use adjuvant chemotherapy in early NSCLC, chemotherapy or new agents in advanced NSCLC extends progression-free survival, time to progressive disease or time to treatment failure [23—27]. In this study, we have shown the cost associated with treatment failure (US$ 19,149 per month) was substantial and exceeded costs associated with each treatment phase. When examining the cost of failed treatment in closer detail, we found that high costs started to accrue as patients were undergoing the initial treatment and thus inducing additional costs of initial therapy. However, among some patients, higher initial treatment costs may have reflected a higher-risk group of patients. Additional costs accrued from subsequent disease management. Existing randomized controlled trials and our results support the hypothesis that treatment

strategies that delay or even prevent disease progression could limit the cost of treatment failure and could make a contribution to lowering the total cost of care in lung cancer. Our Cox proportional hazard analysis suggested some potential risks associated with treatment failure. However, because of the limited availability of potential confounding factors coded in claims data, we were not able to comprehensively examine the reasons for patients failing the initial treatment.

Limitations of this study include those typical of retrospective claims-based studies, most notably, the lack of detailed histological and treatment information. ICD-9 diagnosis codes provided the classification of broad cancer severities; however, more detailed staging, which required pathological findings, was not possible. This information would have allowed for more refined determinations of disease severity and treatment phases. Definitions of treatment phases were limited to the available data and may not always have reflected the actual practice. Owing to the lack of histological data, we were not able to differentiate between SCLC and NSCLC. Given that the latter is more common in the US population (making up 80% of all lung cancer patients [28]), it is likely that the overall findings are more generalized to the NSCLC population at large. Medical and drug claims also do not provide information on lifestyle and environmental exposures that could increase the risk of lung cancer and other conditions that drive health care utilization and costs. In estimating the total healthcare costs to lung cancer patients, costs were not differentiated those specific to lung cancer treatment and those for other treatment. While coding was available to determine if a medical claim had a lung cancer diagnosis or a drug claim was for lung cancer treatment, comparisons in this paper focused on all services. Therefore, some of the incremental costs of cases may be driven by other smoking-related conditions, such as exacerbation of chronic obstructive pulmonary disease. The multivariate estimation of total costs for cancer patients and controls included CCI, to adjust for other major respiratory conditions, however, minor conditions and history of smoking were not included in these models.

Additionally, we may not have had sufficient length of follow-up in all patients to assess costs from diagnosis to death, which may have affected the reported costs, especially costs associated with terminal care. Also, the available length of follow-up may not have been sufficient to detect treatment failure. Among the 2040 lung cancer patients 1224 (60%) had ended follow-up on 31 December 2000, the latest possible date of available data, and among those patients, 365 (30%) had less than 6 months of follow-up before 31 December 2000. These patients were likely to have been censored. The majority of these patients (340, 93%) started the study on initial treatment. Given the prognosis of lung cancer patients (1- and 5-year survival rates of 42 and 15%, respectively) [1], the available follow-up period should have been sufficient to detect the majority of treatment failures.

It should also be noted that the lung cancer population in the current study was somewhat younger and had earlier-stage disease (77% with mild/moderate disease at diagnosis) than expected, based on prior studies of the lung cancer population. The incidence of lung cancer in the MarketScan database was also somewhat lower than expected. The lower incidence is probably driven by the younger average age of patients in MarketScan versus the overall population. This population of commercially insured individuals represented a younger cohort with different socioeconomic characteristics, possible resulting in different lung cancer risk factors and access to care from those of other populations (e.g. Medicare-only populations). The wide range of ages in this study population also may have influenced incidence, but also provided further validation for applying these findings to the lung cancer population at large. Prior studies have noted that inferences to younger populations from Medicare-based cost data are problematic, given the differences in patient populations served and differences in payment and fee structures between commercial insurance and Medicare [7].

5. Conclusion

This study demonstrates that treatment for lung cancer is associated with substantial health care costs that are driven mainly by hospitalization and outpatient office visits, with the highest costs incurring during the initial treatment phase. Costs of treatment are dramatically higher in patients with treatment failure. In addition to the substantially higher costs during the initial treatment phase, these patients face costs resulting from subsequent disease management, such as attempts at alternative regimens and palliative care. Further research is needed to explore cost drivers such as hospitalizations as well as the cost of treatment failure and identification of risks for treatment failure. The burden of lung cancer to the US health care system is significant and suggests a need for increased prevention or new therapies to reduce both resource use and health care costs. New interventions for lung cancer that reduces hospitalizations or pre-

vent/delay treatment failure could offset some of the economic burden associated with the disease.

Acknowledgements

Financial support for this study was provided by Eli Lilly and Company. The authors would like to thank Joseph Hirsch for his editorial assistance.

References

[1] American Cancer Society. Cancer facts and figures 2003. American Cancer Society, 2003.
[2] Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide IARC CancerBase No. 5. version 2.0, IARC Press, Lyon, 2004. Available at: http://www-depdb.iarc.fr/globocan/GLOBOframe.htm.
[3] Rosenthal MA, Webster PJ, Gebski VJ, Stuart-Harris RC, Langlands AO, Boyages J. The cost of treating small cell lung cancer. Med J Aust 1992;156(9):605—10.
[4] Evans WK, Will BP, Berthelot JM, Wolfson MC. The economics of lung cancer management in Canada. Lung Cancer 1996;14(1):19—29.
[5] Brown ML, Fintor L. The economic burden of cancer. In: Greenwald, et al., editors. Cancer Prevention and Control. New York: Marcel Dekker, Inc; 1995.
[6] Brown ML, Riley GF, Schussler N, Etzioni R. Estimating health care costs related to cancer treatment from SEER-Medicare data. Med Care 2002;40(Suppl 8). IV-104—117.
[7] Hillner BE, McDonald K, Desch CE, Smith TJ, Penberthy LT, Maddox P, et al. Costs of care associated with non-small-cell lung cancer in a commercially insured cohort. J Clin Oncol 1998;16:1420—4.
[8] Fireman BH, Quesenberry CP, Somkin CP, Jacobson AS, Baer D, West D, et al. Cost of care for cancer in a health maintenance organization. Health Care Financing Rev 1997;18:51—76.
[9] Du W, Reeves JH, Gadgeel S, Abrams J, Peters WP. Cost-effectiveness and lung cancer clinical trials. Cancer 2003;98:1491—6.
[10] Baker MS, Kessler LG, Urban N, Smucker RC. Estimating the treatment costs of breast and lung cancer. Med Care 1991;29:40—9.
[11] Shoheiber O, Schrogie JJ, Johnson N. Non-small cell lung cancer: a cost of illness study. Pharmacotherapy 1996;16:136 (abstr 72).
[12] Oliver E, Killen J, Kiebert G, Hutton J, Hall R, Higgins B, et al. Treatment pathways, resource use and costs in the management of small cell lung cancer. Thorax 2001;56:785—90.
[13] Chang S, Long SR, Kutikova L, Bowman L, Finley D, Crown WH, et al. Estimating the cost of cancer: results on the basis of claims data analyses for cancer patients diagnosed with seven types of cancer during 1999—2000. J Clin Oncol 2004;22:3524—30.
[14] D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson Comorbidity Index with administrative databases. J Clin Epidemiol 1996;49:1429—33.
[15] Barnes CA. Disease staging: a clinically oriented dimension of case mix. Am Med Rec Assoc 1985;56:22—7.
[16] Duan N. Smearing estimate: a nonparametric retransformation method. JASA 1983;78:605—10.
[17] Brown ML, Lipscomb J, Snyder C. The burden of illness of cancer: economic cost and quality of life. Annu Rev Public Health 2001;22:91—113.
[18] Burkhardt JH, Sunshine JH. Core-needle and surgical breast biopsy: comparison of three methods of assessing cost. Radiology 1999;212:181—8.
[19] Warren JL, Brown ML, Fay MP, Schussler N, Potosky AL, Riley GF. Cost of treatment for elderly women with early-stage breast cancer in fee-for-service settings. J Clin Oncol 2002;20:307—16.
[20] Barnett A, Birnbaum H, Cremieux P-Y, Fendrick M, Slavin M. The costs of cancer to a major employer in the United States: a case-control analysis. Am J Manag Care 2000;6:1243—51.
[21] Boyer M. The economics of lung cancer. Lung Cancer 1996;14:13—7.
[22] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™. Available at: http://www.nccn.org/professionals/physician_gls/default.asp. Accessed 18 January 2005.
[23] Winton TL, Livingston R, Johnson D, Rigas J, Cormier Y, Butts C, et al. A prospective randomised trial of adjuvant vinorelbine (VIN) and cisplatin (CIS) in completely resected stage 1B and II non-small cell lung cancer (NSCLC) Intergroup JBR.10. J Clin Oncol 2004;22(14S) (abstr 7018).
[24] Strauss GM, Herndon J, Maddaus MA, Johnstone DW, Johnson EA, Watson DM, et al. Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): report of cancer and leukemia group B (CALGB) protocol 9633. J Clin Oncol 2004;22(14S) (abstr 7019).
[25] Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med 2002;346:92—8.
[26] Shepherd FA, Pereira J, Ciuleanu TE, Tan EH, Hirsh V, Thongprasert S, et al. A randomized placebo-controlled trial of erlotinib in patients with advanced non-small cell lung cancer (NSCLC) following failure on 1st line or 2nd line chemotherapy. A National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial. J Clin Oncol 2004;22(14S):622s (abstr 7022).
[27] Hanna N, Shepherd FA, Fossela FV, Pereira J, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22(9):1589—97.
[28] American Cancer Society. What is lung cancer? Revised April 2004. Available at: http://www.cancer.org/docroot/CRI/content/CRI_2_2_1X_What_is_lung_cancer_26.asp?sitearea=. Accessed 17 September 2004.