Original Article

Causes of death in long-term survivors of non-small cell lung cancer: A regional Surveillance, Epidemiology, and End Results study

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Abstract:

INTRODUCTION: Survival from lung cancer is improving. There are limited data on the causes of death in 5-year survivors of lung cancer. The aim of this study is to explore the causes of death in long-term survivors of non-small cell lung cancer (NSCLC) and describe the odds of dying from causes other than lung cancer in this patient population.

METHODS: An analysis of 5-year survivors of newly diagnosed NSCLC from 1996 to 2007, in Metropolitan Detroit included in Surveillance, Epidemiology, and End Results program, was done.

RESULTS: Of 23,059 patients identified, 3789 (16.43%) patients were alive at 5-year period (long-term survivors) and 1897 (50.06%) patients died in the later follow-up period (median 88 months; range 1–219 months). The causes of death besides lung cancer were observed in 55.2% of these patients. The most common causes of death were cardiovascular diseases (CVDs) (16%), chronic obstructive pulmonary diseases (11%), and other malignancies (8%). Patients older than 65 years, males, and those who underwent surgery for treatment of lung cancer faced a greater likelihood of death by other causes as compared to lung cancer (OR: 1.45, 95% confidence interval [CI]: 1.18–1.77; OR: 1.24, 95% CI: 1.02–1.51; and OR: 1.39, 95% CI: 1.06–1.82, respectively)

CONCLUSIONS: Five-year survivors of NSCLC more commonly die from causes such as CVDs, lung diseases, and other malignancies. Aggressive preventive and therapeutic measures of these diseases may further improve the outcome in this patient population.

Keywords:

Cause of death, five-year survival, lung neoplasm

Lung cancer is the most common cause of cancer death in men and women. According to the American Cancer Society, the number of deaths from lung cancer surpasses combined deaths from colon, breast, and prostate cancer. Currently, 14% of new cancer diagnoses are from lung cancer, while it accounts for 26.5% of cancer deaths[1,2] Earlier diagnosis and use of newer targeted therapy have resulted in modest improvement in the outcome of these patients even in advanced stages of the disease. In the United States, according to the Surveillance, Epidemiology, and End Results (SEER) program's report, rates of death by lung cancer are declining by an average of 2.2% each year from 2004 to 2013. The 5-year survival rate for lung cancer showed improvement from 11.4% in 1975 to 18.7% in 2011.[2]

Lung cancer is the most common cause of death in non-small cell lung cancer (NSCLC) patients in the first 5 years following diagnosis. There are limited data on the causes of mortality in long-term survivors of lung cancer. The aim of this study is to describe the causes of death in patients with NSCLC, who survive longer than 5 years

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after diagnosis (long-term survivors). Another aim of this study is to describe the variables associated with death due to lung cancer versus other causes.

Methods

Data source

Among the residents of Metropolitan Detroit, all NSCLC patients diagnosed from 1996 to 2007 were included in a population-based registry that is a founding participant in the National Cancer Institute's SEER Program.

Study cohort

During the study period of 1996 to 2007, we identified 23,059 newly diagnosed NSCLC patients. Four patients whose survival times were unknown and two patients whose ages were unknown were excluded from the study. Patients who survived and had follow-up data for >5 years were defined as "long-term survivors." A total of 19,264 patients were followed up for <5 years, of which 19,176 died before 5 years and 88 were alive but lost to follow-up. A total of 3789 patients (16.43%) were alive at 5 years after diagnosis and labeled as "long-term survivors." Of these, 1897 (50.06%) patients died in the follow-up period beyond 5 years and 1892 (49.93%) were alive and followed up for varying time durations till the end of the study. The median survival duration in this group was 88 months (range 1–219 months) [Figure 1].

Outcomes

The primary outcome was the primary cause of death. The SEER registry has recorded the underlying causes of death as listed on the state death certificates (DCs).[3] The International Classification of Diseases (ICD)-9 codes were used to categorize the causes of deaths before 1999 and ICD-10 codes were used to classify cause of death in the years from 1999 to 2007. Causes of death were classified as lung cancer, a second non-lung malignancy, cardiovascular disease (CVD) including coronary and cerebrovascular diseases, chronic obstructive pulmonary diseases (COPD), Other Lung Conditions, Other causes, and State DC is unavailable. Other lung conditions included lung diseases such as pneumonia, pleural effusion, and interstitial lung diseases, while other causes included renal diseases, gastrointestinal conditions, infections, accidental deaths, and poisonings. The records in which the DC was either unavailable or missing were placed into the category of "state DC not available or missing."

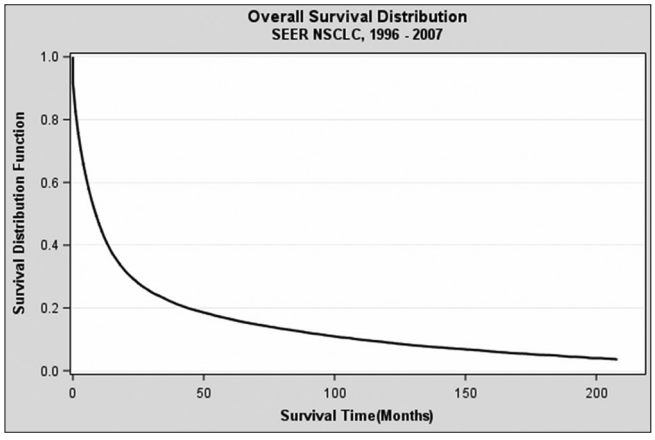

Figure 1: Survival curve for non-small cell lung cancer patients in Surveillance, Epidemiology, and End Results Detroit database from years 1996 to 2007

Statistical analysis

The SEER registry documents information regarding sociodemographic characteristics, including age, gender, marital status, race, median household income level, stage and grade of the NSCLC, modalities of first line of cancer-directed therapy, and primary cause of death.[3] For ease of calculation, the age groups were classified into age <40 years, between 40–59 years and 60–79 years, and >80 years. Race was divided into white, black, and others, and 19 patients of "other races" were excluded. Gender was classified into male and female. Marital status was classified into single, married, divorced, widowed, and unknown. In the absence of individual-level information about socioeconomic status, median income in the census tract of residence at the time of diagnosis was utilized to classify the study group into various strata based on percentage below poverty line. Families and individuals were classified as below poverty line, if their total family or individual income was less than the poverty threshold for the specified threshold for that applicable family size, age of householder, and number of present related children under 18 years of age.

The Stage of the tumor was classified as localized, regional, distant, and unstaged. The grade of the tumor was classified as well differentiated, moderately differentiated, poorly differentiated, undifferentiated, and unknown. The treatment characteristics were divided into patients who underwent surgery or not, received radiation or not, and those who received chemotherapy or not.

The study is a descriptive study, and the population characteristics of long-term NSCLC survivors, the stage and histology of the disease, and the cancer treatment they underwent are described. The causes of death in this survivor population were analyzed. To provide information on whether lung cancer as a cause of death was different between those who died before and after 5 years of diagnosis, we obtained data on the causes of death of NSCLC patients in the registry and compared both groups.

Results

A total of 3789 (16.43%) patients were alive at 5 years after diagnosis of NSCLC and labeled as "long-term survivors." Of these, 1897 (50.06%) patients died in the follow-up period beyond 5 years and 1892 (49.93%) were alive and followed up for varying time durations till the end of the study. The median survival duration in this group was 88 months. Table 1 describes the demographic characteristics of the long-term cancer survivors who died during the follow-up period. In addition, the cancer characteristics and primary treatment modality at the time of diagnosis of NSCLC are reported in Table 2.

We analyzed the causes of death in NSCLC who died after 5 years (n = 1897). The results showed that lung cancer was the primary cause of death in 839 patients (44.2%) and causes other than lung cancer were the primary cause of death in 1058 (55.8%) patients. In comparison, we evaluated the causes of death for those who died before 5 years following the diagnosis of NSCLC, and lung cancer was the cause of death in 82.8% of patients ($P < 0.001$). Death due to causes other than lung cancer in long-term survivors included CVDs (16%), COPD (11%), and other malignancies (8%) [Table 3].

Table 1: Demographic characteristics of long term survivors of non-small cell lung cancer who died during follow up in Surveillance, Epidemiology, and End Results population in Detroit area from 1996 to 2007

	n (%)
Age (years)	
<40	11 (1)
40-79	1726 (91)
>80	160 (8)
Sex	
Female	963 (51)
Male	934 (49)
Race	
White	1540 (81)
Black	338 (18)
Others[a]	19 (1)
Marital status	
Single	122 (6)
Married	966 (51)
Divorced	247 (13)
Widowed	508 (27)
Unknown	54 (3)
Poverty level based on family income (county of residence)[b]	
0%-5%	780 (41)
5%-10%	513 (27)
10%-20%	293 (15)
20%-100%	310 (16)
Unknown	1 (0)

[a]The "other" population group included all others, namely Asian, Asian-American, Japanese etc., [b]In the absence of individual-level information about Socioeconomic status (SES), median income in the census tract of residence at the time of diagnosis was utilized to classify the study group into various strata based on percentage below poverty line. Families and persons were classified as below poverty line, if their total family or individual income was less than the poverty threshold for the specified threshold for that applicable family size, age of householder, and number of related children under 18 present.

We further analyzed the causes of death in the long-term survivors and compared the odds of them dying of causes other than lung cancer after adjusting for various demographic, tumor, and treatment variables. Older patients (≥65 years) had greater odds of dying from causes other than lung cancer (OR: 1.45, 95% confidence interval [CI]: 1.18–1.77). In addition, males were more likely to die from causes other than lung cancer than females (OR: 1.24, 95% CI: 1.02–1.51). On the other hand, patients with regional and distant disease at the time of diagnosis of NSCLC (as compared to those with localized disease) had lower odds of dying from causes other than lung cancer (OR: 0.74, 95% CI: 0.59–0.92; OR: 0.63, 95% CI: 0.45–0.88, respectively). Patients who underwent surgery as the first-line treatment of lung cancer had greater odds of dying from causes other than lung cancer (OR: 1.39, 95% CI: 1.06–1.82). Conversely, patients who received chemotherapy had lower odds of dying from causes other than lung cancer (OR: 0.63, 95% CI: 0.49–0.82).

Discussion

With the advent of newer targeted treatment modalities, the 5-year survival rates for NSCLC are improving.[4] The estimated 5-year survival in patients with lung cancer is 17.4% at this time.[2] It is well documented that lung cancer is the most common cause of death in NSCLC patients within the first 5 years. There are limited data about the causes of death in the patients who live beyond 5 years.[5]

The current analysis of the database from Metro Detroit area shows that long-term survivors of NSCLC are more likely to die from causes other than lung cancer. To our knowledge, this is the first analysis of a SEER large database to identify the causes of death in long-term survivors of NSCLC. There were few similar studies in survivors of other malignancies. In a study of high-risk prostate cancer patients treated with surgery and radiation, it was found that the 10-year risk of dying from cancer was the leading cause of death only in the young and healthy population, while older patients with comorbidities were more likely to die from other causes.[6] Another study of 2705 long-term survivors of testicular cancer demonstrated a 1.9-fold increased risk of developing cardiovascular complications as well as a secondary malignancy in patients who were treated with chemotherapy and radiation.[7,8] Furthermore, a study of long-term survivors of breast cancer reported a 1.76-fold higher risk of dying from cardiac causes and 1.33-fold

Table 2: Tumor and first line of cancer-directed therapy characteristics of non-small cell lung cancer long-term survivor patient population who died after 5 years, in Surveillance, Epidemiology, and End Results population in Detroit area from 1996 to 2007

	n (%)
Grade	
Well-differentiated	182 (10)
Moderately differentiated	548 (29)
Poorly differentiated	590 (31)
Undifferentiated	80 (4)
Unknown	497 (26)
Stage	
Localized	940 (50)
Regional	640 (34)
Distant	229 (12)
Unstaged	88 (5)
Surgery	
Yes	1358 (72)
No	538 (28)
Missing	1 (0)
Radiation	
Yes	615 (32)
No	1282 (68)
Chemotherapy	
Yes	538 (28)
No	1359 (72)

Table 3: Primary causes of death in long-term survivors of non-small cell lung cancer in Surveillance, Epidemiology, and End Results population in Detroit area from 1996 to 2007

Primary causes of death	*n* (%)
Lung cancer	839 (44.2)
All other cause of death	1058 (55.8)
COPD	202 (11)
Other lung conditions	68 (4)
Cardiovascular	299 (16)
Other malignancies	145 (8)
Other causes	241 (13)
State DC not available	103 (5)

COPD=Chronic obstructive pulmonary diseases, DC=Death certificate

higher risk of dying from other vascular causes.[9] The current study of a large database of long-term survivors of NSCLC causes of death other than lung cancer were more common, and these included CVDs, COPD, and other malignancies. These findings highlight the importance of monitoring, assessing, and treating such conditions in patients who are treated for NSCLC.

The reasons why comorbid illnesses may play a larger role in death of long-term survivors of NSCLC are not clear. These could be related to older age and longer duration of these underlying illnesses. Another possibility is that therapies such as radiation and chemotherapy may contribute to organ dysfunction including the lungs –such as radiation and drug-induced pulmonary toxicity – and cardiovascular system. Another concern is related to the possibility of lack of close follow-up and treatment of these underlying illnesses in patients who carry the diagnosis of NSCLC where the focus of the clinicians shifts to the treatment of the cancer and may ignore other illnesses. Further studies are needed to study these and other explanations of higher mortality of causes other than lung cancer in long-term survivors.

A potential benefit from the findings of this study – if confirmed by other studies – is the importance of detection and treatment of comorbid illnesses in patients with NSCLC. Of particular interest would be respiratory and CVDs, and performance of age and gender appropriate screening for other malignancies, such as mammography and colonoscopy. We hypothesized that better control of comorbid illnesses such as COPD, CVDs, and secondary malignancies; both preexisting and those that develop as a consequence of cancer-directed therapy in long survivors of cancer could help improve survival further. Further studies are needed to establish the cost-effectiveness of such measures. In addition, studies that evaluate the positive impact of management of comorbid conditions that affect the causes of death in the form of a prospective cohort studies are warranted.

Søgaard *et al*. performed a meta-analysis to assess the impact of various comorbid conditions on survival of colon, breast, and lung cancer from the years 2002 to 2012. A total of 2500 studies were examined and a few of these studies analyzed the impact of comorbidity on survival. These studies revealed a poorer outcome in patients with comorbidities. Further subgroup analysis revealed that the presence of comorbid conditions may delay diagnosis in some studies, and other conditions that required regular medical visits contributed to early diagnosis. In addition, the presence of comorbid conditions could impact the course of the offered first-line treatment options with an increased likelihood of complications.[10] Further studies that assess the impact of management of these comorbid conditions on the causes of death and survival in these groups are needed.

These studies paved the way for further development and validation of scores such as Charlson Comorbidity Index and the Colinet Simplified Comorbidity Score (SCS) to predict the impact of comorbid conditions on 5-year lung cancer survival. The SCS was initially developed in 2005 and takes into account the presence of comorbid conditions such as cardiovascular and cerebrovascular diseases, smoking, alcoholism, diabetes, hypertension, as well as stage of the disease and Eastern Cooperative Oncology Group performance status. The outcome has been variable with some studies showing correlations and while others did not.[11-14] However, none of

these studies evaluated the impact of these comorbid conditions on long-term survivors of lung cancer. Analyzing the causes of death in this surviving patient population is the first step in this direction.

The study has strengths and a few limitations that should be taken into consideration. The main strengths of the study include the large population-based sample size and detailed amount of information available.[15] However, there are a few limitations of the study as well. The SEER registry analyzed in the study is limited only to the Detroit Metropolitan area and the study population may not be representative of the population at large. In addition, the selection bias may influence the results of this analysis. Comparison of causes of death of this population to the general public adds value to the findings. Causes of death in the SEER registry are determined from the state DCs, which may not be accurate.[16-20] The registry also does not identify whether death in the patient population is from a relapse of the primary lung cancer itself or a second primary lung cancer. Another limitation is the absence of information on other confounding factors such as smoking history, exposure to other chemicals such as radon, and performance status. In addition, the database has limited information about preexistence, severity, and duration of these comorbid conditions. The extent of development and/or worsening of these comorbid conditions because of cancer treatment is also unknown. We have also hypothesized that these comorbid conditions lead to the primary cause of death, which may occasionally be incorrect. The extent of false-positive assumptions is unknown at this time. Further studies that evaluate the causality of morbidity and mortality from the presence of comorbid conditions are warranted. These studies could include predictive models that assess causality. The information analyzed in this study is from years before the widespread use of specific gene-targeted medications, which limits the analysis of the newer NSCLC treatment modalities especially in regional and distantly spread NSCLC. Future large studies are needed to address these issues.

Conclusions

The study demonstrates that long-term survivors of NSCLC are more likely to die from causes other than lung cancer, which includes respiratory and CVDs and other malignancies. Further studies that assess causality of death from these comorbid conditions and impact of appropriate preventive and therapeutic management strategies on survival of these patients are needed.

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Conflicts of interest

There are no conflicts of interest.

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