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Survival Analysis of Advanced Lung Cancer: Examining Factors Impacting Mortality Risk

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Abstract

Aims: We examined the survival differences among the different Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) scores, age groups, and sex. We also examined the effects of age, sex, ECOG PS, weight change, and daily caloric intake on the risk of death in patients with advanced lung cancer. *Methods*: The data used in this study was obtained from a previous cohort study conducted by the North Central Cancer Treatment Group. Information from 1,115 patients with advanced lung or colorectal cancers was collected through a questionnaire just before the patients began their first ever chemotherapy, after which follow-up began. Our study utilized information on 226 patients with advanced lung cancer obtained from the survival package in R. Kaplan-Meir survival estimates and Cox proportional hazard regression models were used to examine the survival differences and hazard ratios. *Results*: 136 (60%) patients were males and the median survival time was 310 days. 163 (72%) patients died from advanced lung cancer during follow-up. 113 (50%) patients had an ECOG PS 1 and none had an ECOG PS greater than 2. The overall survival after 1 year of follow-up was 41%. After 18 months (549 days), the survival of males and females were 19% and 37%, respectively. The median survival times were 394 days, 306 days and 199 days for ECOG PS 0, ECOG PS 1 and ECOG PS 2 patients, respectively. Calories consumed per day, age and weight change did not affect the risk of death from advanced lung cancer. *Conclusion*: Our study showed that sex and ECOG PS are independent factors affecting the survival of advanced lung cancer patients. Age, weight change, and daily caloric intake do not affect the risk of death from advanced lung cancer.

Keywords: Advanced lung cancer; Survival analysis; Eastern Cooperative Oncology Group Performance Status; Mortality risk factors

Introduction

Lung cancer is the second most common type of cancer worldwide as reported in 2020 [1,2]. Cigarette smoking is the number one risk factor for lung cancer [3]. Other risk factors include breathing secondhand smoke, being exposed to substances such as radon or asbestos, and having a family history of lung cancer [3,4]. In the United States, cigarette smoking was found to be linked to 80% to 90% of lung cancer deaths [5]. As of 2020, lung cancers were the most common cause of death due to cancer, accounting for 1.80 million deaths [1], making up 81% of all lung cancer cases. Lung cancer kills almost three times as many men as prostate cancer and three times as many women as breast cancer [4,6]. Currently, 1 in 16 people in the United States are expected to receive a lung cancer diagnosis in their lifetime, that is 1 in every 15 men and 1 in every 17 women [6]. It is estimated that in 2023, approximately 238,340 people will develop lung cancer, and 127,070 people will die as a result of lung cancer [7].

Research has shown that the survival of lung cancer patients after one year of follow-up is approximately 46% for both sexes, 50% for females and 42% for males [8]. In a 20-year study, the 5-year survival of patients with lung and bronchus cancer was 27.1% in patients aged below 50 years, 22.1% for those aged from 50 to 64 years, and 18.2% for those above 64 years [8]. According to the Lung Cancer Foundation of America, early diagnosis of lung cancer (before metastases) increases the 5-year survival probability of lung cancer patients to 60% and decreases lung cancer mortality rates from 20% to 14% among high-risk populations [6].

The Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score is a performance scale that is used to describe or determine "a cancer patient's functioning in terms of their ability to care for themselves daily" [9]. The ECOG PS values range from 0 (asymptomatic) to 5 (dead), with high values indicating poor performance scores [10]. ECOG PS has been found to correlate negatively with the survival rates of many cancer forms [11,12], that is, patients with poor performance scores are associated with an increased risk of death from several cancer types, and those with good scores are associated with a reduced risk of death from several cancer types. Although several studies have been conducted to determine the survival and risk of death associated with several factors among early-stage lung cancer patients, these studies rarely consider how daily functioning abilities and lifestyle factors affect the survival of patients with advanced lung cancers. PS and lifestyle in cancer treatment and research are of significant importance because several clinical decisions such as planning, randomization, eligibility for and evaluation of clinical trials, the optimal therapeutic approach in routine clinical practice, and allocation of health resources are based upon a patient's PS or lifestyle [13].

The aim of our study was to compare the Kaplan-Meir survival probabilities of advanced lung cancer patients among the different ECOG PS scores, sex, and age groups. We also examined the effects of ECOG PS, age, sex, weight change, and daily caloric intake on the risk of death from advance lung cancer. The findings from this study could have meaningful implications for clinical practice. By analyzing the survival probabilities and risk factors associated with advanced lung cancer, healthcare professionals can better tailor treatment approaches and supportive care strategies. This research may ultimately contribute to more personalized and effective interventions, improving the overall quality of care and prognosis for patients with advanced lung cancer.

Material and Methods

Study Design and Data Source

The dataset used in this study was secondary and was obtained from a cohort study designed by the North Central Cancer Treatment Group (NCCTG) [14]. The aim of the original study was to determine whether descriptive information from a patient completed questionnaire could provide prognostic information that was independent from that already obtained by the patient's physician. . The participants of the original study were patients who were diagnosed with advanced lung or colorectal cancers. That is, patients with end-stage lung or colorectal cancers. Information from 1,115

patients who simultaneously were each entered into the NCCTG treatment protocol, was collected through the administration of a questionnaire. The questionnaire was completed before the patient's first dose of chemotherapy for the disease, after which follow-up began.

The raw data used in their study has been made public and can be found in the "survival" package in the R statistical software. The dataset used in this current study utilized the publicized version of the original study's dataset, and initially contained 228 observations. After cleaning the data, information on 226 patients remained.

Variables

In our analysis, we employed the dataset from the NCCTG lung cancer data available in the "survival" package in the R programming language. Within this dataset, we made use of the "time" variable, which represented the patients' follow-up durations, and "status," indicating whether a patient was censored or died at the end of the follow-up period. These two variables were used to generate survival times.

Additionally, our study incorporated demographic and health-related information, including the patients' age, gender, ECOG PS scores, average daily caloric intake during main meals (excluding snacks and desserts), and changes in weight (whether increased, decreased, or no change) within the six months preceding their enrollment in the NCCTG treatment protocol. For comparison purposes, we categorized the age variable into three groups: individuals younger than 50 years constituted one group, those aged 50 to 64 formed the second group, and individuals aged 65 or older comprised the third group.

The ECOG PS values within our dataset ranged from 0 to 3, with 0 indicating asymptomatic patients, 1 denoting symptomatic but fully ambulatory patients, 2 signifying patients spending less than 50% of the day in bed, and 3 representing patients spending over 50% of the day in bed but not bedbound. Notably, there was only one instance of a patient with an ECOG PS score of 3, leading us to exclude this particular observation from our analysis. Similarly, we omitted one case due to missing data in the ECOG PS variable. Furthermore, we identified 47 missing values in the daily caloric intake variable and 14 missing values in the change in weight variable. To address this, we applied the maximum likelihood multiple imputation method to impute these missing values [15].

Statistical Analysis

Descriptive statistics such as frequencies and percentages were used to describe categorical data. Mean, median, and quartiles were used to describe quantitative variables. Survival times were calculated from the time of patients were enrolled into NCCTG treatment protocol to the time of death or last follow-up. Survival probabilities and curves were generated using Kaplan-Meir survival estimates. Log-rank tests were used to compare the survival curves among different groups.

A Cox Proportional Hazard (PH) model was used to generate the hazard ratios for the risk factors. A hazard ratio over 1 indicates higher odds for the specific category, while below 1 suggests lower odds compared to the reference. A hazard ratio of 1 indicates no change. Percentage interpretation involves calculating the hazard change percentage for a one-unit predictor change. For instance, a hazard ratio of 1.20 suggests a 20% increase in risk for the outcome, and hazard ratio of 0.85 signifies a 15% decrease for each predictor unit change, with other variables constant.

Schoenfeld residuals were utilized to examine the proportional hazards assumption for the Cox PH model. The level of significance used throughout this study was 0.05. All statistical analyses were performed using R Statistical software (version 4. 3. 0).

Results

Descriptive Statistics

The minimum and maximum follow-up times were 5 and 1022 days, respectively, and the median follow-up time was 262.5 days (Table 1).

Out of the 226 patients, 136 (60%) were males (Table 2). 163 (72%) patients died from advanced lung cancer during follow-up and the remaining 63 (28%) were censored (Table 2). Of the 136 male patients, 110 (80%) of them died during follow-up (Table 2). 53 (60%) female patients died from advanced lung cancer and 37 (40%) were censored (Table 2).

The minimum and maximum ages of the patients were 39 and 82 years respectively (Table 1). The mean and median ages were 62.42 and 63 years, respectively (Table 1). 107 (47%) patients were aged from 50 to 64 years, 99 (44%) patients were above 64 years and 20 (9%) patients were below 50 years (Table 2).

The majority of the patients were symptomatic but ambulatory (ECOG PS 1), making up 113 (50%) cases (Table 2). 63 (27.9%) patients were asymptomatic (ECOG PS 0) and 50 (22.1%) patients were in bed less than 50% of the day (ECOG PS 2) (Table 2). No patient had an ECOG PS score of 3 or 4.

Table 1. Summary of ages of patients and follow-up time

	Minimum	1st Quartile	Median	Mean	3rd Quartile	Maximum
Age, years	39.00	56.00	63.00	62.42	69.00	82.00
Follow-up time, days	5.00	170.80	262.50	307.10	401.50	1022.00

Table 2. Frequency distribution of categorical variables

Variable	Classes	Frequency (%)
Sex	Female	90 (40)
	Male	136 (60)
Status	Censored	63 (28)
	Dead	163 (72)
ECOG PS	0 (Asymptomatic)	63 (27.9)
	1 (Symptomatic but ambulatory)	113 (50.0)
	2 (In bed <50% of the day)	50 (22.1)
Age Group	<50	20 (9)
	50-64	107 (47)
	>64	99 (44)
Status * Sex	Male * Censored	26 (20)
	Male * Dead	110 (80)
	Female * Censored	37 (40)
	Female * Dead	53 (60)

Kaplan-Meir Survival Estimates and Log-Rank tests

Overrall Suvrvival

Table 3 contains the Kaplan-Meir survival probabilities for the patients at different intervals. From Table 3, the 6 months survival was 0.7098 (95% C.I. = [0.6527, 0.7720]), meaning that approximately 71% of the patients survived past the first six months after diagnosis. The one-year (366 days) survival probability was 0.4129 (95% C.I. = [0.3479, 0.4900]) (Table 3), indicating that about 41% of the patients survived after 1 year. The survival probability continues to decrease until the end of the study (1022 days, approximately 2.8 years), where only about 5% of the patients survived (Table 3).

Gender

The survival probabilities were clearly higher in females than males throughout the follow-up period (Table 4, Figure 1). The log-rank test return a p-value of 0.002 (Table 5), showing that the survival for males and females were significantly different from each other.

Table 3. Kaplan-Meir survival estimates of advanced lung cancer patients

Time expressed in days (months)	Survival	95% C.I.
183 (6 mos)	0.7098	[0.6527, 0.7720]
366 (12 mos)	0.4129	[0.3479, 0.4900]
549 (18 mos)	0.2577	[0.1980, 0.3350]
732 (24 mos)	0.1077	[0.0651, 0.1780]
915 (30 mos)	0.0508	[0.0209, 0.1240]
1022 (34 mos)	0.0508	[0.0209, 0.1240]

Table 4. Kaplan-Meir survival probabilities by sex

Time expressed in days (months)	Males		Females	
	Survival	95% C.I.	Survival	95% C.I.
183 (6 mos)	0.6316	[0.5555, 0.7180]	0.8305	[0.7559, 0.9130]
366 (12 mos)	0.3410	[0.2650, 0.4390]	0.5265	[0.4215, 0.6580]
549 (18 mos)	0.1925	[0.1294, 0.2860]	0.3678	[0.2628, 0.5150]
732 (24 mos)	0.0793	[0.0396, 0.1590]	0.1560	[0.0743, 0.3280]
915 (30 mos)	0.0362	[0.0111, 0.1190]	0.0832	[0.0257, 0.2700]
1022 (34 mos)	0.0362	[0.0111, 0.1190]	0.0832	[0.0257, 0.2700]

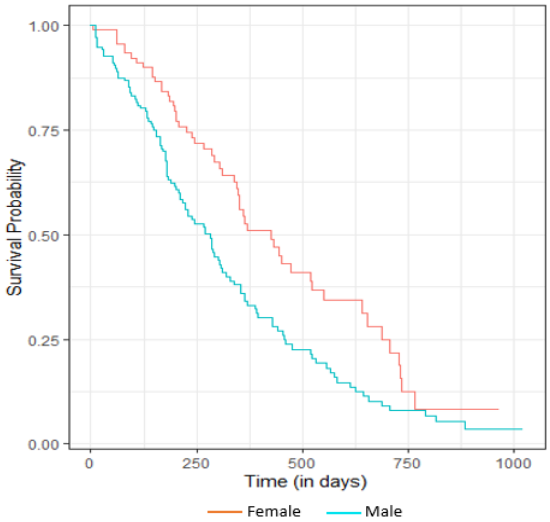

Figure 1. Kaplan-Meir survival curves for sex

Age

The study analyzed the survival times of patients in three age groups: below 50 years, 50 to 64 years, and above 64 years. From Table 5, the median survival time for the 50 to 64 age group was the highest at 363 days, followed by 320 days for those below 50 years and 288 days for those above 64 years. The p-value from the log-rank test was 0.1000, indicating that there was no statistically significant difference in survival among these age groups.

ECOG PS

Table 5 shows that ECOG PS 0 patients had the highest median survival (394 days), ECOG PS 1 patients had the second highest (306 days), and ECOG PS 2 patients had the lowest (199 days), indicating worse survival with higher ECOG PS scores. Figure 2 visually confirms better survival for ECOG PS 0 patients. The log-rank test (p-value = 0.0001) in Table 5 indicates significant differences

in survival among ECOG PS scores, emphasizing the strong association between ECOG PS and survival, with higher scores linked to poorer outcomes.

Table 5. Median survival times and log-rank p-values for categorical variables

Variable	Classes	Median Time (Days)	95% C.I.	p-value
Overall		310	[285, 363]	-
Sex	Male	283	[218, 320]	0.0020
	Female	426	[348, 550]	
Age group	<50	320	[223, *]	0.1000
	50-64	363	[286, 457]	
	>64	288	[267, 353]	
ECOG PS	0 (Asymptomatic)	394	[348, 574]	0.0001
	1 (Symptomatic but ambulatory)	306	[268, 429]	
	2 (In bed <50% of the day)	199	[156, 288]	

** - Not available*

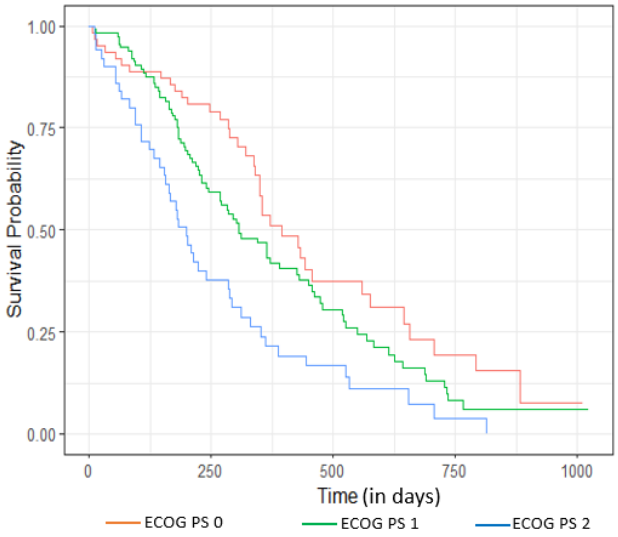

Figure 2. Kaplan-Meir survival curves for ECOG PS scores

Cox Proportional Hazard Regression Analysis

In the Cox PH model (Table 6) for advanced lung cancer, female patients had a significantly lower risk of death (HR = 0.5597) compared to males, highlighting a gender-based survival advantage. Daily caloric intake showed no significant effect on the risk of death (HR = 0.9998). However, ECOG PS 1 (HR = 1.5451) and ECOG PS 2 (HR = 2.6051) were associated with significantly higher risks of death. Age and weight change did not significantly influence the risk of death (p = 0.3177 and p = 0.2879, respectively).

Proportional Hazards Assumption

Table 7 displays the results of Schoenfeld residuals used to examine the proportional hazards assumption for the variables included in Cox PH regression model in Table 6. The p-values associated with the Schoenfeld residuals for age, sex, weight change, and ECOG PS all exceed the significance level of 0.05, indicating that these variables adhere to the proportionality assumption and do not violate it. However, it is noteworthy that the p-value associated with caloric intake suggests a violation of the proportionality assumption. The violation of the proportionality assumption by caloric intake

implies that its effect on the hazard rate is not constant over time. In practical terms, this suggests that the impact of caloric intake on the risk of death from advanced lung cancer may vary as time progresses.

Table 6. Summary results of Cox PH model

Risk Factor	Coefficient	Hazard Ratio (HR)	95% C.I.	P-value
Age	0.0094	1.0094	[0.9910, 1.0282]	0.3177
Sex (Female)	-0.5803	0.5597	[0.4002, 0.7828]	0.0007
Caloric Intake	-0.0002	0.9998	[0.9994, 1.0003]	0.4565
Weight Change	-0.0069	0.9932	[0.9806, 1.0058]	0.2879
ECOG PS 1	0.4351	1.5451	[1.0400, 2.2954]	0.0312
ECOG PS 2	0.9575	2.6051	[1.6167, 4.1976]	0.0001

Table 7. Results of Schoenfeld residuals

Risk Factor	Chisquare	df	P-value
Age	0..1451	1	0.7033
Sex	2.7613	1	0.0966
Caloric Intake	6.7723	1	0.0093
Weight Change	0.0714	1	0.7893
ECOG PS	2.2810	2	0.3197
Global Model	10.6195	6	0.1009

Discussion

The main findings from this study were (a) there was no significant difference in the Kaplan-Meir survival probabilities among the age groups, however the survival estimates among sex and ECOG PS scores were significantly different from each other, (b) daily caloric intake, weight change and age did not have any significant effects on the risk of death from advanced lung cancer, while sex (female), ECOG PS 1 and ECOG PS 2 had significant effects on the risk of death from advanced lung cancer.

In our study, we found that women's survival was better than men's throughout the entire follow-up time. Previous studies evaluating survival in lung cancer have reported strong gender differences in the survival of patients, with survival being consistently higher in females than in males [16,17,18,19]. Ferguson et al. found sex to be an independent prognostic factor for survival and that women with all types of lung cancer tumors lived longer than their male counterparts [19]. From our study, the risk of death from advanced lung cancer in women was 44% (Table 6) less than in men. This is slightly different from a study that reported on survival with relative risk being 33% lower in females compared to males [18]. The reasons for this gender-based difference remain unclear. Some studies have suggested that hormonal influences might play a role in lung cancer progression [20,21], as estrogen receptor β has also been detected in lung cancer tumors [22]. Metabolic and genetic factors have also been attributed to the sex-based differences in survival [23,24].

In our study, survival probabilities of advanced lung cancer patients worsened as the ECOG PS score increased. The survival for ECOG PS 0 patients was the highest throughout the entire follow-up period followed by ECOG PS 1 patients. According to Radzikowska et al, the risk of death from lung cancer was 63% higher in ECOG PS 2 patients compared to ECOG PS 0/1 patients and the risk of death for ECOG PS 3/4 patients was 167% higher when compared to ECOG PS 0/1 patients [25]. These risk differences were consistent with the results from our study where the risk of death from advanced lung cancer was 55% higher in ECOG PS 1 patients compared to ECOG PS 0 patients and 161% higher in ECOG PS 2 patients compared with ECOG PS 0 patients (Table 6). Our study's finding was consistent with the findings from the works of Radzikowska et al. [25], Bangash et al. [26], Simmons et al. [27], and Laird et al. [28].

Among the three age groups, we found that the survival estimates were not significantly different from each other. This finding was similar to the findings from the work of Hensing et al, where they found no significant difference in the survival estimates for patients who were younger than 70 years and patients who were 70 years and above [29]. We also found that the risk of death from advanced lung cancer increased by 0.94% per 1 year increase in age (Table 6). However, this effect was not statistically significant indicating that age did not affect the risk of death in advanced lung cancer patients.

Previous literature have shown that continuous weight loss indicates poor treatment and contributes significantly to mortality in lung cancer patients [30,31]. Martin et al. found that severe weight loss was associated with poor survival [31]. In contrast to their findings, we found that change in a patient's weight (whether increased, decreased or unchanged) did not significantly affect the risk of death from advanced lung cancer.

Limitations

Several limitations must be acknowledged in our research study. Firstly, the dataset utilized in our analysis was relatively old, which may limit the generalizability of our findings to more recent populations and healthcare practices. Secondly, our dataset exclusively focused on lung cancer patients, encompassing both small cell and non-small cell lung cancers. This heterogeneity in patient types could introduce variability, as conditions affecting one subgroup may not affect the other in the same way, potentially confounding our results. Thirdly, in order to protect patient identity, modifications to the original dataset were made, this may have altered some key variables or introduced errors. Lastly, due to the secondary nature of our study, we had access to a limited number of variables compared to the original research. Consequently, we may not have accounted for all potential confounding variables that could impact the outcomes of our analysis, such as socioeconomic factors, genetic markers, specific treatment regimens, histological type of the lung cancer, types of performed treatment, and cancer stage. These limitations should be considered when interpreting the results of our study and may warrant further investigation in future research.

Conclusions

In summary, our study reveals significant differences in survival probabilities among various ECOG PS scores, indicating that a higher score is strongly linked to poorer survival outcomes. Furthermore, our findings demonstrate distinct survival disparities between genders, with females exhibiting notably better survival rates and a reduced risk of death from advanced lung cancer when compared to men. Additionally, while we explored the impact of age, weight change, and daily caloric intake on survival, our analysis did not find statistically significant effects of these factors on the survival of advanced lung cancer patients.

These conclusions carry important implications for clinical practice and future research. The strong association between ECOG PS scores and survival underscores the clinical relevance of assessing performance status in lung cancer patients, guiding treatment decisions, and optimizing supportive care strategies for those with higher scores. The observed gender-based differences in survival warrant further investigation into potential biological, social, or healthcare-related factors contributing to these disparities. Lastly, the non-significant effects of age, weight change, and daily caloric intake suggest that other unexplored factors may play a more critical role in determining the survival of advanced lung cancer patients, offering avenues for future research and therapeutic interventions.

List of abbreviations

ECOG - Eastern Cooperative Oncology Group
PS - Performance Status
C.I. - Confidence Interval

PH – Proportional Hazard
HR – Hazard Ratio
NCCTG - North Central Cancer Treatment Group

Conflict of Interest

The authors declare that they have no conflict of interest.

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