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Risk Factors Associated with a Second Primary Lung Cancer in Patients with an Initial Primary Lung Cancer

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Abstract

Targeted surveillance strategies following initial primary lung cancer (IPLC) treatment are currently limited. One hundred twenty patients diagnosed with IPLC who did not develop second primary lung cancer (SPLC) were matched to 121 patients who developed SPLC. Our analysis found IPLC surgical resection increases SPLC emergence risk regardless of procedure type. Increased survival after IPLC resection warrants close SPLC monitoring.

Background: Increased patient survivorship following initial primary lung cancer (IPLC) diagnosis and treatment has uncovered new clinical challenges as individuals post-IPLC are at growing subsequent risk of developing second primary lung cancer (SPLC). Proper SPLC surveillance guidelines aimed at monitoring IPLC survivors are crucial to enhancing health outcomes. This study aims to categorize risk factors associated with SPLC emergence in IPLC survivors for clinical use following IPLC treatment.

Materials and Methods: Using the Karmanos Cancer Institute Tumor Registry, patients diagnosed with IPLC from 2000 to 2017 were identified. Patients diagnosed with SPLC were matched to individuals who did not develop SPLC. Logistic and Cox regression analyses were performed to identify risk factors for SPLC emergence and overall survival (OS).

Results: One hundred twenty-one patients diagnosed with IPLC who later developed SPLC were identified and compared with 120 patients with IPLC who did not develop SPLC. Several factors such as stage at first diagnosis, histology, age, and smoking history were not associated with SPLC risk. The median time to SPLC was 1.79 years. Patients who were treated with surgical resection

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Disclosure

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Supplementary materials

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had a significantly higher probability of developing SPLC. After correcting for potential immortal time bias, the median OS was 3.63 years (95% confidence interval [CI], 3.05–5.00) and 7.31 years (95% CI, 4.62–10.90) for SPLC and no SPLC groups, respectively.

Conclusion: This study uncovered notable associations and lack thereof between several competing SPLC risk factors, as well as mortality. Further characterization of SPLC risk factors is essential for enhancing surveillance recommendations.

Keywords

Mortality; Surgical resection; Surveillance; Survival; Targeted monitoring

Introduction

In the United States, lung cancer is the leading cause of cancer-related deaths. Lung cancer was estimated to account for more than 1 in 5 of all cancer deaths in 2020.[1] Proper surveillance of individuals with a history of lung cancer is crucial for decreasing mortality and improving health outcomes. Patients diagnosed with initial primary lung cancer (IPLC) are at high subsequent risk for developing second primary lung cancer (SPLC). SPLC is a primary lung cancer that develops following treatment of IPLC.[2] More specifically, SPLC is defined as a distinct pulmonary malignancy that arises in different segments of the same lobe or different lobes, displays different histology, and/or is diagnosed 2 or more years after IPLC.[3] The risk of development of SPLC after an IPLC is approximately 1% to 2% per patient-year.[2] Appropriate surveillance recommendations that enable early detection of SPLC are essential for increasing life expectancy post-treatment of IPLC. Currently, guidelines for monitoring SPLC development are limited.[4,5] Understanding risk factors associated with SPLC is imperative for developing surveillance strategies and improving results following IPLC treatment.

The aim of this study was to characterize the risk factors associated with the development of SPLC using the Karmanos Cancer Institute Tumor Registry. To attain this objective, we sought to uncover associations or lack thereof between several characteristics of patients with a history of IPLC who went on to develop SPLC compared with those who did not. Our intention was to categorize these considerations for clinical use following treatment of IPLC.

Materials and Methods

Database and Study Parameters

Patients diagnosed with IPLC between 2000 and 2017 were identified from the Karmanos Cancer Institute Tumor Registry and included in this retrospective analysis. For our study's time frame, the Registry received 6651 reports of malignant lung cancer. The Tumor Registry includes abstracted medical records from all patients diagnosed or treated at the Karmanos Cancer Institute. Abstracted and coded data follow guidelines set by the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program and include age and date of diagnosis, primary site, histology, stage at diagnosis, treatment, race/ethnicity, and sex. The Registry also conducts annual follow-up for the occurrence of new primaries and overall survival (OS). A case–control study was used over a retrospective

cohort study mainly because there were too many patients in the control group to handle with limited resources, as well as for other reasons (ie, long latency between initial diagnosis and development of SPLC, the relative rare nature of the SPLC, and the limited resources to be able to examine multiple exposures). Standard multivariable analysis is generally recommended over propensity score matching when adjusting covariates.[6,7] In addition, in case–control studies, it is also recommended that matching factors be included in multivariate analysis.[8] For these reasons, we have used the frequency matching, not propensity score matching, along with standard multivariable analysis.

Individuals who later developed SPLC were matched for age, histology, and stage to patients with IPLC who did not develop SPLC. For our study, we identified patients with SPLC using the clinical definitions as described by Martini and Melamed.[3] SPLC is defined as a distinct pulmonary malignancy that arises in different segments of the same lobe or different lobes, displays different histology, and/or is diagnosed 2 or more years after IPLC[3]. Each individual case was examined and confirmed by the study investigator to be SPLC based on clinician notes, diagnostic tests, and course of treatment. This determination was important for ensuring the patients we selected most likely had SPLC, as SPLC can often be difficult to distinguish from IPLC recurrences.

Patient characteristics were collected including age at first diagnosis, sex, histology, family history, race, smoking history, stage of first diagnosis, treatment modality, whether a patient had surgery after IPLC diagnosis, and patient living status. Patient histological classifications were categorized as small-cell carcinoma, adenocarcinoma, squamous cell carcinoma, and other non–small-cell lung cancer (NSCLC). Family history was classified as to whether patients had a first-degree relative with a diagnosis of lung cancer. Smoking behaviors were examined in several ways. Patient smoking history at first diagnosis, as well as smoking status following IPLC treatment, were recorded. Patients were also divided into nonsmokers, light smokers, and heavy smokers based on their number of pack years at first diagnosis. Heavy smokers were defined as having a 30 or more pack year smoking history. Patients were assigned as light smokers if they had a history of smoking less than 30 pack years. Nonsmokers were denoted to patients with no history of smoking.

Stage at first diagnosis was categorized as localized, regional, or distant. Localized classification was given if the cancer was found limited to an individual lung on diagnosis. Regional stage of diagnosis was denoted if the cancer had metastasized to mediastinal lymph nodes. Distant stage of diagnosis was determined if metastasis had advanced to the contralateral lung or other organs. IPLC treatment modality was classified as surgery, chemotherapy, chemoradiation, or radiation. If a patient received multiple treatment options, modality was segregated by most definitive and prominent treatment. For example, if a patient had surgery and chemotherapy, their treatment modality was classified as surgery because of the more definitive nature of surgical resection. Whether a patient had surgery after their IPLC was individually isolated and compared with patients who did not receive resection following their first diagnosis.

Statistical Analysis

Patient characteristics were summarized by count and percentage for categorical variables and median and range for continuous variables. Those characteristics were further compared by the status of second diagnosis using the χ^2 test or the Fisher exact tests for categorical variables and the Wilcoxon rank-sum tests for continuous variables. The time to SPLC was defined as the duration from the date of first diagnosis to the date of SPLC, and OS was defined as the duration from the date of first diagnosis to the date of death from any cause. The distributions of time to SPLC and OS were summarized by Kaplan-Meier (KM) curves and their median and 95% confidence interval (CI) were estimated by KM estimates. The uni- and multivariable logistic analyses were performed to compare the associations between 6 prechosen variables (smoking status after treatment, histology, age, smoking history at first diagnosis, stage at first diagnosis, and surgery after first diagnosis) with the status of second diagnosis. After including the status of second diagnosis as additional covariate, uni- and multivariable Cox regression analyses were carried out for OS. In particular, in order for OS analysis to correct the potential immortal time bias due to patients who had second diagnosis, the status of second diagnosis was considered a time-varying covariate.[9,10] The proportional hazard assumption was validated, and no violation was found except for the status of second diagnosis that was resolved by the time-dependent covariate. The follow-up time was calculated using the reverse KM estimate.

Results

Using the Karmanos Cancer Institute Registry, 121 patients with IPLC who later developed SPLC were identified and compared with 120 patients with IPLC who did not develop SPLC. Table 1 depicts the patient characteristics collected. On logistic regression analysis, several factors were not relevant for increased risk of SPLC. In this study, individuals who later developed SPLC were matched for age, histology, and stage to patients with IPLC who did not develop SPLC. Therefore age at first diagnosis, histology, and stage at diagnosis were not correlated with SPLC emergence as seen in Table 1. Sex, patient living status, race, tobacco use after IPLC treatment, family history, and smoking history were also not associated with a second diagnosis on logistic regression analysis. However, surgery after first diagnosis was significantly associated with SPLC development on both uni- and multivariable analysis ($P < .001$) demonstrated in Table 2. Patients who were treated with surgical resection had a significantly higher probability of developing SPLC whether the surgery was suboptimal or adequate with odds ratio (OR) of 53.150 (95% CI, 9.181–1037.984; $P < .001$) and OR of 3.380 (95% CI, 9.181–1037.984; $P = .001$), respectively (Table 2). This association was intriguing because surgery was definitively associated with increased SPLC emergence compared with other treatment modalities, such as chemotherapy and radiation. Suboptimal resection included wedge resection and other procedures such as segmentectomy, subsegmentectomy, and endobronchial resection, which did not include lymph node evaluation. Surgical resection that was categorized under adequate included lobectomy, bilobectomy, and pneumonectomy with lymph node evaluation. Compared with those who did not have surgical resection, those who had surgical resection were significantly likely to develop SPLC on both uni- and multivariable analysis, regardless of the type of procedure. Supplemental Table 1 shows the characteristics

of those who had surgery versus those who did not have surgery, including the association between stage and surgery (see Supplemental Table 1 in the online version at doi: 10.1016/j.cllc.2021.04.004).

Table 2 also displays that smoking status after treatment and smoking history at first diagnosis by pack year were not associated with second diagnosis based on uni- and multivariable analysis for each of these risk factors.

A subgroup analysis of smoking following treatment and second diagnosis was examined and is depicted in Supplemental Table 2 (see Supplemental Table 2 in the online version at doi: 10.1016/j.cllc.2021.04.004). SPLC histology was broken up into 2 groups with adenocarcinoma and other NSCLCs in one group and small cell and squamous cell in another. On analysis, smoking status after treatment, as well as smoking history, were not correlated with either of the 2 SPLC histology groups. However, the histology at first diagnosis was significantly associated with histology at second diagnosis (see Supplemental Table 3 in the online version at doi: 10.1016/j.cllc.2021.04.004).

The KM curve for the time to SPLC among patients who had a second diagnosis is shown in Figure 1. The median time to SPLC was 1.79 years (95% CI, 1.06–2.52).

Table 3 demonstrates our examination of several risk factors and their association with OS using uni- and multivariable Cox analysis. Smoking status after treatment, histology, and smoking history at first diagnosis were not associated with OS. Age was found to be highly correlated with decreased OS on uni- and multivariable analysis, as depicted in Table 3. Second diagnosis was significantly associated with decreased OS after conducting uni- and multivariable analyses. Although later stage (regional, distant) at first diagnosis appeared to be correlated with decreased OS with the univariable analysis (regional hazards ratio [HR] 1.431; $P = .025$ and distant HR 2.954; $P < .001$), this was not seen with the multivariable analysis (regional HR 1.137; $P = .509$, distant HR 1.699; $P = .115$). Surgery after first diagnosis was significantly associated with better OS on both uni- and multivariable analysis, regardless of the type of surgical resection.

Figure 2 shows the KM curves of OS by the status of SPLC (A) before and (B) after correcting potential immortal time bias using time-varying covariate. After correcting for potential immortal time bias, the median OS was 3.63 years (95% CI, 3.05–5.00) and 7.31 years (95% CI, 4.62–10.90) for SPLC and no SPLC groups, respectively (Figure 2).

Discussion

Through advancements in research and clinical practice, survival rates after cancer diagnosis continue to improve.[11] However, increased patient longevity brings new clinical challenges. This retrospective analysis of the internal Karmanos Cancer Institute Tumor Registry database suggests that increased OS is associated with heightened risk of SPLC development. With increased OS following a diagnosis, patients with lung cancer are now at subsequently higher risk for SPLC development following IPLC.[2,12,13] Patients with a history of IPLC are 4 to 6 times more likely to develop SPLC compared with the general population.[14] In addition, individual SPLC risk is cumulative and does not plateau over

time.[2,13] Increased patient survivorship and growing cumulative SPLC risk highlight the necessity of formulating effective surveillance guidelines. This need is only compounded by the finding that 86% of patients are asymptomatic at SPLC diagnosis.[2] The risk factors for SPLC development are considerably less understood, which is reflected in the lack of surveillance strategies geared toward SPLC detection.[4,5]

Age at first diagnosis was not at increased risk of SPLC development. However, older patients had a decreased association with OS. This is likely owing to increased likelihood of frailty and death with advancing age.

In our analysis, family history was not correlated with SPLC development. Although family history of lung cancer could be a risk factor for acquiring the disease in rare situations,[15,16] this correlation may be owing to environmental influences such as living in a shared space with individuals who smoke as opposed to the development of lung cancer owing to hereditary influences. Other cancers, such as breast cancer, have been much more closely linked to having an association between genetic predisposition and disease emergence.[17,18] Therefore our finding that family history was not associated with a second diagnosis was not completely unexpected.

In our analysis, we examined a wide range of lung cancer histologies. Prior to our examination we anticipated that perhaps adenocarcinoma or other nonspecified NSCLC, which both hold better prognoses, to differ from the smoking-related small cell and squamous cell lung cancers in their association with SPLC development and mortality.[19] This was not our finding, although if tested in larger datasets, this hypothesis may be valid. It is likely we were unable to uncover a significant relationship between histology and SPLC in our study with our smaller sample size in our subgroup analysis.

Another counterintuitive finding uncovered in our study was the relationship between smoking and SPLC. Smoking history, as well as continued tobacco use after first diagnosis, were not associated with increased SPLC risk, as seen in Tables 1 and 2. In addition, smoking behaviors were not correlated with OS, as displayed in Table 3. These findings were of definite interest as smoking is a highly cited risk factor for lung cancer.

Smoking is more closely associated with certain lung cancer histology types including small cell and squamous cell lung cancers, which is why we proceeded with a subgroup analysis that examined SPLC histology and smoking.[20] Although one may expect that our subgroup examination would yield statistically significant results as small cell and squamous cell, the cancers known to be associated with smoking, our subgroup analysis did not find associations between smoking and SPLC histology or OS, which again could be because of the limitation in sample size.

Smoking’s connection to SPLC and SPLC mortality is an area that has seen mixed results in several articles and requires further investigation. Ripley et al.[21] found no correlation between SPLC emergence and smoking in patients after undergoing resection. Meanwhile, Boyle et al.[22] found that tobacco exposure increases SPLC development, and that SPLC is particularly rare in never-smokers. Other studies found that smoking at diagnosis, during treatment, and post-treatment to be associated with increased overall mortality—an

association we did not uncover in our analysis on examination of similar variables.[23,24] Although our analysis found a lack of statistical significance between smoking and SPLC, our study population was predominantly comprised of individuals with a considerable smoking history. Of the 241 individuals in our cohort, 192 were categorized as heavy smokers with a smoking history of greater than 30 pack years. Because of our study's strong inclusion of heavy smokers, our results after examining smoking behaviors may not be an adequate representation of smoking's association with SPLC. This area warrants further study to resolve conflicting results about smoking's connection with SPLC emergence.

Despite examining diversified disease stage at diagnosis, including localized, regional, and distant, no stage was associated with increased SPLC emergence, as seen in Tables 1 and 2. However, distant stage at first diagnosis was correlated with a higher hazard of death than patients diagnosed at less progressive stages on univariable analysis (Table 3). This can be attributed to poorer prognoses for patients with more advanced stage.

Several patient characteristics were found to be significantly correlated with SPLC, as well as mortality. Treatment modality and surgery after first diagnosis were found to be significantly associated with the development of SPLC regardless of the type of surgical procedure that was performed. After correcting for potential immortal time bias, the median OS was 3.63 years and 7.31 years for those who developed SPLC and those who did not develop SPLC, respectively (Figure 2).

Hence we suggest surgical resection is an important aspect to consider when screening for SPLC. Patients who underwent surgery after IPLC were associated with increased SPLC emergence. This finding corroborates documented literature that surgical resection is a highly effective means of treating IPLC.[25,26] In this study, those with lower stage (localized) were more likely to undergo surgical resection when compared with those with higher stage (regional and distant stage), consistent with standard of care (see Supplemental Table 1 in the online version at doi: 10.1016/j.cllc.2021.04.004).

With that said, our study highlights the importance of follow-up of resected patients in the outpatient setting to detect possible SPLC development in its early stages. A retrospective study by Leroy et al.[12] found that 10 years post-surgery 20.2% of resection patients developed SPLC—a value that increased to 25.2% at 14 years postoperation. Patients who have had surgical resection for IPLC are a high-risk population when it comes to SPLC development and must be monitored closely.

Several studies have examined the risk factors associated with SPLC development.[2,12,13,27–30] In our analysis, we were able to analyze a smaller cohort of patients in depth. This was both a limitation and a strength. Because of our smaller cohort size, some of our findings may reflect the associations only within our specific study population, which may differ on a broader scale. In addition, our analysis was limited because of the inherent biases related to a retrospective study. Although some patients had a baseline positron emission tomography (PET) scan to rule out metastatic disease at diagnosis, data regarding PET scan utilization and its results were not fully captured in this database. Also, data on pulmonary function tests and comorbidities including

cardiovascular and pulmonary conditions, which may have contributed when determining surgical candidacy, were also not collected. This study focused on those with IPLC who developed SPLC. The control group of those who did not develop SPLC following their IPLC diagnosis were matched based on age, histology, and stage but not matched for their follow-up time because until the final analysis was performed, the median follow-up time for both groups were unknown. Through this analysis, we were not able to determine a meaningful cumulative incidence rate of SPLC because all patients in this group developed SPLC, thereby lacking a fair denominator that would reflect the entire population at risk.

For the ascertainment of SPLC, we used the clinical definitions as described by Martini and Melamed.[3] Although this is a widely used definition, differentiating recurrence of initial cancer from SPLC is sometimes challenging and misclassification of SPLC could be a possibility. Despite the inherent limitations of a retrospective study, we were able to examine a smaller cohort in greater detail. This was an essential aspect for our study to ensure the identification of patients with SPLC, as it can be difficult to distinguish SPLC from metastatic disease.[31] We were able to utilize patient-specific information to formulate a better understanding of the risk factors associated with patients in our geographic region, which had not been done by national studies as they do not examine as much patient-specific information. In addition, our study was able to utilize a previously untapped internal database to compare with the findings of other studies that employed broader and national databases. Our analysis of the risk factors associated with SPLC development and overall mortality uncover important correlations for patients in our geographic area, and demonstrate the importance of conducting population-specific analyses to enhance our understanding of what our individual patient populations may face that differs from a broader scale.

Conclusion

In this study, we demonstrated that surgical resection at first diagnosis was an important factor to consider when screening for SPLC. Although healthier individuals were likely to be selected for surgical resection, these were the patients most likely to develop SPLC and who may benefit from lifetime screening. Further prospective studies to better characterize SPLC risk factors is essential for implementing effective surveillance recommendations at the population level.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points

Patient monitoring for SPLC following IPLC treatment currently lacks effective strategies. This is highly problematic in the setting of increasing patient survivorship following IPLC treatment and a majority of asymptomatic patient presentation at SPLC diagnosis.

Targeted guidelines that consider individual patient risk factors are crucial for enhancing SPLC detection and health outcomes.

In our analysis, patients who did not undergo surgical resection had a significantly lower probability of developing SPLC. This supports close surveillance of IPLC in patients who had surgical resection for IPLC treatment. Our study did not find an association between smoking history and behaviors and SPLC. This is an area that has seen mixed results in several publications and requires further exploration to produce effective monitoring guidelines for patients with a history of smoking. Our findings contribute to other efforts to categorize SPLC risk factors with the goal of producing patient-specific surveillance guidelines for future clinical use.

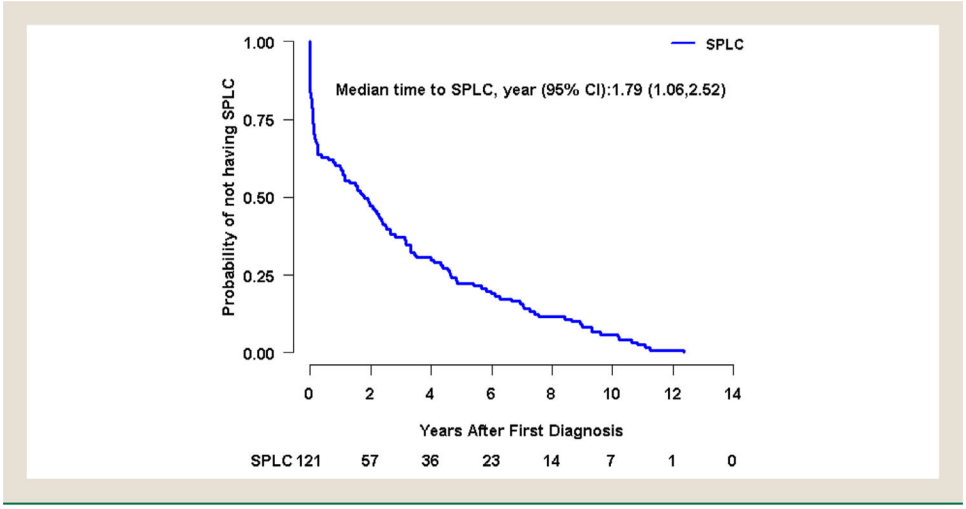

Figure 1.

Kaplan-Meier curve of time to second primary lung cancer (SPLC) among patients who had second diagnosis. Abbreviations: CI = confidence interval.

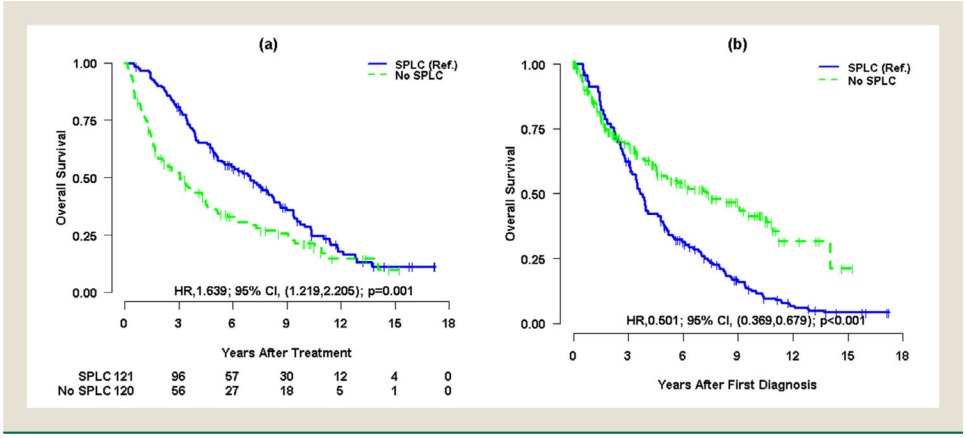

Figure 2.

Kaplan-Meier curve of overall survival by the status of second primary lung cancer (SPLC) **(A)** before and (B) after correcting potential immortal time bias using time-varying covariate. **(A)** The median overall survival is 6.96 years (95% CI, 5.17–8.32) and 3.09 years (95% CI, 2.11–4.49) for group 1 (SPLC) and group 2 (no SPLC), respectively. The median follow-up time of overall survival is 13.20 years (95% CI, 11.18–16.00) and 10.30 years (95% CI, 7.84–13.30) for groups 1 and 2, respectively. **(B)** The median overall survival is 3.63 years (95% CI, 3.05–5.00) and 7.31 years (95% CI, 4.62–10.90) for group 1 (SPLC) and group 2 (no SPLC), respectively. The median follow-up time of overall survival is 10.41 years (95% CI, 8.81–14.41) and 4.86 years (95% CI, 4.09–6.11) for groups 1 and 2, respectively. The follow-up time was calculated using the reverse Kaplan-Meier estimate. Abbreviations: CI = confidence interval; HR = hazards ratio.

Table 1

Patient Characteristics

	Second Diagnosis		All (N = 241)	*P* Value
	Yes (N = 121)	No (N = 120)		
Age at first diagnosis, year - median (range)	64 (45–88)	64 (45–87)	64 (45–88)	.826
Sex - no. (%)				.333
Male	47 (39)	55 (46)	102 (42)	
Female	74 (61)	65 (54)	139 (58)	
Patient status - no. (%)				.823
Alive	32 (26)	34 (28)	66 (27)	
Deceased	89 (74)	85 (71)	174 (72)	
Missing	0 (0)	1 (1)	1 (0)	
Race - no. (%)				.462
American Indian	0 (0)	1 (1)	1 (0)	
Asian	2 (2)	1 (1)	3 (1)	
African American	43 (36)	51 (42)	94 (39)	
White	76 (63)	67 (56)	143 (59)	
Continued tobacco use after tx - no. (%)				.454
Yes	42 (35)	33 (28)	75 (31)	
No	71 (59)	72 (60)	143 (59)	
Missing	8 (7)	15 (12)	23 (10)	
Histology - no. (%)				.731
Small cell carcinoma	8 (7)	8 (7)	16 (7)	
Adenocarcinoma	52 (43)	52 (43)	104 (43)	
Squamous cell carcinoma	44 (36)	44 (37)	88 (37)	
Other NSCLC	15 (12)	16 (13)	31 (13)	
Other lung malignancy	2 (2)	0 (0)	2 (1)	
Family history - no. (%)				> .99
Yes	23 (19)	23 (19)	46 (19)	
No	83 (69)	79 (66)	162 (67)	
Missing	15 (12)	18 (15)	33 (14)	

	Second Diagnosis		All (N = 241)	*P* Value
	Yes (N = 121)	No (N = 120)		
Smoking history defined by pack years at diagnosis - no. (%)				.259
Nonsmoker	4 (3)	8 (7)	12 (5)	
Light smoker	10 (8)	13 (11)	23 (10)	
Heavy smoker(>30)	104 (86)	88 (73)	192 (80)	
Missing	3 (2)	11 (9)	14 (6)	
Stage at first diagnosis - no. (%)				.771
Localized	58 (48)	57 (48)	115 (48)	
Regional	53 (44)	50 (42)	103 (43)	
Distant	9 (7)	12 (10)	21 (9)	
Missing	1 (1)	1 (1)	2 (1)	
Treatment modality - no. (%)				***< .001***
Surgery	82 (68)	41 (34)	123 (51)	
Chemotherapy	11 (9)	16 (13)	27 (11)	
Chemoradiation	17 (14)	21 (18)	38 (16)	
Radiation	11 (9)	27 (22)	38 (16)	
Missing	0 (0)	15 (12)	15 (6)	
Had surgery after first diagnosis - no. (%)				***< .001***
Yes	86 (71)	41 (34)	127 (53)	
Surgery Type				
Wedge	17 (20)	2 (5)	19 (15)	
Lobectomy	58 (67)	35 (85)	93 (73)	
Bilobectomy	2 (2)	0 (0)	2 (2)	
Pneumonectomy	1 (1)	1 (2)	2 (2)	
Other	6 (7)	0 (0)	6 (5)	
Unknown	2 (2)	3 (7)	5 (4)	
No	35 (29)	65 (54)	100 (41)	
Missing	0 (0)	14 (12)	14 (6)	

Abbreviations: NSCLC = non–small-cell lung cancer; tx = treatment.

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Table 2

Uni- and Multivariable Logistic Regression Analysis for Risk Factors Associated with Second Diagnosis

	Univariable		Multivariable	
	OR (95% CI)	***P* Value**	**OR (95% CI)**	***P* Value**
Age, year	1.003 (0.977,1.031)	.807	1.019 (0.984,1.055)	.293
Smoking status after treatment				
Yes	Reference		Reference	
No	0.775 (0.440,1.356)	.373	0.747 (0.374,1.473)	.403
Histology				
Adenocarcinoma and other NSCLC	Reference		Reference	
Small and squamous cell carcinoma	0.986 (0.591,1.642)	.955	0.994 (0.526,1.883)	.984
Smoking history at first diagnosis, pack year				
Nonsmoker	Reference		Reference	
Light smoker	1.538 (0.368,7.144)	.562	2.771 (0.439,20.345)	.289
Heavy smoker (>30)	2.364 (0.719,9.099)	.172	3.957 (0.841,23.082)	.095
Stage at first diagnosis				
Localized	Reference		Reference	
Regional	1.042 (0.612,1.775)	.880	1.591 (0.813,3.185)	.181
Distant	0.737 (0.281,1.875)	.524	1.710 (0.477,5.961)	.400
Surgery after first diagnosis				
No	Reference		Reference	
Suboptimal	21.357 (5.857,138.047)	< ***.001***	53.150 (9.181,1037.984)	< ***.001***
Adequate	3.147 (1.771,5.681)	< ***.001***	3.380 (1.701,6.946)	***.001***

Abbreviations: CI = confidence interval; NSCLC = non–small-cell lung cancer; OR = odds ratio.

Table 3

Uni- and Multivariable Cox Regression Analysis for Risk Factors Associated with Overall Survival

	Univariable		Multivariable	
	HR (95% CI)	***P* Value**	**HR (95% CI)**	***P* Value**
Age, year	1.027 (1.011,1.044)	***.001***	1.033 (1.013,1.054)	***.001***
Second diagnosis status [a]				
Yes	Reference		Reference	
No	0.501 (0.369,0.679)	< ***.001***	0.463 (0.324,0.662)	< ***.001***
Smoking status after treatment				
Yes	Reference		Reference	
No	0.952 (0.689,1.315)	.765	0.760 (0.527,1.096)	.141
Histology				
Adenocarcinoma and other NSCLC	Reference		Reference	
Small and squamous cell carcinoma	1.298 (0.965,1.746)	.085	1.236 (0.872,1.753)	.233
Smoking history at first diagnosis, pack year				
Nonsmoker	Reference		Reference	
Light smoker	0.866 (0.388,1.932)	.725	0.667 (0.246,1.810)	.426
Heavy smoker (>30)	0.995 (0.523,1.892)	.988	0.743 (0.340,1.626)	.457
Stage at first diagnosis				
Localized	Reference		Reference	
Regional	1.431 (1.046,1.959)	***.025***	1.137 (0.777,1.664)	.509
Distant	2.954 (1.778,4.908)	< ***.001***	1.699 (0.880,3.282)	.115
Surgery after first diagnosis				
No	Reference		Reference	
Suboptimal	0.421 (0.255,0.697)	***.001***	0.346 (0.191,0.628)	< ***.001***
Adequate	0.312 (0.220,0.441)	< ***.001***	0.334 (0.222,0.503)	< ***.001***

Abbreviations: CI = confidence interval; HR = hazards ratio; NSCLC = non–small-cell lung cancer.

[a]Time-varying covariate-based correction for potential immortal time bias.