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Risk Factors Associated with a Second Primary Lung Cancer (SPLC) in Patients with an Initial Primary Lung Cancer (IPLC)

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INTRODUCTION

Second primary lung cancer (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 two or more years after initial primary lung cancer (IPLC). The risk of development of SPLC after an IPLC is about 1% to 2% per patient year. Appropriate surveillance recommendations that enable early detection of SPLC are essential for increasing life expectancy post treatment of IPLC. Current guidelines for monitoring SPLC development are limited.

The aim of this study was to characterize risk factors associated with the development of SPLC. Our intention was to categorize these considerations for clinical use following treatment of IPLC.

METHODS

Patients diagnosed with IPLC between 2000 and 2017 were identified from the Karmanos Cancer Institute Tumor Registry and included in this retrospective analysis. Individuals who later developed SPLC were matched for age, histology and stage to patients with IPLC who did not develop SPLC.

Age at first diagnosis, gender, histology, family history, race, smoking history, stage of first diagnosis, treatment modality, whether a patient had surgery after IPLC diagnosis, and patient living status were collected and reviewed. Logistic and Cox regression analyses were performed to identify risk factors for SPLC emergence and overall survival.

TABLE 2

Table 2. Univariable and multivariable logistic regression analysis for risk factors associated with second diagnosis

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p	OR (95% CI)	p
Smoking status after treatment				
Yes	Reference		Reference	
No	0.775 (0.440,1.356)	0.373	0.780 (0.393,1.529)	0.472
Histology				
Adenocarcinoma and Other NSCLC	Reference		Reference	
Small and Squamous Cell Carcinoma	0.986 (0.591,1.642)	0.955	1.003 (0.530,1.902)	0.994
Age				
<60	Reference		Reference	
>=60	1.012 (0.585,1.752)	0.966	1.280 (0.633,2.612)	0.493
Smoking history at first diagnosis, pack year				
Nonsmoker	Reference		Reference	
Light Smoker	1.538 (0.368,7.144)	0.562	2.603 (0.414,18.871)	0.317
Heavy Smoker(>30)	2.364 (0.719,9.099)	0.172	3.688 (0.795,21.057)	0.108
Stage at first diagnosis				
Localized	Reference		Reference	
Regional	1.042 (0.612,1.775)	0.880	1.586 (0.810,3.177)	0.184
Distant	0.737 (0.281,1.875)	0.524	1.724 (0.473,6.124)	0.399
Surgery after first diagnosis				
No	Reference		Reference	
Sub-optimal	21.357 (5.857,138.047)	***<0.001***	52.662 (9.070,1031.037)	***<0.001***
Adequate	3.147 (1.771,5.681)	***<0.001***	3.365 (1.689,6.935)	***0.001***

OR, odds ratio; CI, confidence interval

Resources: [1]Johnson, B. E. (1998). Second Lung Cancers in Patients After Treatment for an Initial Lung Cancer. *JNCI: Journal of the National Cancer Institute, 90*(18), 1335-1345. doi:10.1093/jnci/90.18.1335 [2]Martini, N., & Melamed, M. R. (1975). Multiple primary lung cancers. *The Journal of Thoracic and Cardiovascular Surgery, 70*(4), 606-612. doi:10.1016/s0022-5223(19)40289-4 [3]National Comprehensive Cancer Network. (2020). *Non-Small Cell Lung Cancer (Version 3.2020).* Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

TABLE 1

Patient Characteristics

	Second diagnosis		All (N = 241)	p
	Yes (N = 121)	No (N = 120)		
Age at first Diagnosis - median (range)	64 (45-88)	64 (45-87)	64 (45-88)	0.826
Age				>0.99
<60	37 (31)	37 (31)	74 (31)	
>=60	84 (69)	83 (69)	167 (69)	
Sex - no. (%)				0.333
Male	47 (39)	55 (46)	102 (42)	
Female	74 (61)	65 (54)	139 (58)	
Patient Status - no. (%)				0.823
Alive	32 (26)	34 (28)	66 (27)	
Deceased	89 (74)	85 (71)	174 (72)	
missing	0 (0)	1 (1)	1 (0)	
Race - no. (%)				0.462
American Indian	0 (0)	1 (1)	1 (0)	
Asian	2 (2)	1 (1)	3 (1)	
African American	43 (36)	51 (42)	94 (39)	
Caucasian	76 (63)	67 (56)	143 (59)	
Continued Tobacco Use After Tx - no. (%)				0.454
Yes	42 (35)	33 (28)	75 (31)	
No	71 (59)	72 (60)	143 (59)	
missing	8 (7)	15 (12)	23 (10)	
Histology - no. (%)				0.731
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. (%)				>0.99
Yes	23 (19)	23 (19)	46 (19)	
No	83 (69)	79 (66)	162 (67)	
missing	15 (12)	18 (15)	33 (14)	
Smoking History defined by Pack Years at Diagnosis - no. (%)				0.259
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. (%)				0.771
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. (%)				***<0.001***
Surgery	82 (68)	41 (34)	123 (51)	
Chemo	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. (%)				***<0.001***
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)	

TABLE 3

Table 3. Univariable and multivariable Cox regression analysis for risk factors associated with OS

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p	HR (95% CI)	p
Second diagnosis status*				
Yes	reference		reference	
No	1.998 (1.473,2.710)	***<0.001***	2.261 (1.588,3.218)	***<0.001***
Smoking status after treatment				
Yes	reference		reference	
No	0.952 (0.689,1.315)	0.765	0.764 (0.529,1.102)	0.150
Histology				
Adenocarcinoma and Other NSCLC	reference		reference	
Small and Squamous Cell Carcinoma	1.298 (0.965,1.746)	0.085	1.191 (0.832,1.706)	0.339
Age				
<60	reference		reference	
>=60	1.472 (1.047,2.070)	***0.026***	1.835 (1.183,2.848)	***0.007***
Smoking history at first diagnosis, pack year				
Nonsmoker	reference		reference	
Light Smoker	0.866 (0.388,1.932)	0.725	0.697 (0.259,1.871)	0.473
Heavy Smoker(>30)	0.995 (0.523,1.892)	0.988	0.631 (0.292,1.364)	0.242
Stage at first diagnosis				
Localized	reference		reference	
Regional	1.431 (1.046,1.959)	***0.025***	1.148 (0.781,1.687)	0.483
Distant	2.954 (1.778,4.908)	***<0.001***	1.809 (0.939,3.486)	0.077
Surgery after first diagnosis				
No	reference		reference	
Sub-optimal	0.421 (0.255,0.697)	***0.001***	0.331 (0.183,0.601)	***<0.001***
Adequate	0.312 (0.220,0.441)	***<0.001***	0.334 (0.222,0.503)	***<0.001***

HR, hazard ratio; CI, confidence interval; *, time-dependent variable

RESULTS

121 patients diagnosed with IPLC who later developed SPLC were identified and compared to 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 (Table 1). Patients who did not undergo surgical resection had a significantly lower probability of developing SPLC (OR 0.235, 95% confidence interval [CI]: 0.118 to 0.450; p<0.001, Table 2). Compared to surgical resection patients, individuals who did not have surgery as their primary treatment for IPLC had a significantly higher hazard of death (HR 3.088, 95% CI: 2.114 to 4.512; p<0.001, Table 3, Figure 1).

FIGURE 1

Kaplan-Meier curve of OS by the status of second diagnosis (Yes vs. No). The median OS is 6.96 years (95% CI, 5.17 to 8.32) and 3.09 years (95% CI, 2.11 to 4.49) for Group 1 (Yes) and Group 2 (No), respectively. The median follow-up time of OS is 13.20 years (95% CI, 11.18 to 16.00) and 10.30 years (95% CI, 7.84 to 13.30) for Group 1 and Group 2, respectively. The follow-up time was calculated using the reverse Kaplan-Meier estimate.

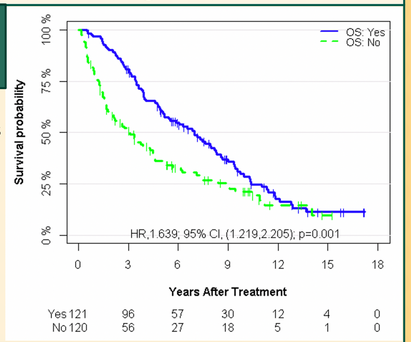

TABLE 4 AND S1

Table 4. Subgroup analysis of smoking status after treatment associated with second diagnosis by histology.

	Histology				Interaction p
	Adenocarcinoma and Other NSCLC		Small and Squamous Cell Carcinoma		
	OR (95% CI)	p	OR (95% CI)	p	
Smoking status after treatment					0.808
Yes	reference		reference		
No	0.821 (0.384,1.735)	0.606	0.713 (0.302,1.661)	0.435	
Smoking history					0.649
Non or light smoker	reference		reference		
Heavy smoker	1.549 (0.644,3.808)	0.330	2.667 (0.694,12.98)	0.174	

Table S1. Association between stage and surgery

	Yes (N = 127)	No (N = 100)	All (N = 227)	p
Stage – no. (%)				***<0.001***
Low	77 (61)	30 (30)	107 (44)	
High	50 (39)	68 (68)	118 (49)	
missing	0 (0)	2 (2)	2 (1)	

CONCLUSION

We demonstrated that surgical resection at first diagnosis was an important factor to consider when screening for SPLC. While healthier individuals were likely to be selected for surgical resection, thereby contributing to longer survival, 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.