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Tumor Location and Survival Outcomes in Lung Adenosquamous Carcinoma: A Propensity Score Matched Analysis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: There is little information in the literature available on lung adenosquamous carcinoma (LASC). The association between tumor location and survival outcomes in LASC is poorly understood. Our study was designed to probe the effect of tumor location on survival outcomes of LASC.

Material/Methods: Patients with LASC between 2004 and 2015 were identified using the Surveillance, Epidemiology and End Results (SEER) databases. The patients were divided into 2 groups, a main bronchus group and a peripheral group, according to their primary sites. The Propensity Score Matching (PSM) method was used to reduce possible bias between groups. The primary endpoints were overall survival (OS) and cancer-specific survival (CSS).

Results: A total of 3176 patients, afflicted with LASC between 2004 and 2015, were extracted from the SEER databases. Of these, 212 patients were found to be eligible for analysis after a propensity 1: 1 nearest neighbor matched analysis. After PSM, multivariate Cox regression analysis showed that primary site, American Joint Committee on Cancer (AJCC) stage, T stage and surgery were independent predictors of LASC in both OS and CSS. Kaplan-Meier survival analysis showed that patients with LASC located in a peripheral site had better survival outcomes than those with LASC located in the main bronchus. In subgroup analysis, the advantages of tumor located in a peripheral site were more pronounced in female patients and AJCC stage I patients.

Conclusions: Tumor location may have an impact on the survival outcomes of patients with LASC. Patients with LASC located in a peripheral site had better survival outcomes than patients with LASC located in the main bronchus, particularly in female patients and AJCC stage I patients.

MeSH Keywords: Carcinoma, Adenosquamous • Location Directories and Signs • SEER Program • Treatment Outcome

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Background

Lung cancer is one of the most common devastating tumors with a high incidence and mortality rate worldwide [1]. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the major histopathologic types of lung cancer. NSCLC usually includes adenocarcinoma (AC), squamous cell carcinoma (SCC), and adenosquamous carcinoma (ASC). According to the 2015 WHO pathological classification, lung adenosquamous carcinoma (LASC) has been categorized as a carcinoma; it contains components of both AC and SCC with each component constituting at least 10% of the tumor [2]. The proportion of AC or SCC is also an essential factor that affects the prognosis of LASC; the predominant histological subtype of AC may be an independent prognostic factor for LASC [3]. LASC is widely known as an extremely rare subtype of lung cancer, only accounting for approximately 0.4–4% of all lung carcinoma [4,5].

Because of the low incidence of LASC and a subsequent lack of large-scale clinical outcome data, there is little information currently available on LASC. However, previous studies have shown that LASC is relatively aggressive and has worse survival outcomes compared with AC and SCC [6,7]. Although LASC has the same clinical manifestations as other subtypes of NSCLC, it was usually diagnosed at an advanced stage due to its high frequency of lymph node metastasis, vascular invasion, and parietal pleural involvement [8,9]. Age, sex, histologic grade, and tumor stage are considered to be potential prognostic factors, but the effects of tumor location on survival outcomes of LASC are still poorly understood. Thus, it is desirable to conduct large-scale multicenter clinical studies to evaluate the effect of tumor location on survival outcomes of patients with LASC. The SEER database is an open database that consists of 18 population-based cancer registries and has numerous case series representing 30% of the US population [10]. We analyzed the data extracted from the SEER databases through regular and Propensity Score Matching (PSM) methods.

Material and Methods

Ethics statement

We conducted this study by acquiring clinical data from the SEER databases; the username of the SEER database is 12158-Nov2018. SEER*Stat 8.3.5 software was applied for extraction. Due to the openness of the SEER databases, our research was exempted from the need for approval by the Ethics Committee of the Affiliated Hospital of Yangzhou University.

Data extraction

Data of all the patients with LASC between 2004 and 2015 were extracted from the SEER databases. Inclusion criteria for our study were listed as follows: 1) the histology/behavior codes (ICD-0-3 8560/3) and restriction on site recode ICD-0-3/WHO 2008 (International Classification of Diseases for Oncology, Third Edition) to "Lung and Bronchus" were applied to confirm LASC; 2) patients with year of diagnosis were between 2004 and 2015; 3) patients with active follow-ups; 4) patients with survival time more than 0 days. Exclusion criteria were as follows: 1) patients with the history of other tumors; 2) patients without accurate diagnosis based on pathological confirmation; 3) patients with unknown clinical characteristics information including age, race, sex, tumor primary site, American Joint Committee on Cancer (AJCC) stage group, cause of death, surgery, radiation and chemotherapy; and 4) patients with incomplete survival data.

Covariates were listed as follows: age, sex, primary site, grade, TNM stage (6th edition), cancer-specific death, surgery, radiation, chemotherapy, survival month and vital status. The primary endpoints were overall survival (OS) and cancer-special survival (CSS).

A total of 3176 patients with LASC were recruited in this study and were divided into 2 groups, according to tumor location. In our study, the main bronchus was defined as a tumor located in primary bronchus, including left or right primary bronchus; the peripheral site was defined as a tumor located in a position other than primary bronchus including upper lobe, middle lobe, lower lobe, and overlapping lesion of the lung. The group of main bronchus contains 107 patients, and the peripheral group contains 3069 patients.

Propensity Score Matching (PSM)

The Propensity Score Matching (PSM) method was used to reduce potential bias between the main bronchus group and the peripheral group. In our study, we conducted a propensity 1: 1 nearest neighbor matched analysis to minimize potential bias between groups. The propensity score was calculated using the logistic regression model. Chi-squared tests were used to examine the covariate balance before and after PSM.

Statistical analysis

In our study, OS and CSS were calculated using Kaplan-Meier survival analysis. A chi-squared test was conducted to test the statistical difference of age, sex, grade, AJCC stage, AJCC T stage, AJCC N stage, AJCC M stage, surgery, radiation and chemotherapy between the groups.

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Table 1. Baseline characteristics for patients with LASC before and after PSM.

Variables	Before PSM			After PSM		
	Main bronchus	Peripheral	P-value	Main bronchus	Peripheral	*P*-value
Age			<0.001			0.395
<60	38	640		37	43	
≥60	69	2429		69	63	
Sex			0.152			0.583
Male	51	1678		51	55	
Female	56	1391		55	51	
Race			0.054			0.501
Black	18	309		17	17	
White	84	2532		84	87	
Other	5	228		5	2	
Grade			<0.001			0.784
I–II	10	736		10	13	
III–IV	49	1529		49	46	
Unknown	48	804		47	47	
AJCC stage			<0.001			0.346
I	4	1046		4	4	
II	7	311		7	13	
III	39	756		38	43	
IV	57	956		57	46	
T stage			<0.001			0.327
T1	6	734		6	6	
T2	37	1287		37	50	
T3	8	250		8	6	
T4	56	798		55	44	
N stage			<0.001			0.870
N0	16	1475		16	14	
N1	13	374		13	14	
N2	63	922		62	59	
N3	15	298		15	19	
M stage			<0.001			0.131
M0	50	2113		49	60	
M1	57	956		57	46	
Surgery			<0.001			0.549
No/unknown	94	1448		93	90	
Yes	13	1621		13	16	

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Table 1 continued. Baseline characteristics for patients with LASC before and after PSM.

Variables	Before PSM			After PSM		
	Main bronchus	Peripheral	P-value	Main bronchus	Peripheral	*P*-value
Radiation			<0.001			0.763
No/Unknown	32	1883		32	30	
Yes	75	1186		74	76	
Chemotherapy			0.006			0.395
No/unknown	44	1677		43	37	
Yes	63	1392		63	69	

PSM – Propensity Score Matching; LASC – lung adenosquamous carcinoma; AJCC – American Joint Committee on Cancer.

Univariate and multivariate Cox proportional hazards regression models were used to evaluate the risk of mortality and conduct subgroup analyses. All statistical analyses were conducted with SPSS 22.0 (Chicago, IL, USA). GraphPad- Prism 8.0 software was used to generate survival curves. Microsoft Excel 2016 software was used to generate a forest plot. $P<0.05$ was considered statistically significant.

Results

Baseline characteristics of patients with LASC before and after PSM

A total of 3176 patients were selected for this study before PSM, 212 were deemed eligible for analysis after a propensity 1: 1 nearest neighbor matched analysis. According to primary tumor sites, the 212 patients were divided into 2 groups, with each group containing 106 patients. Baseline characteristics of patients before PSM and after PSM are shown in Table 1. Such characteristics included: age, sex, race, AJCC stage, T stage, N stage, M stage, surgery, and radiation and chemotherapy. Before PSM, covariates- such as age, grade, AJCC stage, T stage, N stage, M stage, surgery, radiation, and chemotherapy had a significant difference between groups(all *P*-value <0.05). After PSM, there were no major differences in the multiple variables that were compared between the main bronchus group and the peripheral group (all *P*-value >0.05).

Survival outcomes of patients with LASC before and after PSM

Before PSM, the 5-year OS and CSS rates were 25.44% and 32.10%, respectively. The OS and CSS curves are shown in Figure 1. The peripheral group had better survival outcomes compared with the main bronchus group both in OS and CSS (Figure 2). The 5-year OS and CSS rates in the peripheral group were 26.09% and 32.89%, and in main bronchus group was 7.06% and 8.79%. After PSM, curves of OS and CSS were shown in Figure 3. Similar results between groups were also obtained for the survival curve (Figure 4). The 5-year OS and CSS rates in the peripheral group were 10.77% and 18.02%, and in the main bronchus group were 7.13% and 8.89%.

Univariate and multivariate analysis after 1: 1 PSM analysis

After PSM, factors including age, sex, race, primary site, grade, AJCC stage, T stage, N stage, M stage, surgery, radiation, and chemotherapy were selected as factors with which to conduct univariate survival analysis. Upon univariate analyses, the presence of factors- including primary sites, AJCC stage, T stage, M stage, surgery and chemotherapy were the predictive prognosis of patient survival outcomes (all *P*-value >0.05). These factors were associated with OS and CSS (Tables 2, 3). Tumors located in the main bronchus, advanced cancer stage, T4 stage, M1 stage, without surgery, and without chemotherapy were associated with worse survival outcomes both in OS and CSS. Cox regression analysis was performed to identify independent predictors of LASC. Significant univariate factors were additionally analyzed in regression models. Multivariate Cox regression analysis showed that the primary site, AJCC stage, T stage and surgery were independent predictors of LASC both in OS and CSS (*P*-value <0.05).

Subgroup analysis for OS and CSS after 1: 1 PSM analysis

Subgroup analysis showed that a tumor located in a peripheral location was associated with better survival outcomes (Figures 5, 6). OS was statistically significant in the subgroups stratified by female (hazard ratio [HR]: 1.510, 95% confidence interval [CI]: 1.001–2.277, *P*=0.039); other race (HR: 0.173, 95% CI: 0.008–3.515, *P*=0.008); unknown stage (HR: 1.561, 95% CI: 1.008–2.418, *P*=0.030); AJCC stage I (HR: 5.022, 95% CI: 0.626–40.310, *P*=0.025); T4 stage (HR: 1.475, 95% CI: 0.978–2.225, *P*=0.047); undergoing radiation (HR: 1.606, 95% CI:

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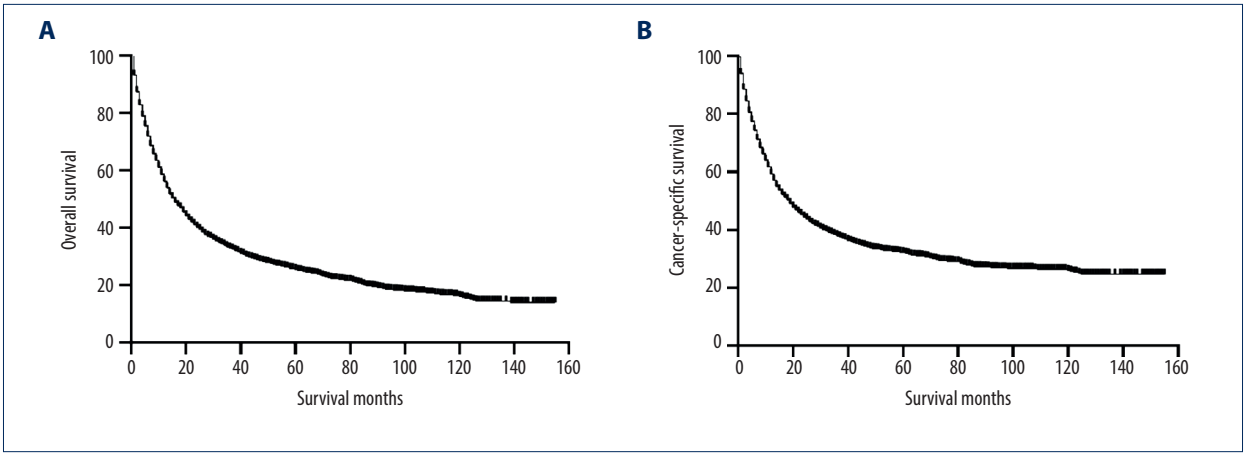

Figure 1. Kaplan-Meier curves of OS (**A**) and CSS (**B**) before PSM. OS – overall survival; CSS – cancer-specific survival; PSM – Propensity Score Matching.

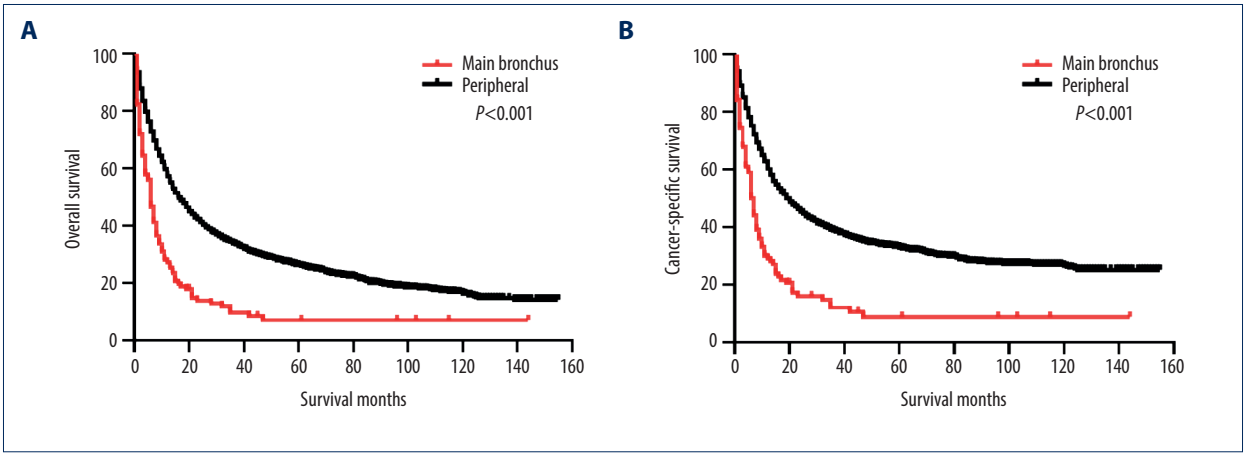

Figure 2. Kaplan-Meier curves of OS and CSS before PSM. OS (**A**) and CSS (**B**) between main bronchus and peripheral groups, before 1: 1 PSM analysis. OS – overall survival; CSS – cancer-specific survival; PSM – Propensity Score Matching.

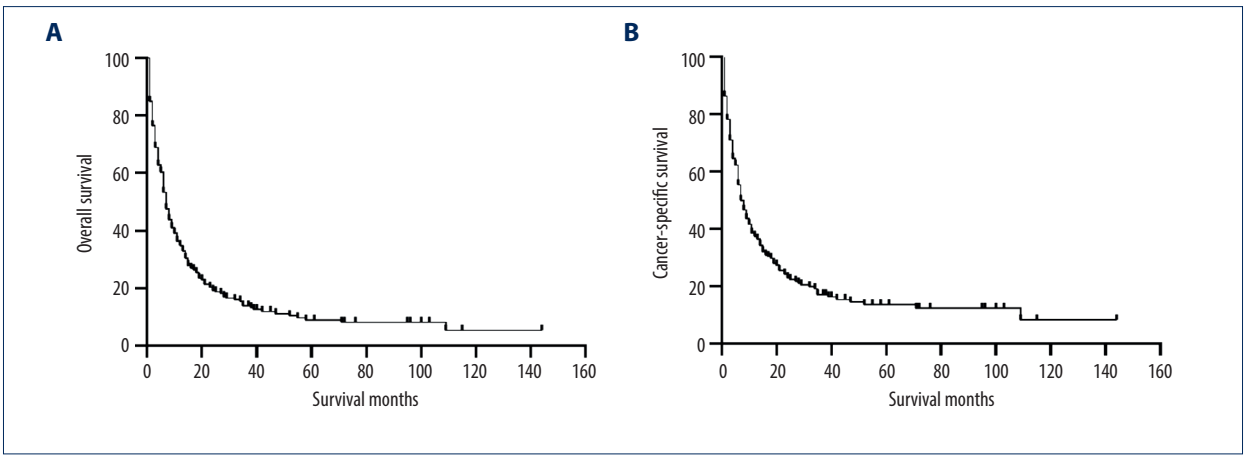

Figure 3. Kaplan-Meier curves of OS (**A**) and CSS (**B**) after PSM. OS – overall survival; CSS – cancer-specific survival; PSM – Propensity Score Matching.

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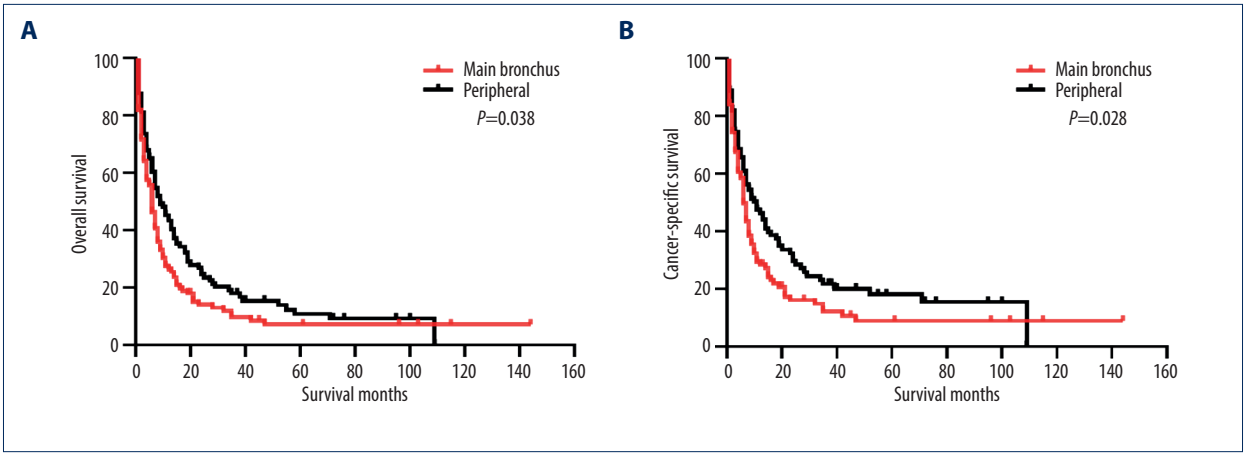

Figure 4. Kaplan-Meier curves of OS and CSS after PSM. OS (**A**) and CSS (**B**) between main bronchus and peripheral groups, after 1: 1 PSM analysis. OS – overall survival; CSS – cancer-specific survival; PSM – Propensity Score Matching.

Table 2. Univariate and multivariate analyses of OS after PSM.

Variables	Univariate analysis	Multivariate analysis
	P-value	HR (95% CI), *P*-value
Age	0.339	Not included
<60		
≥60		
Sex	0.328	Not included
Male		
Female		
Race	0.662	Not included
Black		
White		
Other		
Primary site	0.038	0.041
Main bronchus		Reference
Peripheral		1.362 (1.012–1.834)
Grade	0.917	Not included
I–II		
III–IV		
Unknown		
AJCC stage	<0.001	0.007
I		Reference
II		2.873 (1.045–7.899) 0.041
III		3.129(1.204–8.126) 0.019
IV		4.160 (1.582–10.938) 0.004

Variables	Univariate analysis	Multivariate analysis
	P-value	HR (95% CI), *P*-value
T stage	<0.001	0.004
T1		Reference
T2		1.510 (0.778–2.928) 0.223
T3		0.950 (0.403–2.239) 0.906
T4		2.203 (1.155–4.205) 0.017
N stage	0.182	Not included
N0		
N1		
N2		
N3		
M stage	<0.001	Not included
M0		
M1		
Surgery	<0.001	0.002
No/Unknown		Reference
Yes		0.419 (0.243–0.722)
Radiation	0.535	Not included
No/Unknown		
Yes		
Chemotherapy	<0.001	<0.001
No/Unknown		Reference
Yes		0.336 (0.244–0.464)

OS – overall survival; PSM – Propensity Score Matching; HR – hazard ratio; CI – confidence interval; AJCC – American Joint Committee on Cancer.

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Table 3. Univariate and multivariate analyses of CSS after PSM.

Variables	Univariate analysis	Multivariate analysis
	P-value	HR (95% CI), *P*-value
Age	0.844	Not included
<60		
≥60		
Sex	0.593	Not included
Male		
Female		
Race	0.314	Not included
Black		
White		
Other		
Primary site	0.028	0.038
Main bronchus		
Peripheral		Reference
Grade	0.901	1.392 (1.019–1.903)
I–II		
III–IV		
Unknown		
AJCC stage	<0.001	0.006
I		Reference
II		2.818 (0.913–8.701) 0.072
III		3.409 (1.184–9.818) 0.019
IV		4.726 (1.622–13.774) 0.004
T stage	<0.001	0.004
T1		Reference
T2		1.710 (0.828–3.528) 0.147
T3		0.992 (0.385–2.557) 0.987
T4		2.432 (1.198–4.938) 0.014
N stage	0.285	Not included
N0		
N1		
N2		
N3		
M stage	<0.001	Not included
M0		
M1		
Surgery	<0.001	0.009
No/Unknown		Reference
Yes		0.464 (0.260–0.828)
Radiation	0.784	Not included
No/Unknown		
Yes		
Chemotherapy	<0.001	<0.001
No/Unknown		Reference
Yes		0.353 (0.251–0.494)

CSS – cancer-specific survival; PSM – Propensity Score Matching; HR – hazard ratio; CI – confidence interval; AJCC – American Joint Committee on Cancer

0.992–2.2559, *P*=0.035). CSS was statistically significant in the subgroups stratified by female (HR: 1.599, 95% CI: 1.017–2.390, *P*=0.033); white race (HR: 1.437, 95% CI: 1.028–2.010, *P*=0.025); other race (HR: 0.173, 95% CI: 0.008–3.515, *P*=0.008); AJCC stage I (HR: 7.435, 95% CI: 0.853–64.810, *P*=0.025); without chemotherapy (HR: 1.571, 95% CI: 1.044–3.142, *P*=0.034). All subgroup analysis of OS and CSS showed survival rates in favor of tumors located in peripheral sites, especially for female and AJCC stage I patients.

Discussion

LASC is a rare subgroup of lung cancer, accounting for only 0.4–4% of all lung carcinomas [7,11]. Little information is available on the clinical characteristics of LASC due to its low incidence [12]. Additionally, LASC is more challenging to diagnose than AC and SCC since it is a mixture of the 2. A low under sampling puncture can lead to an incorrect diagnosis of squamous cell carcinoma or adenocarcinoma. Instead, the key to a successful diagnosis lies in pathological diagnosis by cytology or tissue, and resection is a relatively safe and reliable diagnostic method. The accuracy of non-resection approaches for the diagnosis of LASC is relatively low, and many LASC patients may miss the best time for interventions because of the non-resected biopsies. Uramoto et al. described a case of pulmonary adenosquamous carcinoma, which was confirmed via histological examination of the resection specimen that showed only adenocarcinoma in the biopsy and only squamous cell carcinoma in the bronchial wash and brushing

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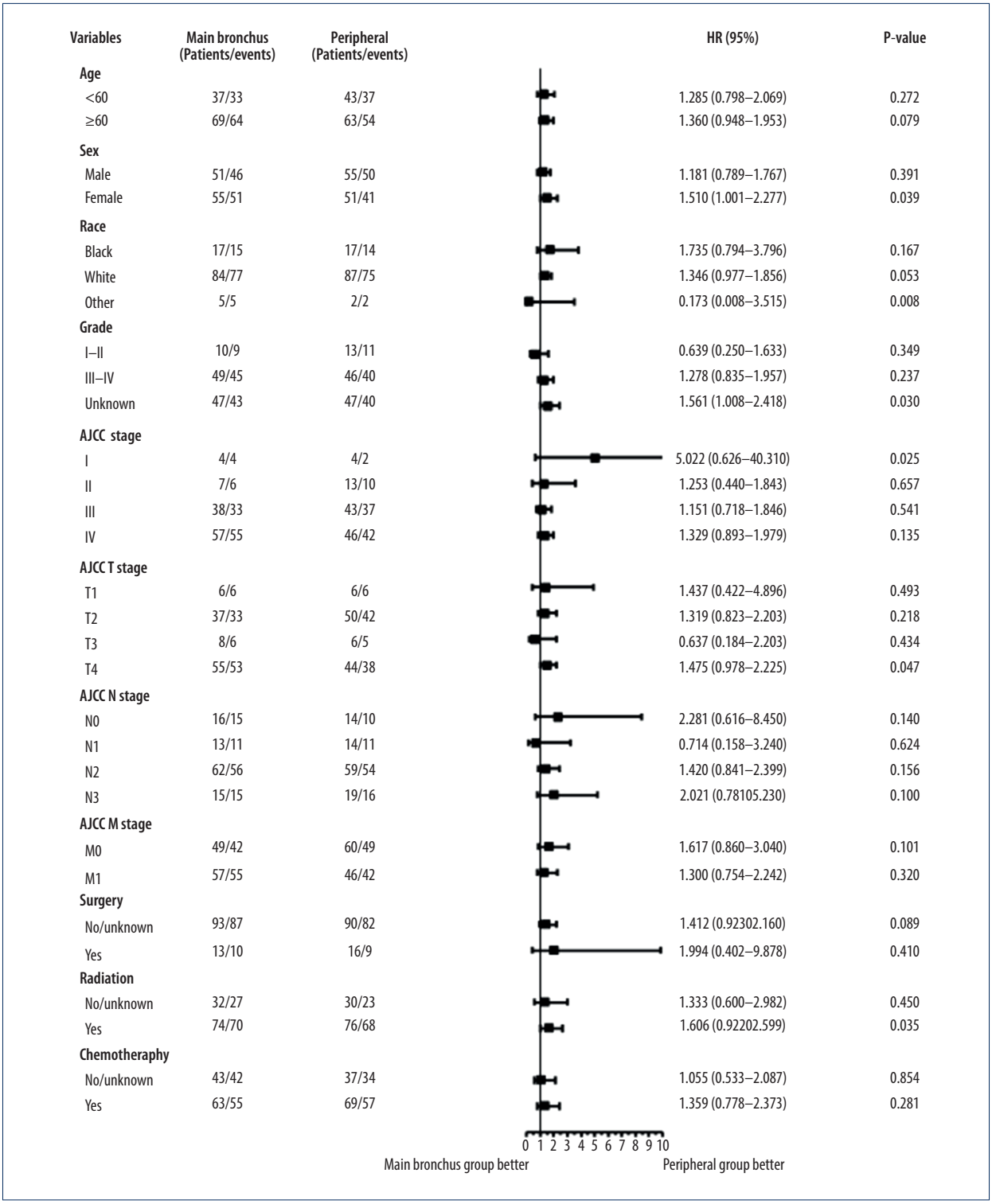

Figure 5. Subgroup analysis between main bronchus and peripheral groups for OS after PSM. OS – overall survival; PSM – Propensity Score Matching.

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Variables	Main bronchus (Patients/events)	Peripheral (Patients/events)	HR (95%)	P-value
Age				
<60	37/32	43/35	1.312 (0.806–2.134)	0.245
≥60	69/57	63/45	1.427 (0.967–2.106)	0.061
Sex				
Male	51/41	55/43	1.209 (0.786–1.860)	0.362
Female	55/48	51/37	1.599 (1.017–2.390)	0.033
Race				
Black	17/11	17/12	1.385 (0.60103.191)	0.412
White	84/73	87/66	1.437 (1.028–2.010)	0.025
Other	5/5	2/2	0.173 (0.008–3.515)	0.008
Grade				
I–II	10/8	13/10	0.658 (0.260–1.664)	0.343
III–IV	49/43	46/34	1.418 (0.90602.217)	0.111
Unknown	47/38	47/36	1.508 (0.949–2.395)	0.060
AJCC stage				
I	4/3	4/1	7.436 (0.853–64.810)	0.025
II	7/5	13/8	1.285 (0.403–4.092)	0.655
III	38/30	43/32	1.207 (0.731–1.993)	0.443
IV	57/51	46/39	1.325 (0.876–2.003)	0.156
AJCC T stage				
T1	6/4	6/5	1.447 (0.370–5.662)	0.545
T2	37/31	50/36	1.419 (0.86602.325)	0.139
T3	8/5	6/4	0.714 (0.183–2.776)	0.600
T4	55/49	44/35	1.490 (0.972–2.286)	0.053
AJCC N stage				
N0	16/15	14/9	1.955 (0.87604.363)	0.081
N1	13/11	14/9	1.749 (0.695–4.399)	0.204
N2	62/56	59/48	1.084 (0.728–1.614)	0.677
N3	15/15	19/14	2.423 (1.100–5.335)	0.007
AJCC M stage				
M0	49/38	60/41	1.316 (0.841–2.059)	0.208
M1	57/51	46/39	1.325 (0.876–2.003)	0.156
Surgery				
No/unknown	93/80	90/72	1.327 (0.965–1.827)	0.066
Yes	13/9	16/8	1.772 (0.668–4.700)	0.219
Radiation				
No/unknown	32/25	30/21	1.467 (0.820–2.623)	0.160
Yes	74/64	76/59	1.367 (0.95801.951)	0.071
Chemotheraphy				
No/unknown	43/38	37/29	1.571 (1.044–3.142)	0.034
Yes	63/51	69/51	1.198 (0.812–1.769)	0.348

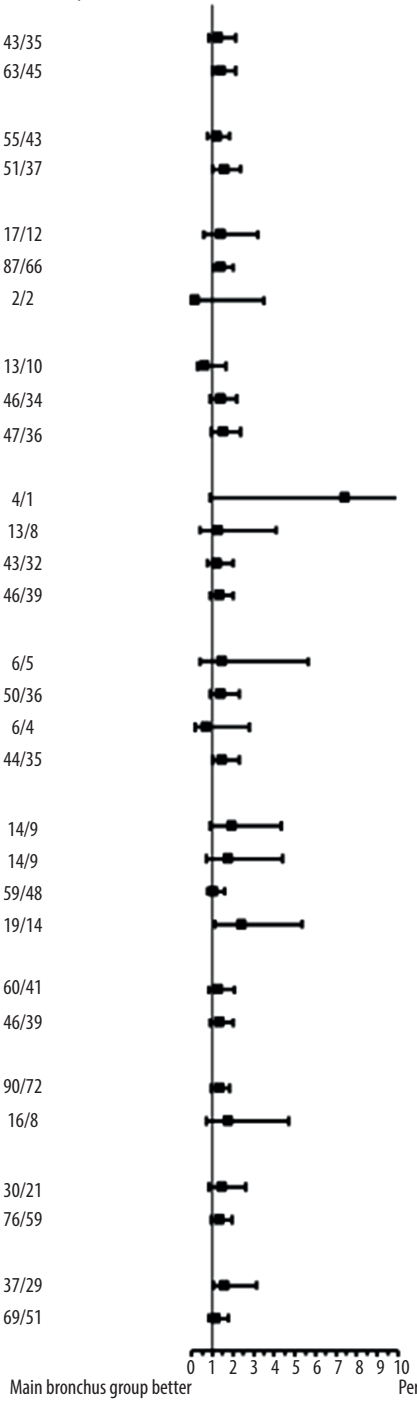

Figure 6. Subgroup analysis between main bronchus and peripheral groups for CSS after PSM. CSS – cancer-specific survival; PSM – Propensity Score Matching.

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specimens [13]. Therefore, the correct tumor classification of diagnosis is necessary.

Some studies have been shown that LASC was more commonly seen in male smokers who were over the age of 65 years old [6,14]. In our study, the number of enrolled patients with age over 60 years was 2498 (78.65%); this was a similar result in a review conducted by Li and Lu [15]. Besides, the male-to-female ratio was 1.19: 1 (1729 versus 1447) in our research, which was lower than the previously reported in the literature. However, a report comes from SEER databases showed a similar result: the male-to-female ratio was 1.24: 1 (2349 versus 1896) [16]. Considering that both studies included more than 3000 patients, we have reason to believe that the data of this research are worthy of belief. The primary condition of patients, their pathological grade, and additional therapy received are favorable prognostic factors for LASC, which are parallel to our study. According to multivariate analysis, primary site, AJCC stage, T stage and surgery were all independent predictors of LASC. Besides, the proportion of AC or SCC is also an essential factor that affects the prognosis of LASC. LASC, with balanced adenomatous and squamous components, was associated with better survival outcomes than those with one predominant component [9,17]. However, in contrast to these results, some authors also observed that SCC-predominant histology represents a better prognosis of ASC [18]. Therefore, further research on this topic is warranted.

In our study, the 5-year OS rate was 25.44%, which is similar to previously reported ranged from 6.2% to 25.4% [19]. Compared with AC or SCC, LASC usually Nakagawa et al. found that LASC also had a significantly poorer prognosis than AC or SCC (the 5-survival rate was 6.2% versus 41.5%) [20]. Besides, LASC tended to be diagnosed at a more advanced stage, with a high rate of lymph node metastasis, more frequent vascular invasion, and parietal pleural involvement than AC [21]. Similarly, high cell grading, advanced stage, and intratumoral perineural invasion were more prevalent in ASC than the single histology tumor [22]. Surgery is the main treatment of LASC, but the rate of survival at post-surgery is unsatisfactory. In comparison, Maeda et al. had shown that the 5-year survival rate was 23.3% for ASC patients, 58% for AC patients, and 40.8% for SCC patients [6]. The site of lesion is essential for the decision of surgery, and there may be a few mortalities related or consequences of surgery. In our study, the proportion of operation in main bronchus group and peripheral group was 12.14% versus 38.64%, according to subgroup analysis results, surgery is not the major factor for the less OS and CSS between 2 groups(P>0.05). It should be noted that surgery is an independent prognostic factor for LASC, Surgical treatment can improve the survival of patients with LASC [16]. Nowadays, besides surgery, chemotherapy, and radiotherapy, EGFR tyrosine kinase inhibitors may be an alternative treatment for EGFR mutation positive LASC patients [23,24]. Unfortunately, there is no information about gene mutation in the SEER databases. Through the search of the literature in PubMed, there are few articles on EGFR gene mutation in adenosquamous carcinoma of the lung. Despite this, research from a single center showed that LASC patients harboring EGFR mutations who were treated with EGFR-TKIs had a better prognosis than those receiving chemotherapy or chemoradiotherapy alone. Delete in exon 19 and point mutation at codon 858 (L858R) in exon 21 are the 2 most common gene mutations in LASC [23,25]. Additionally, third generation TKI is still useful for the patients harboring T790M with first-generation targeted drug resistance [26].

To our knowledge, this is the first paper to describe tumor location relating to the survival outcomes of LASC. In our study, Kaplan-Meier survival analysis and subgroup analysis showed that patients with LASC located in peripheral sites had better survival outcomes than those located in the main bronchus. The 5-year survival rates of OS and CSS in the peripheral group were higher than in the main bronchus group. Patients of LASC, particularly female patients, other race, AJCC stage I, and those with peripherally located tumors, have a significantly better prognosis. The possible reasons are as follows. First, Watanabe et al. found that larger tumor size, subjective symptoms, and a more advanced disease stage (stage III or stage IV) were more prevalent among main bronchus located LASC than among peripherally located LASC [14]. Second, the frequency of obstructive pneumonia was higher in patients with main bronchus-located tumors than in those with peripherally located tumors, which suggests a poor prognosis [27]. The incidence of LASC varies significantly in different locations, and tumors are most often deemed to be peripheral by radiology [27]. LASC might originate from a peripherally located cancer stem cell [8]. Third, in a previous report, it was shown that main bronchus located LASC had a larger SCC component than peripherally located LASC [27], and the proportion of AC or SCC may have an impact on survival outcomes of LASC. Last but not least, higher SUVmax was also a significant prognostic factor for the recurrence of LASC [7]. Maximum standardized uptake value (SUVmax) is higher in main bronchus-located tumors than in peripherally located tumors. Shimoji et al. found that the SUVmax of main bronchus tumors ranged from 2.0 to 24.5, with a median SUV max of 9.3. In comparison, they found that the median SUVmax of the peripheral tumors was 8.1, which was significantly lower than that of the central tumors [28]. This is in keeping with the results of the previous studies in NSCLC [29].

Not surprisingly, in patients with lung adenocarcinoma, tumor location can be used as a useful predictor for lymph node metastasis and survival outcomes [30,31]. Adenocarcinoma of the lung located in a central location had a high risk of lymph node metastasis and poor prognosis. The situation is different

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for lung squamous cell carcinoma. Serval studies have shown that tumor location was not significantly associated with OS in lung squamous cell carcinoma [32–34]. However, peripheral squamous cell carcinoma of the lung has advantages compared with central lung squamous cell carcinoma, such as an earlier stage, good differentiation, less pleural invasion, less frequent lymph node metastasis, and lymphovascular invasion.

Several limitations of our study deserve mention. First, there was a lack of blood index data, such as tumor markers like carcinoembryonic antigen, cytokeratin-19-fragment; besides, genetic mutation detection (including EGFR, KRAS, ROS1, and BRAF mutation) is very popular among NSCLC patients, which can provide guidance for clinicians to make a reasonable treatment plan. Second, information regarding patients' comorbidities and smoking history is not included because they are not available in SEER databases. Third, this was a retrospective study, as opposed to a randomized experiment. Fourth, PSM might increase the bias due to matching as it does not account for dormant and unobserved confounding variables.

Conclusions

Tumor location may have an impact on the survival outcomes of LASC. Patients with LASC located in a peripheral site had better survival outcomes than those located in main bronchus, particularly in female and AJCC stage I patients.

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