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ORIGINAL SCIENTIFIC REPORT

Lung Adenocarcinoma has a Higher Risk of Lymph Node Metastasis than Squamous Cell Carcinoma: A Propensity Score-Matched Analysis

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Abstract

Background Controversy still exists in which subtype of non-small-cell lung cancer [squamous cell carcinoma (SCC) or adenocarcinoma] is more likely to have lymph node (LN) metastasis. The aim of this study is to compare the pattern of LN metastasis in two cohorts of matched patients surgically treated for SCC or adenocarcinoma.

Methods A retrospective analysis of patients undergoing lobectomy or segmentectomy with systematic lymphadenectomy without preoperative treatment for lung SCC or adenocarcinoma was conducted in this study. Data for analysis consisted of age, gender, tumor size, lobe-specific tumor location, tumor location (peripheral or central), and pathologic findings. We conducted the propensity score-matched (PSM) analysis to eliminate potential bias effects of possible confounding factors.

Results From January 2015 to December 2016 in our department, we finally included a total of 387 patients (including 63 patients with SCC and 324 patients with adenocarcinoma) for analysis. For the unmatched cohort, there was no sufficient evidence of significantly different number of positive LNs ($P = 0.90$) and rate of LN metastasis ($P = 0.23$) between SCC patients and adenocarcinoma patients. However, potential confounding factors, for example gender, tumor size, tumor location, tumor differentiation, and total number of dissected LNs, were significantly different between patients with SCC and those with adenocarcinoma. In the analysis of matched cohort after PSM analysis, those above confounding factors were comparable between the two groups. However, patients with adenocarcinoma had significantly more mean positive LNs (2.2 and 0.7; $P = 0.008$) and a higher rate of LN metastasis (53% and 29%; $P = 0.016$) than those with SCC.

Conclusions Lung adenocarcinoma had a higher risk of LN metastasis than SCC, suggesting that different therapeutic modalities may be indicated for the two different subtypes of lung cancer.

Introduction

Lung cancer still remains to be the leading cause of cancer-related death worldwide, and non-small-cell lung cancer (NSCLC) has accounted for about 80% of all lung cancers, in which squamous cell carcinoma (SCC) and adenocarcinoma are two major histological subtypes [1]. Lung SCC and adenocarcinoma are reported to have different molecular origins and biologies as well as different prognosis [1, 2]. Considering that the status of lymph node (LN) metastasis remains to be an important predictor of poor prognosis of NSCLC [3] and that lung adenocarcinoma is

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now being surgically treated and staged similarly to SCC [4], it is of great value to explore the different tendency of LN metastasis in the two predominant histological subtypes of NSCLC. Regarding the comparison of different pattern of LN metastasis between lung SCC and adenocarcinoma, previous studies have drawn contradictory conclusions. Some found that lung adenocarcinoma was more likely to have LN metastasis than SCC [5–7]. However, on the contrary, some reported that lung SCC had a higher rate of LN metastasis than adenocarcinoma [2, 8]. Moreover, other studies even showed no sufficient evidence of different tendency of LN metastasis between lung SCC and adenocarcinoma [9–12]. Considering that the pattern of LN metastasis in NSCLC correlates significantly with tumor size, tumor location, and differentiation [13], it is reasonable to believe that these above contradictory conclusions could result from those unbalanced confounding factors as mentioned above. Therefore, in this study, we aimed to apply the propensity score-matched (PSM) analysis, which was commonly applied for analyzing causal inference in observational studies to reduce possible bias via balancing potential confounding factors between two groups [14], to draw a relatively objective conclusion of the different pattern of LN metastasis between lung SCC and adenocarcinoma. We applied this method to compare the tendency of LN metastasis between patients with lung adenocarcinoma and patients with SCC, aiming to provide evidence of justifying for offering different surgical therapies and staging strategies for these two major subtypes of NSCLC.

Methods and materials

Patients

We collected the clinicopathologic data of patients who underwent lobectomy or segmentectomy with systematic LN dissection for lung cancer retrospectively from our department between January 2015 and December 2016. Contrast-enhanced chest computed tomography (CT), magnetic resonance imaging or CT of the brain, upper abdominal CT, bone scanning, and cardiopulmonary tests were routinely performed for preoperative assessment in all patients. LN with a short-axis diameter of more than 10 mm on CT scan was defined as positive LN metastasis. For patients with cT1-3N0-1M0 diseases, upfront surgical resection was performed, while for patients with clinical T4 or N2 diseases induction chemoradiotherapy was initially conducted. Inclusion criteria included: (1) patients received lobectomy or segmentectomy with systematic LN dissection; (2) patients with either lung adenocarcinoma or SCC. The patients were excluded as follows: (1) patients who received neoadjuvant chemotherapy, radiotherapy, and/or chemoradiotherapy; (2) patients with synchronous multiple primary lung cancers or secondary pulmonary cancers. Since our study analyzed anonymously and retrospectively, the Ethic Committee waived the need for consent.

We subgrouped those included patients by their histopathology into two groups (SCC group and adenocarcinoma group). The data for analysis consisted of age, gender, lobe-specific tumor size, tumor location, tumor location (peripheral or central), pathologic findings, and status of LN metastasis. Pathological findings included tumor differentiation, degrees of lymphovascular invasion and visceral pleural invasion, and numbers of LNs dissected as well as positive LNs. As for tumor location, tumors were classified into peripherally located tumor and centrally located tumor in accordance with the National Comprehensive Cancer Network guideline, where peripheral one was defined as outer one-third of the hemithorax and central one was defined as within the inner two-thirds of the hemithorax according to the chest CT [15]. Here, we further subgrouped LNs into N1 (hilar/intrapulmonary LNs) and N2 stations (mediastinal LNs) according to the eighth edition of TNM staging system [4].

Statistical analysis

All those data for analysis were presented as number and percentage for categorical data or mean ± standard deviation for continuous variables. For the comparison of categorical data, Fisher's exact test or Chi-squared test was applied, while for those continuously distributed data, Mann–Whitney nonparametric U test or independent-sample Student's t test was used. We used the PSMATCHING 3.04 software and R-2.15.1-win to perform PSM analysis for generating well-matched pairs as we have previously described [14]. The propensity score was developed by a logistic regression model with the covariates consisting of age, gender, tumor size, lobe-specific tumor location, tumor location (peripheral or central), tumor differentiation, visceral pleural invasion, lymphovascular invasion, and total number of LNs dissected. By using the nearest neighbor method, cases selected from the two groups were matched at a ratio of 1:1 with a caliper width of 0.20. Standardized differences between means and proportions were applied to evaluate the differences between the two groups and to test whether an adequate balance was achieved by matching, and a standardized difference of >10% represents meaningful imbalance for a given covariate between the two groups [16]. We performed all these statistical analyses by applying IBM SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). All those P values were reported as 2-sided, and a P value of less than 0.05 was considered as statistical significance.

Results

Comparison of LN metastasis in the unmatched cohort

We included a total of 387 patients (including 63 patients with SCC and 324 patients with adenocarcinoma) who met our inclusion criteria for analysis. The data of the unmatched cohort are shown and compared in Table 1. For patients with adenocarcinoma, the mean age was 58.6 ± 9.7 years and the male/female ratio was 0.8:1, while it was 59.7 ± 8.4 years and 11.6:1, respectively, for those with SCC. No significant difference of age ($P = 0.37$) between the two unmatched groups was found, but significantly more male patients were observed in SCC group than in adenocarcinoma group (92% vs 45.7%; $P < 0.001$). Most of the lung cancers were located in bilateral upper lobes and right lower lobe for both SCC and adenocarcinoma, and there was also no significantly different lobe-specific tumor location between the two groups ($P = 0.12$). Lung SCCs had a significantly larger mean tumor size than adenocarcinomas (mean 4.2 cm vs 2.6 cm; $P < 0.001$), and significantly more SCCs were centrally located than adenocarcinomas (75% vs 43.5%; $P < 0.001$). Most of the lung SCCs (79%) were poorly differentiated, while only about a third of adenocarcinomas (36.7%) were poorly differentiated, and statistically significant difference of tumor differentiation between the SCC group and adenocarcinoma group was found ($P < 0.001$). Only a small number of patients with adenocarcinoma (2.5%) and those with SCC (6%) were found to have lymphovascular invasion, and there was no statistically significant difference of lymphovascular invasion between the two unmatched groups ($P = 0.10$). About half of patients with adenocarcinoma (49.7%) and those with SCC (56%) were found to have visceral pleural invasion, and no statistically significant difference of visceral pleural invasion was also found between SCC group and adenocarcinoma group ($P = 0.39$). However, there were more total LNs dissected in patients with SCC than in patients with adenocarcinoma (mean number 16.5 and 13.1; $P < 0.001$). Standardized difference analysis showed meaningful imbalance in gender, tumor size, tumor location, tumor differentiation, and total number of LNs dissected between the two groups. There was no sufficient evidence of significantly different positive LNs (mean number 1.0 and 1.0; $P = 0.90$) and rate of LN metastasis (25.9% and 33%; $P = 0.23$) between lung SCC group and adenocarcinoma group. When LNs were subgrouped into N1 and N2 stations based on the eighth edition of TNM staging system, for both N1 LNs and N2 LNs, the numbers of dissected N1 and N2 LNs in SCC group were significantly higher than that in adenocarcinoma group, but there was also no sufficient evidence of significantly different number of positive N1 and N2 LNs and rate of N1 and N2 LN metastasis between lung SCC group and adenocarcinoma group (Table 1).

Comparison of LN metastasis in the matched cohort

In order to compare the actual different tendencies of LN metastasis between lung SCC and adenocarcinoma, we applied PSM analysis to match the following covariates: age, gender, tumor size, lobe-specific tumor location, tumor location (peripheral or central), tumor differentiation, lymphovascular invasion, visceral pleural invasion, and total number of LNs dissected. We finally matched a total of 102 patients, and the clinical characteristics of the matched cohort were presented in Table 2. All these baseline characteristics between the two groups were well matched after PSM analysis, and the standardized difference analysis showed that an adequate balance was achieved. However, significant differences in the number of positive LNs and rate of LN metastasis between the two groups were found. Patients with adenocarcinoma showed significantly more positive LNs (mean number 2.2 and 0.7; $P = 0.008$) and a higher rate of LN metastasis (53% and 29%; $P = 0.016$) than those with SCC. Moreover, patients with adenocarcinoma had significantly more positive N1 (mean number 1.0 and 0.5; $P = 0.021$) and N2 LNs (mean number 1.2 and 0.2; $P = 0.009$) and higher rates of N1 (47% and 24%; $P = 0.013$) and N2 LN metastasis (37% and 14%; $P = 0.006$) than those with SCC (Table 2).

Discussion

Lung adenocarcinoma and SCC are two major subtypes of NSCLC, which accounts for over 70% of all NSCLC cases [17, 18]. Evidence has shown that lung adenocarcinoma and SCC are two distinct subtypes of NSCLC with different clinical and molecular features and divergent therapeutic responses [17–19]. However, as for the tendencies of LN metastasis of the two subtypes, previous studies have drawn contradictory conclusions. Therefore, in this study, we applied PSM analysis trying to draw an objective conclusion regarding the comparison of different tendencies of LN metastasis between lung SCC and adenocarcinoma. To our best knowledge, this is the first study focusing on this topic by applying PSM analysis.

In the analysis of the unmatched cohort, we found that there was no sufficient evidence of significantly different number of positive LNs ($P = 0.90$) and rate of LN metastasis ($P = 0.23$) between SCC group and adenocarcinoma group. Moreover, there was also no sufficient evidence of significantly different rate of N1 and N2 LN metastasis

Table 1 Baseline characteristics of unmatched patients with adenocarcinoma and squamous cell carcinoma

Characteristics	Adenocarcinoma (N = 324)	Squamous cell carcinoma (N = 63)	P value	Standardized difference[a] (%)
Age (mean ± SD, years)	58.6 ± 9.7	59.7 ± 8.4	0.37	12.1
Gender			<0.001	
Male	148 (45.7%)	58 (92%)		115.7
Female	176 (54.3%)	5 (8%)		− 115.7
Lobe-specific tumor location			0.12	
Left upper lobe	88 (27.2%)	13 (21%)		− 15.3
Left lower lobe	38 (11.7%)	6 (9%)		7.6
Right upper lobe	114 (35.2%)	17 (27%)		− 17.8
Right middle lobe	25 (7.7%)	8 (13%)		16.5
Right lower lobe	59 (18.2%)	19 (30%)		28.2
Tumor size (mean ± SD, cm)	2.6 ± 1.4	4.2 ± 1.9	<0.001*	95.9
Tumor location			<0.001	
Central	141 (43.5%)	47 (75%)		66.6
Peripheral	183 (56.5%)	16 (25%)		− 66.6
Tumor differentiation			<0.001	
Poor differentiation	119 (36.7%)	50 (79%)		95.8
Moderate differentiation	195 (60.2%)	13 (21%)		− 88.1
Well differentiation	10 (3.1%)	0 (0%)		− 25.2
Lymphovascular invasion			0.10	
Yes	8 (2.5%)	4 (6%)		19.0
No	316 (97.5%)	59 (94%)		− 19.0
Visceral pleural invasion			0.39	
Yes	161 (49.7%)	35 (56%)		11.8
No	163 (50.3%)	28 (44%)		− 11.8
Total number of dissected lymph nodes (mean ± SD)	13.1 ± 6.3	16.5 ± 6.5	<0.001	53.1
Total number of positive lymph nodes (mean ± SD)	1.0 ± 2.5	1.0 ± 2.0	0.90	
Total lymph node metastasis			0.23	
Yes	84 (25.9%)	21 (33%)		
No	240 (74.1%)	42 (67%)		
Total number of dissected N1 lymph nodes (mean ± SD)	5.1 ± 3.6	6.9 ± 4.1	0.001	
Total number of positive N1 lymph nodes (mean ± SD)	0.5 ± 1.2	0.7 ± 1.4	0.25	
N1 lymph node metastasis			0.24	
Yes	66 (20.3%)	17 (27%)		
No	258 (79.7%)	46 (73%)		
Total number of dissected N2 lymph nodes (mean ± SD)	8.0 ± 4.6	9.6 ± 5.1	0.013	
Total number of positive N2 lymph nodes (mean ± SD)	0.5 ± 1.6	0.3 ± 0.9	0.25*	
N2 lymph node metastasis			0.45	
Yes	59 (18.2%)	9 (14%)		
No	265 (81.8%)	54 (86%)		

SD standard deviation

*Mann–Whitney test

[a]Standardized difference: reported for the covariates included in the propensity score-matching process

Table 2 Baseline characteristics of matched patients with adenocarcinoma and squamous cell carcinoma

Characteristics	Adenocarcinoma ($N = 51$)	Squamous cell carcinoma ($N = 51$)	P value	Standardized difference[a] (%)
Age (mean ± SD, years)	59.0 ± 10.3	58.7 ± 8.5	0.72	−3.5
Gender			0.75	
Male	45 (88%)	46 (90%)		6.3
Female	6 (12%)	5 (10%)		−6.3
Lobe-specific tumor location			0.85	
Left upper lobe	12 (24%)	13 (25%)		4.6
Left lower lobe	4 (8%)	5 (10%)		6.9
Right upper lobe	18 (35%)	13 (25%)		4.6
Right middle lobe	7 (14%)	7 (14%)		0
Right lower lobe	10 (20%)	13 (25%)		14.1
Tumor size (mean ± SD, cm)	4.0 ± 1.9	4.0 ± 1.9	1.00	0
Tumor location			0.82	
Central	38 (75%)	37 (73%)		−4.4
Peripheral	13 (25%)	14 (27%)		4.4
Tumor differentiation			0.65	
Poor differentiation	37 (73%)	39 (76%)		9.0
Moderate differentiation	14 (27%)	12 (24%)		−9.0
Well differentiation	0 (0%)	0 (0%)		0
Lymphovascular invasion			0.36[#]	
Yes	4 (8%)	1 (2%)		−27.5
No	47 (92%)	50 (98%)		27.5
Visceral pleural invasion			1.00	
Yes	23 (45%)	23 (45%)		0
No	28 (55%)	28 (55%)		0
Total number of dissected lymph nodes (mean ± SD)	15.2 ± 6.6	15.0 ± 6.1	0.85	−3.1
Total number of positive lymph nodes (mean ± SD)	2.2 ± 3.6	0.7 ± 1.4	0.008*	
Total lymph node metastasis			0.016	
Yes	27 (53%)	15 (29%)		
No	24 (47%)	36 (71%)		
Total number of dissected N1 lymph nodes (mean ± SD)	6.2 ± 3.8	6.2 ± 3.8	0.98	
Total number of positive N1 lymph nodes (mean ± SD)	1.0 ± 1.3	0.5 ± 0.9	0.021*	
N1 lymph node metastasis			0.013	
Yes	24 (47%)	12 (24%)		
No	27 (53%)	39 (76%)		
Total number of dissected N2 lymph nodes (mean ± SD)	9.0 ± 4.4	8.8 ± 4.7	0.76	
Total number of positive N2 lymph nodes (mean ± SD)	1.2 ± 2.5	0.2 ± 0.7	0.009*	
N2 lymph node metastasis			0.006	
Yes	19 (37%)	7 (14%)		
No	32 (63%)	44 (86%)		

SD standard deviation

*Mann–Whitney test; [#]Fisher's exact test

[a]Standardized difference: reported for the covariates included in the propensity score-matching process

between the two groups. However, these results may be biased since they were based on unmatched patients and many confounding factors, such as gender, tumor location (peripheral or central), tumor size and differentiation, and total number of LNs dissected, have not been well balanced during analysis. This may be the reason why previous studies drew contradictory conclusions on the same topic, because most of them had not balanced above confounding factors between the two groups when they were making comparisons [2, 5, 8, 9, 20, 21]. Hence, for further analysis, we used PSM method to balance those confounding factors by generating well-matched patient pairs to decrease potential bias. As a result, one hundred and two well-matched patients have been generated after PSM analysis. However, during the analysis of the matched cohort, we found that patients with adenocarcinoma had significantly more positive LNs ($P = 0.008$) and a higher rate of LN metastasis ($P = 0.016$) than those with SCC. Moreover, patients with adenocarcinoma showed more positive N1 ($P = 0.021$) and N2 LNs ($P = 0.009$) and higher rates of N1 ($P = 0.013$) and N2 LN metastasis ($P = 0.006$) than those with SCC. Therefore, lung adenocarcinoma is more likely to have LN metastasis (including both hilar/intrapulmonary and mediastinal LN stations) than SCC.

Previously, controversy still exists in the comparison of LN metastasis between lung adenocarcinoma and SCC. Kawase et al. [2] have found that SCC patients had significantly higher rate of LN metastasis than adenocarcinoma patients (36% vs 26%; $P < 0.001$). Moreover, in patients with pT1 lung cancer, patients with SCC were also found to have a significantly higher rate of LN metastasis than those with adenocarcinoma (40.3% vs 13.0%; $P < 0.001$) [8]. However, the above studies [2, 8] did not balance confounding factors (such as gender, tumor size, and differentiation) between groups when making comparisons, which could significantly impact the validity of their results. Moreover, even though Kawase et al. [2] reported that lung SCC had more positive LNs than adenocarcinoma, they found significantly more lung cancer-related deaths in patients with adenocarcinoma than in those with SCC ($P = 0.001$), indicating that adenocarcinoma had biologically more aggressive nature than SCC. Even though previous studies [9–13, 21, 22] found that there was no sufficient evidence of significant difference of LN metastasis between lung SCC and adenocarcinoma, most of them [9, 13, 21, 22] reported that the rate of LN metastasis in adenocarcinoma patients was numerically higher than that in SCC patients. Therefore, if given more cases with appropriate adjustments for confounding factors for analysis, these above studies may find the actual different tendency of LN metastasis between lung SCC and adenocarcinoma.

As a result, with relatively large sample size and PSM analysis for adjusting confounding factors, our study found that lung adenocarcinoma was more likely to have LN metastasis than SCC. Previously, Watanabe et al. [23] found that in small-sized ($\leq$2 cm) lung cancers adenocarcinoma had a higher rate of LN metastasis than SCC (22.3% vs 10.0%) and adenocarcinoma had 14.7% incidence of mediastinal LN metastasis, while SCC showed no mediastinal LN metastasis. Interestingly, Ohta et al. [24] also showed that in lung cancers of 2 cm or less the rate of nodal micrometastasis was as high as 21.7% in adenocarcinoma, while no nodal micrometastasis was observed in SCC. Moreover, Lee et al. [25] showed that in clinical stage I lung cancers adenocarcinoma showed a rate of 9.0% of occult N2 metastasis, while there was no occult N2 metastasis in SCC and found that adenocarcinoma was a risk factor for occult mediastinal LN metastasis. These above studies [23, 24] suggested that adenocarcinoma might be more likely to have LN (especially mediastinal LN) metastasis than SCC. Similarly to our study, Oda et al. [5] also found that in clinical stage I lung cancers adenocarcinoma showed a significantly higher rate of mediastinal LN metastasis than SCC (16.5% vs 6.5%; $P = 0.021$), and Funakoshi et al. [6] also found that adenocarcinoma patients were more likely to be upstaged from clinical N0 disease to pathologic N2 disease than SCC patients ($P = 0.04$). Moreover, Kazaki et al. [26] and Saeteng et al. [7] also found that adenocarcinoma was a significant risk factor for mediastinal LN metastasis. Lung adenocarcinoma was even found to have a significantly higher risk of distant metastasis (especially for brain metastasis) than SCC [27, 28]. Previous experimental study has also shown that lung adenocarcinoma was more aggressive and invasive than SCC with a poorer prognosis [29]. Therefore, taken together, our study proved that lung adenocarcinoma had a significantly higher risk of LN metastasis (for both N1 and N2 LNs) than SCC, adding to the evidence that lung adenocarcinoma is more likely to have LN metastasis and thus is more aggressive than SCC. Therefore, our study may justify that different workup strategies may be indicated for lung SCC and adenocarcinoma in the future. For example, prior to surgery, positron emission tomography (PET)/CT scan, brain imaging, and mediastinoscopy may be performed more aggressively for patients with lung adenocarcinoma for preoperative nodal staging. Moreover, neoadjuvant and adjuvant therapy may be more emphasized for adenocarcinoma, and more extensive and aggressive lymphadenectomy might be required for accurate pN staging of clinical stage I lung adenocarcinoma.

Several limitations existed in the study. First, even though our study had a large number of total patients, the matched cohort had a relatively small sample size, which could influence our analytical power. Second, for

preoperative staging, only a small proportion of patients underwent PET/CT because PET/CT examination is extremely expensive and not covered by medical insurance in China yet, and as a result, PET/CT is not routinely performed for every patient with lung cancer in our department. Because of their relatively early-stage diseases, all patients underwent surgical resection of the lung cancers without mediastinoscopy or endobronchial ultrasound. Because in our whole patients, the prevalence of pN2 disease was only about 15% in both groups without significant difference, we think that preoperative nodal staging methods have little impact on study bias during analysis. Moreover, even though there were biases between the two groups before surgery, it could only have impact on results of the unmatched patients but have little impact on results of those matched patients since the baseline characteristics between the matched patients were well balanced. Finally, we found the phenomenon only in Chinese patients, but whether similar results could be found in Western patients requires further investigation since the pathology of lung adenocarcinoma might be different between the two ethnic groups [30]. Therefore, further similar researches applying PSM analysis are badly needed to update and confirm our conclusions.

Conclusions

In this study, we compared the different tendency of LN metastasis between lung SCC and adenocarcinoma through PSM analysis. Lung adenocarcinoma was found to be more likely to have LN metastasis than SCC, which may indicate the need for different therapeutic strategies for the two different tumor entities.

Author's contributions HYD and MZ drafted the manuscript. GL, GA, and JL collected the data. HYD, MZ, LXL, QZ, and YDL revised the manuscript. HYD, GL and YDL designed the study.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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