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Original Article

Comprehensive analysis of clinicopathological profiles in adenosquamous carcinoma of the lung

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Abstract: Objectives: Adenosquamous carcinoma (ASC), an uncommon subtype within non-small cell lung cancer (NSCLC), manifests distinctive traits of aggressiveness, embodying a fusion of both adenocarcinoma (AC) and squamous cell carcinoma (SCC) components. The clinicopathological characteristics of distinct subtypes of ASC remain unclear. Methods: This retrospective study included 226 patients diagnosed with lung ASC who consecutively underwent surgical resection at Shanghai Pulmonary Hospital, Tongji University, between January 2015 and March 2021. Data regarding the clinical features and pathological features were collected. Results: Out of this study cohort, 125 patients exhibited AC-predominant ASC, while 81 had SCC-predominant ASC. No significant differences were observed between the two subgroups in terms of age, gender, smoking history, primary site, and T, N classification. AC-Predominant ASC displayed a higher susceptibility to genetic alterations compared to SCC-Predominant ASC (P=0.02). Additionally, we showed that irrespective of the predominant pathological subtype in ASC, when lymph node metastasis occurred, the lymph node biopsies were more likely to exhibit AC, and a chi-square test confirmed that the primary predominant pathological subtype was not associated with the lymph node metastasis subtype. Conclusions: In conclusion, we describe an overview of ASC in the Chinese population, and upon stratifying into predominant pathological subgroups, we observed a higher frequency of driver gene mutations in AC-predominant ASC. We found that the AC component in ASC has a higher propensity for lymph node metastasis. These findings may suggest the predominant role of the AC component within the context of ASC.

Keywords: Lung adenosquamous carcinoma, surgery resection, pathological subtypes, EGFR, lymph node metastasis

Introduction

Adenosquamous carcinoma (ASC) is a relatively rare subtype within non-small cell lung cancer (NSCLC), accounting for only 0.4% to 4% of all lung cancers [1]. In 1999, the World Health Organization (WHO) set criteria for ASC diagnosis, defining it as a carcinoma with at least 10% each of squamous cell carcinoma (SCC) and adenocarcinoma (AC) components when examined under a light microscope [2]. ASC can be classified into dominant subtypes based on the ratio of glandular and squamous components, namely AC- and SCC-predominant subtypes, each exhibiting distinct features [3].

Studies have indicated that ASC demonstrates a poorer prognosis compared to pure AC or SCC [4-6]. In a recent study involving Asian populations, it was noted that the 5-year overall survival (OS) rate was lower in the ASC group (66.7%) compared to the AC and SCC groups (88.7% and 75.5%, respectively). Likewise, the 5-year recurrence-free survival (RFS) rate in the ASC group was significantly lower than that in the AC and SCC groups (44.9% vs. 86.0% and 62.3%, respectively) [7].

Given the low frequency of this disease, there is a paucity of empirical data available to inform clinical decision-making for ASC. Currently, there is no standardized chemotherapy regimen specifically tailored for ASC, and treatment protocols rely on general NSCLC guidelines. Surgical resection remains the sole effective method for curing ASC. Chemotherapy, radio-

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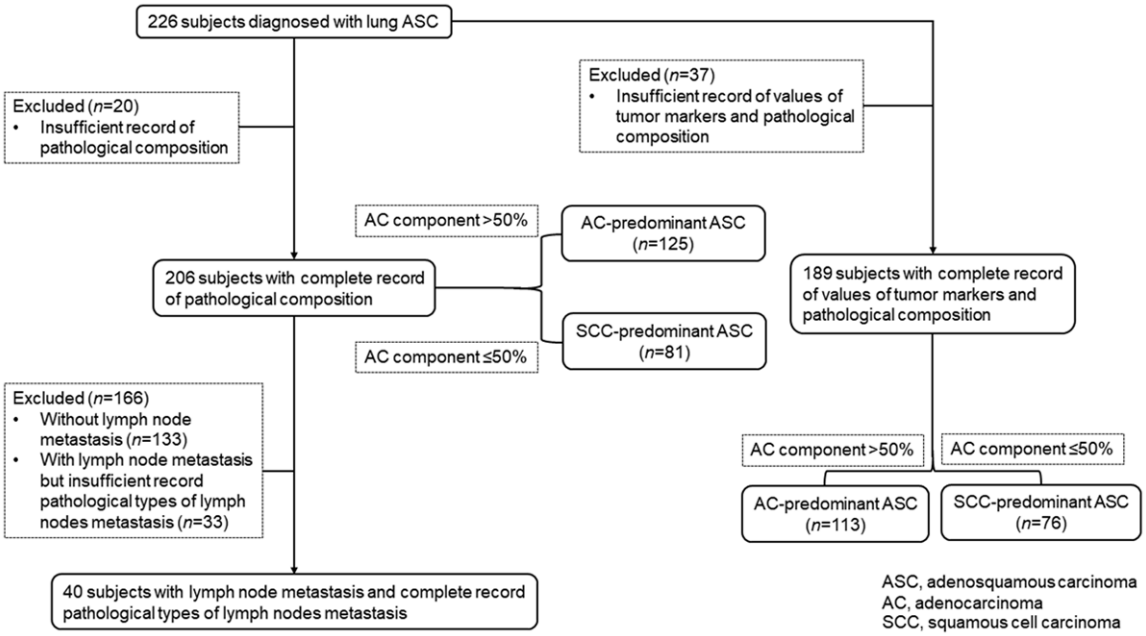

Figure 1. Patient group and protocol.

therapy, targeted therapy and immunotherapy are also used in ASC, however, there is a lack of consensus regarding the treatment regimen for advanced cases [1, 8, 9].

Our study encompassed a relatively large cohort of individuals (n=226), involving an extensive analysis of clinical, pathological, genetic, and molecular characteristics in Chinese patients with lung ASC. This research aims to provide support for future investigations into the treatment of lung ASC.

Materials and methods

Patients

In this retrospective study, 226 patients diagnosed with ASC underwent consecutive surgical resection at Shanghai Pulmonary Hospital, Tongji University, from January 2015 to March 2021 (**Figure 1**). Demographic and clinical characteristics including gender, age, smoking history, pathological features, molecular diagnosis, mutation status, primary site, and tumor, node, metastases (TNM) stages (the International Association for the Study of Lung Cancer 8th version) were collected. The study followed the principles outlined in the Declaration of Helsinki (2013 revision). Approval for the research was obtained from the Ethics Committee of Shanghai Pulmonary Hospital (K21-313Y).

Pathological diagnosis

Two experienced pathologists reviewed the pathological diagnoses of lung ASC by H&E staining or immunohistochemistry according to the WHO criteria, confirming that each component of AC and SCC represented at least 10% of tumor cells [2]. The morphological characteristics of AC and SCC were detailed as follows: AC typically exhibited acinar, lepidic, micropapillary, or papillary structures, whereas SCC displayed characteristics such as discernible keratinization, pearl formation, and/or intercellular bridges.

In this study, we stipulated that if the AC component was less than or equal to 50%, the ASC would be classified as SCC-predominant. Conversely, if the AC component exceeded 50%, the ASC would be categorized as AC-predominant (**Figure 2**) [3].

Driver alteration analysis

At the Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, we examined genomic alterations in driver genes such as epidermal growth factor receptor (*EGFR*),

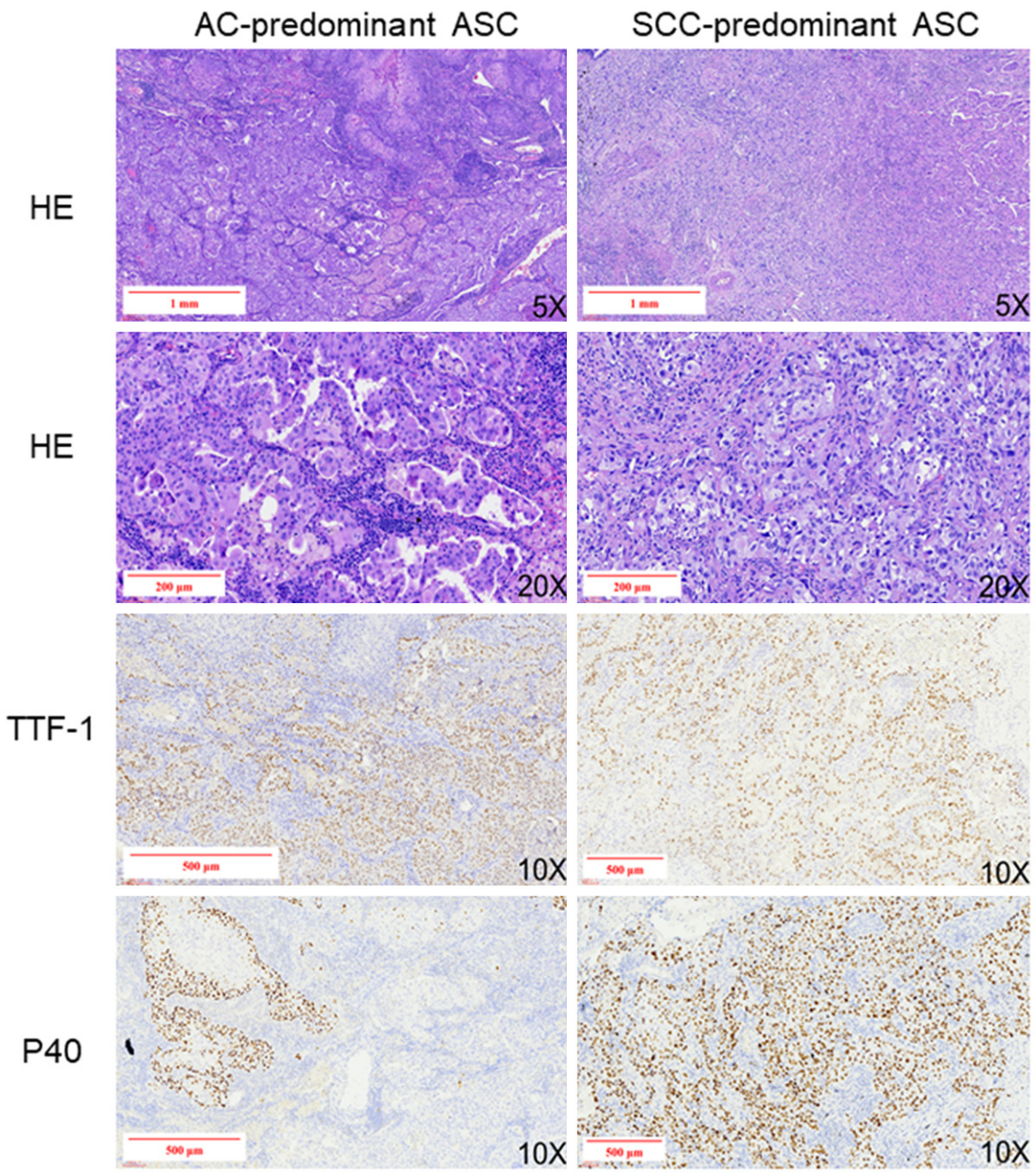

Figure 2. Representative images of immunohistochemistry staining for hematoxylin and eosin (H&E), thyroid transcription factor-1 (TTF-1) and DeltaNp63 (P40) in resected tumor tissues of lung ASC. ASC, adenosquamous carcinoma; SCC, squamous cell carcinoma; AC, adenocarcinoma.

Kirsten rat sarcoma viral oncogene (*KRAS*), ROS proto-oncogene 1 (*ROS1*), and anaplastic lymphoma kinase (*ALK*). Briefly, tumor tissue DNA extraction was performed using the DNeasy Blood and Tissue Kit or the QIAamp DNA FFPE Tissue Kit (both purchased from Qiagen, Hilden, Germany). Consistent with our earlier research protocols, the mutation status was determined using the amplification refractory mutation system method provided by Amoy Diagnostics Co Ltd, Xiamen, China [10, 11].

Statistical analysis

We conducted statistical analyses using SPSS 27.0 (SPSS, Chicago, IL) and Prism 9.0 (GraphPad Software Inc., La Jolla, CA, USA). Group comparisons were performed using either

Table 1. Clinicopathologic features of patients with ASC of the lung[a]

Variable	ASC Total (N, %)
Age (y) (mean ± SD)	63.0±8.7
Gender	
Male	130 (57.5%)
Female	96 (42.5%)
Smoking history	
No	173 (76.5%)
Yes	53 (23.5%)
Histological type[b]	
AC-Predominant	125 (55.3%)
SCC-Predominant	81 (35.8%)
Unknow	20 (8.8%)
Primary site[c]	
LLL	27 (11.9%)
LUL	66 (29.2%)
RLL	42 (18.6%)
RML	12 (5.3%)
RUL	79 (35%)
T-stage	
T1	113 (50%)
T2	83 (36.7%)
T3	18 (8%)
T4	12 (5.3%)
N-stage	
N0	150 (66.4%)
N1-2	76 (33.6%)
TNM-stage	
I	120 (53.1%)
II	44 (19.5%)
III	62 (27.4%)
Mutation status[d]	
EGFR mutation	110 (48.7%)
KRAS mutation	6 (2.7%)
ALK rearrangement	5 (2.2%)
ROS1 rearrangement	1 (0.4%)
No mutations	91 (40.3%)
Unknow	13 (5.8%)
EGFR mutation type	
19del	57 (25.2%)
L858R	37 (16.4%)
L858R/T790M	3 (1.3%)
G719X	3 (1.3%)
19del/T790M	2 (0.9%)
20ins	2 (0.9%)
G719X/L861Q	2 (0.9%)
L861Q	2 (0.9%)
L858R/S768I	1 (0.4%)
T790M	1 (0.4%)
Wild-type	103 (45.6%)
Unknow	13 (5.8%)

[a]Values are numbers (percentages), and percentages may not total 100 because of rounding. ASC, adenosquamous carcinoma. [b]SCC, squamous cell carcinoma; AC, adenocarcinoma. [c]LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe. [d]EGFR, epidermal growth factor receptor; KRAS, Kristen rat sarcoma viral oncogene; ALK, anaplastic lymphoma kinase; ROS1, ROS proto-oncogene 1.

Student t-test or Wilcoxon's rank sum test. Categorical variables were assessed through contingency table analysis, Fisher's exact test, and chi-squared tests. Statistical significance was defined as a two-sided *P*-value of less than 0.05.

Results

Overall clinical and pathological features of patients

Our study gathered data on 226 patients from Shanghai Pulmonary Hospital who underwent surgical resection for lung cancer between January 2015 and March 2021, with pathological specimens confirming ASC. Upon analyzing the entire patient dataset (**Table 1**), we discerned that the average age was 63 years. Males predominated over females. Most of the patients had no history of smoking (76.5%). The most common primary tumor location was the right upper lobe of the lung (35%). The majority of the tumors were at stage T1 (50%), with only a few having lymph node metastasis (33.6%). Based on the 8th edition of lung cancer staging, most patients were at stage I (53.1%).

Comparison of clinical and pathological features between AC-predominant ASC and SCC-predominant ASC patients

Of the 226 patients with ASC, 206 had pathological reports that detailed the proportional composition of AC and SCC. The main component of 125 cases was AC, while 81 were predominantly SCC. A comparative analysis based on age, gender, smoking history, primary tumor location, T stage, N stage, and TNM staging revealed no statistically significant differences (**Table 2**). This indicates that there were no discernible differences in the clinical and patho-

Table 2. Comparison of clinical and pathological features between AC-predominant ASC and SCC-predominant ASC patients[a]

Variable	AC-predominant (n=125)	SCC-predominant (n=81)	*p*-value[b]
Age (y) (mean ± SD)	63.3±8.5	62.8±8.6	0.695
Gender			0.112
Male	67 (53.2%)	53 (66.3%)	
Female	58 (46.4%)	28 (34.6%)	
Smoking history			0.064
No	102 (81.6%)	57 (70.4%)	
Yes	23 (18.4%)	24 (29.6%)	
Primary site[c]			0.165
LLL	16 (12.8%)	9 (11.1%)	
LUL	30 (24%)	28 (34.6%)	
RLL	21 (16.8%)	17 (21%)	
RML	6 (4.8%)	6 (7.4%)	
RUL	52 (41.6%)	21 (25.9%)	
T-stage			0.178
T1	68 (54.4%)	33 (40.7%)	
T2	42 (33.6%)	35 (43.2%)	
T3	10 (8%)	6 (7.4%)	
T4	5 (4%)	7 (8.6%)	
N-stage			0.477
N0	80 (64%)	53 (65.4%)	
N1-2	45 (36%)	28 (34.6%)	
TNM-stage			0.327
I	67 (53.6%)	38 (46.9%)	
II	27 (21.6%)	15 (18.5%)	
III	31 (24.8%)	28 (34.6%)	
Mutation status[d]			0.02
EGFR mutation	66 (52.8%)	34 (42%)	
KRAS mutation	4 (3.2%)	0 (0%)	
ALK rearrangement	3 (2.4%)	2 (2.5%)	
ROS1 rearrangement	1 (0.8%)	0 (0%)	
No mutations	43 (34.4%)	44 (54.3%)	
Unknow	8 (6.4%)	1 (1.2%)	

[a]Values are numbers (percentages), and percentages may not total 100 because of rounding. ASC, adenosquamous carcinoma; SCC, squamous cell carcinoma; AC, adenocarcinoma. [b]Categorical variables were compared using contingency table analysis, Fisher's exact test and chi-squared tests. A two-sided P<0.05 was considered statistically significant. [c]RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; [d]EGFR, epidermal growth factor receptor; KRAS, Kristen rat sarcoma viral oncogene; ALK, anaplastic lymphoma kinase; ROS1, ROS proto-oncogene 1.

logical characteristics between the two types of patients in our study.

AC-predominant ASC showed higher susceptibility to genetic alterations

Out of the 226 ASC patients, 216 underwent genetic testing. Among them, 122 were found to have driver gene alterations, including *EGFR* mutation, *KRAS* mutation, *ALK* rearrangement and *ROS1* rearrangement. Among patients with EGFR mutations, the most frequent ones were 19del and L858R (**Table 2**) (**Figure 3A**, **3B**). After excluding the 20 patients for whom detailed pathological composition data were unavailable, a notable statistical difference emerged between AC-Predominant ASC and SCC-Predominant ASC (**Figure 3C**, **3D**). Specifically, AC-Predominant ASC displayed a higher susceptibility to genetic mutations compared to SCC-Predominant ASC.

Serum tumor marker levels exhibit no variation among ASC subtypes.

Among the 206 patients with documented proportional composition of AC and SCC, 189 had complete records for serum tumor markers such as carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), cytokeratin fragment antigen 21-1 (CYFRA21-1), and squamous cell carcinoma antigen (SCCA) (**Table 3**). A previous study suggested that CYFRA21-1 combined with CEA assists in diagnosing AC, while CYFRA21-1 combined with SCCA assists in diagnosing SCC [12]. We aimed to determine if dominant components in ASC correlate with their respective tumor marker levels. Unfortunately, independent sample t-test results showed no statistically significant differences.

The AC component is more prone to lymph node metastasis compared to the SCC component in pulmonary ASC

Among the 206 patients with documented proportional composition, 40 exhibited lymph node metastasis and had corresponding lymph node biopsy pathological records (**Table 4**;

Figure 3. The profile of gene alterations in ASC of the lung. A. The profile of gene alterations in all cases. B. Subtype distribution in cases with EGFR mutations. C. The profile of gene alterations in AC-predominant ASC. D. The profile of gene alterations in SCC-predominant ASC. ASC, adenosquamous carcinoma; SCC, squamous cell carcinoma; AC, adenocarcinoma; EGFR, epidermal growth factor receptor; KRAS, Kristen rat sarcoma viral oncogene; ALK, anaplastic lymphoma kinase; ROS1, ROS proto-oncogene 1.

Table 3. Serum tumor marker levels of AC-predominant and SCC-predominant ASC patients[a]

Tumor marker[b]	AC-predominant (n=113)	SCC-predominant (n=76)	*p*-value[c]
CEA (mean ± SD)	12.4±25.8	7.1±10.1	0.053
NSE (mean ± SD)	13.5±3	13.8±3	0.441
CYFRA21-1 (mean ± SD)	3.1±5.2	3.7±3.7	0.432
SCCA (mean ± SD)	1.2±0.2	1.4±1.5	0.095

[a]ASC, adenosquamous carcinoma; SCC, squamous cell carcinoma; AC, adenocarcinoma; [b]CEA, carcinoembryonic antigen (ng/ml); NSE, neuron-specific enolase (ng/ml); CYFRA21-1, cytokeratin fragment antigen 21-1 (ng/ml); SCCA, squamous cell carcinoma antigen (ng/ml). [c]Categorical variables were compared using contingency table analysis, Fisher's exact test and chi-squared tests. A two-sided P<0.05 was considered statistically significant.

Table 4. Pathological features of lymph node biopsies after lymph node metastasis in AC-predominant and SCC-predominant ASC patients[a]

Histological type of primary lesion	Histological type of metastasis lymph node		
	AC (n=31)	SCC (n=7)	Mixed (n=2)
AC-predominant ASC (n=24)	20 (83.3%)	3 (12.5%)	1 (4.2%)
SCC-predominant ASC (n=16)	11 (68.8%)	4 (25%)	1 (6.3%)
Fisher-Freeman-Halton precise test[b]		P=0.590[c]	

[a]Values are numbers (percentages), and percentages may not total 100 because of rounding. ASC, adenosquamous carcinoma; SCC, squamous cell carcinoma; AC, adenocarcinoma. [b]Categorical variables were compared using Fisher-Freeman-Halton precise test. A two-sided P<0.05 was considered statistically significant. [c]P>0.05 confirmed that histological type of metastasis lymph node of different primary predominant pathological subtype was not considered statistically significant.

Figure 4). Out of these 40 patients, 24 were AC-predominant, with 20 lymph node biopsies showing AC, 3 indicating SCC and 1 with concurrent AC and SCC. Of the 16 SCC-predominant patients, 11 biopsies displayed AC, 4 indicated SCC and 1 with concurrent AC and SCC. Our analysis revealed that, irrespective of the predominant pathological subtype in ASC,

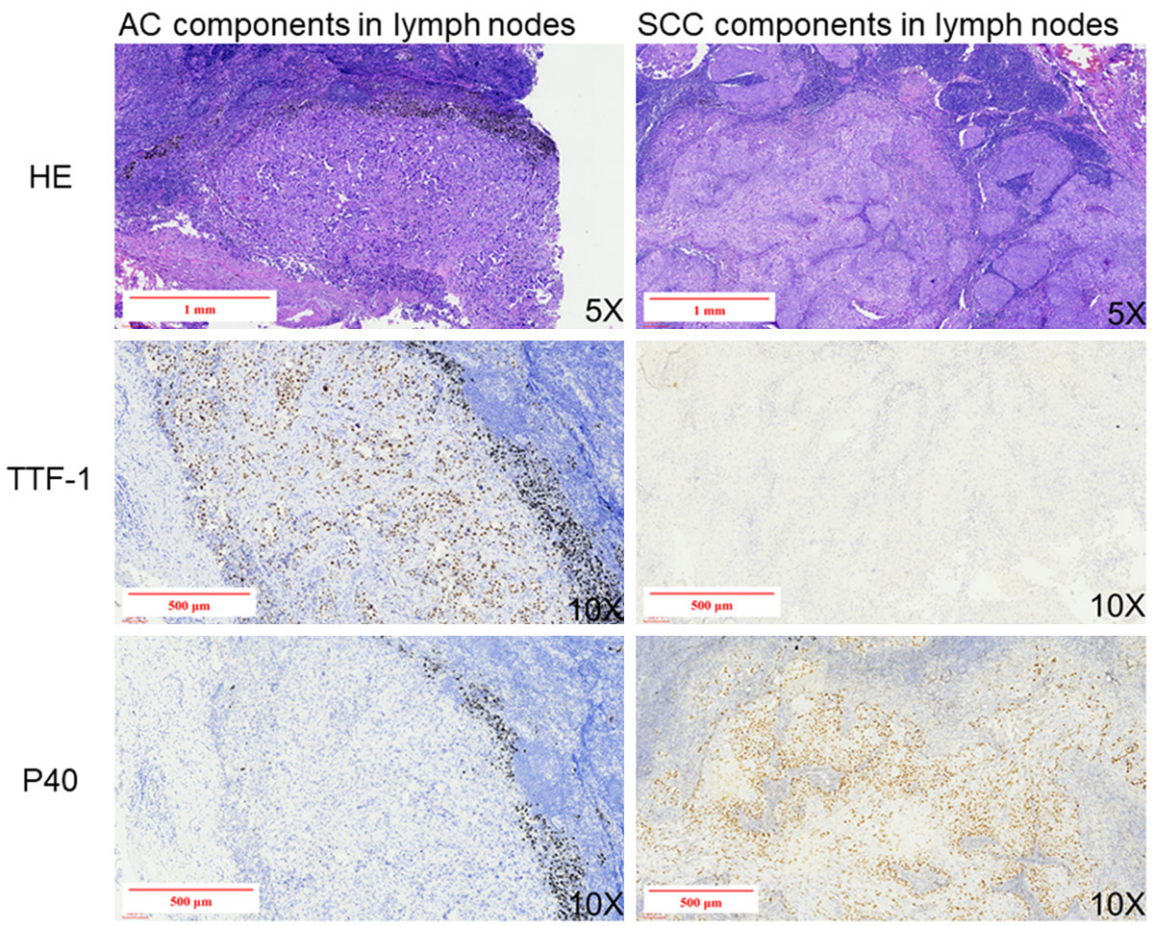

Figure 4. Representative images of immunohistochemistry staining for hematoxylin and eosin (H&E), thyroid transcription factor-1 (TTF-1) and DeltaNp63 (P40) in resected tissues of lymph node metastasis. SCC, squamous cell carcinoma; AC, adenocarcinoma.

when lymph node metastasis occurred, the lymph node biopsies were more likely to exhibit AC, and a chi-square test confirmed that the primary predominant pathological subtype was not associated with the lymph node metastasis subtype.

Discussion

We conducted an analysis of the overall clinical and pathological characteristics of lung ASC and found that the majority of patients were elderly and had no history of smoking. Subsequent intergroup comparisons based on dominant pathological classifications of ASC, such as age, gender, smoking history, TNM stage, and other factors, did not reveal statistically significant differences. This outcome aligns with findings from some prior research studies [3, 7, 13].

In this study, the EGFR mutation rate of 48.7% in the total population is similar to several previous results of *EGFR* mutation rate in Chinese ASC patients (48-55.1%) [13-15]. According to the PIONEER study, the overall *EGFR* mutation frequency of lung AC for the mainland China subset was 50.2% [16]. However, the *EGFR* mutation rate of patients with lung SCC is much lower, about 4.2-23.8% only [17]. The *EGFR* mutation rate of ASC is more like that of AC. The implication is that EGFR-TKIs can be employed as a treatment option for ASC, mirroring their use in AC. In a comprehensive retrospective series study assessing the effectiveness of EGFR-TKIs in EGFR-mutant ASC patients, a median progression-free survival (PFS) of 10.1 months [95% confidence interval (CI): 9.0-11.2 months] was reported [18]. Among patients with adenocarcinoma who received EGFR-TKIs, the tumor response rate ranged from 50% to

80%. The median PFS ranged from 10 to 14 months [19-22]. These studies demonstrated that the efficacy of EGFR-TKI treatment in EGFR-positive ASC was comparable to that observed in conventional lung adenocarcinoma.

Furthermore, we observed that AC-predominant ASC is more likely to exhibit driver gene alterations, resembling the pattern observed in pure AC. Reviewing the origin of ASC, there is no definitive conclusion, but it is supported by several studies that AC and SCC components of ASC shared clonal origins and could disseminate separately during tumor evolution [23, 24]. In addition, other studies have suggested that driver positive ASC could originate from AC cells. The reported differences in SCC proportion within ASC cases upon clinical diagnosis signify the degree of transition towards squamous cell characteristics. Therefore, some researchers propose the hypothesis that, in AC cells with driver gene mutations, which serve as the origin of ASC, the proportion of subsequent squamous cell transition increases during progression [23-25].

Through an analysis of four tumor markers, CEA, NSE, CYFRA21, and SCCA, we aimed to explore the relationship among different subtypes of lung ASC. Given the variation in the adenocarcinoma-squamous cell ratio within ASC, we hypothesized that tumors with a predominant adenocarcinoma component might exhibit higher expression levels of adenocarcinoma-associated tumor markers, and it is the same for squamous cell carcinoma. Unfortunately, the hypothesis was not confirmed. Some studies have suggested a correlation between CEA levels and the recurrence of ASC [7, 13]. It is with regret that a significant portion of our study's patients lacked postoperative follow-up and treatment information, and there was a lack of prognostic data tracking.

Subsequently, in the cases of ASC with lymph node metastasis, we conducted an analysis of the predominant pathological component of ASC and its corresponding lymph node metastasis's pathological characteristics. To our surprise, we found that regardless of whether the ASC's pathological type was predominantly AC or SCC, after the occurrence of lymph node metastasis, the lymph node biopsy's pathological nature was more likely to be AC. This may suggest that the AC component within ASC is more prone to lymph node metastasis. There was a previous study conducted with a limited sample size also found that AC was the dominant component of lymph node metastasis [26]. A study reconstructed phylogenetic trees using a maximum parsimony approach based on single-nucleotide variants and copy number variations (CNVs) in both primary and lymph node samples, suggesting that lymph node metastasis may be initiated by tumor cells of the corresponding pathological type [23]. Further research is needed to elucidate the reasons behind the higher propensity of AC components compared to SCC components for lymph node metastasis.

Conclusion

In summary, our study provides a retrospective analysis of the clinical history and pathological characteristics of 226 ASC patients in the Chinese population. We describe an overview of ASC in the Chinese population, and upon stratifying into predominant pathological subgroups, observed a higher frequency of driver gene mutations in primary AC-predominant ASC. Additionally, we found that the AC component in ASC has a higher propensity for lymph node metastasis. These findings may suggest the predominant role of the AC component within the context of ASC.

Acknowledgements

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Disclosure of conflict of interest

None.

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