

Adenosquamous carcinoma of the lung

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Abstract: Adenosquamous carcinoma of the lung (ASC), a relatively rare subtype of non-small-cell lung cancer, is defined as a malignancy containing components of lung adenocarcinoma (ADC) and lung squamous cell carcinoma (SCC). Although ASC has biological characteristics of ADC and SCC, it is not by any means a simple hybrid of two components above. It is extremely difficult to diagnose preoperatively; pathology of surgically resected gross specimen is the most effective means for adequate diagnosis of ASC. Platinum-based postoperative adjuvant chemotherapy for at least four cycles can significantly improve the survival in stage III patients with ASC. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) such as erlotinib and gefitinib can be the effective therapeutic strategies for advanced EGFR-mutant ASC. The studies of crizotinib in the treatment of patients with ASC are very limited. Immune checkpoint blockade therapy may be a potential treatment choice for ASC patients.

Keywords: adenosquamous carcinoma of the lung, clinicopathological characteristics, histogenesis, prognosis, chemotherapy, targeted therapy, immunotherapy

Introduction

Adenosquamous carcinoma of the lung (ASC) is a subtype of non-small-cell lung cancer (NSCLC), containing components of lung adenocarcinoma (ADC) and lung squamous cell carcinoma (SCC). Prior to 1999, the definition of ASC was a debatable point (Table 1). On one hand, although investigators reached consensus on the presence of definite components of ADC and SCC in ASCs, they disagreed over the cutoffs for the proportion of each component. The first diagnostic criterion for ASC was published in 1978 by the Japan Lung Cancer Society, which suggested that components of SCC and ADC should account for at least 20% of the tumor tissue examined using H&E staining under the light microscope.¹ In 1981, the WHO published a second edition of Histological Typing of Lung Tumors, which did not stipulate the proportion and differentiation of two components for ASCs.² Based on these standards, in 1985, Fitzgibbons and Kern³ have suggested that in the diagnosis of a squamous component, a simple “pavementing” appearance does not suffice, that is, intracellular keratinization in the form of keratin pearl or intercellular bridges should be observed; similarly for ADC components, glandular, papillary, or tubular structures should be observed within the tumor. Nonetheless, under this rigorous classification, the incidence of ASC has shown to be only 0.6% (7/1,125). Conversely, another study have relied on electron microscope instead of light microscope for diagnosing ASCs.⁴ McDowell et al⁵ have reported that, based on the ultrastructural appearance, >46% of lung carcinomas are ASCs, which further caused great disparity in the incidence of ASC. In 1999, WHO uniformed the definition of ASC as a carcinoma containing components of both SCC and ADC, which is diagnosed when each component constitutes at least 10% of the tumor under a light microscope. This definition was published in 2015, in the fifth

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Table 1 Development of definition of ASC

Author	Year of publication	Main points
The Japan Lung Cancer Society ¹	1978	Components of SCC and ADC should account for at least 20% of the tumor
WHO ²	1981	Diagnosis of ASC can be established once components of ADC and SCC are identified
Fitzgibbons and Kern ³	1985	Diagnosis of components of ADC and SCC must be based on the corresponding typical characteristics
WHO ⁶	1999	Each component constitutes at least 10% of the tumor under a light microscope

Abbreviations: ADC, adenocarcinoma; ASC, adenosquamous carcinoma of the lung; SCC, squamous cell carcinoma.

edition of WHO Classification of Lung Cancer and is currently valid;⁶ nevertheless, it still causes controversies among some of the researchers.⁷

ASC is a malignancy with low incidence, strong aggressiveness and poor prognosis. There is no unified standard chemotherapy for ASC, and current treatment options rely on the NSCLC guidelines; surgical resection is the only effective means to cure ASC. The following review focuses on the clinicopathological characteristics, histogenesis and treatment of ASC.

Clinicopathological characteristics of ASC

ASC is a relatively rare subtype of lung carcinoma, which accounts for 0.4%–4% of all lung carcinomas.⁶ The proportion of ASC in lung carcinoma reported by different countries has no significant dissimilarities with that reported by WHO.^{8–13} Many studies have shown that ASC occurs more likely in men, while the proportion of patients with ADC and SCC varies.^{8,12–14} Maeda et al¹² have identified 114 ASC cases in 4,668 postoperative patients with pulmonary malignancy, indicating that the ratio of male to female was 3.38:1 (ADC: 1.13:1; SCC: 10.9:1), and the average age at the time of diagnosis of ASC was higher compared to age at the diagnosis of ADC (68.7 and 65.2 years, respectively, $P < 0.0001$). Furthermore, high rates (74.4%–88.5%) of smoking in patients with ASC have been confirmed by many studies.^{9,12,15} Watanabe et al⁹ have analyzed 52 surgically resected ASC patients and have shown a decrease in proportion of smoking among females compared to males (42% and 94%, respectively). Interestingly, the two proportions were above the corresponding smoking rates counted among female and male patients with lung carcinoma in a larger cohort study (22.9% and 88.5%, respectively), which included 26,957 patients with NSCLC.¹⁶ To summarize, ASC is more prevalent in older male smokers (Table 2).

Making a definite preoperative diagnosis of ASC is very difficult. Biopsy sections usually contain only ADC or SCC components because of sample limitation. Jin et al¹⁷ have

retrospectively analyzed preoperative serum carcinoembryonic antigen (CEA) and SCC antigen levels in patients with lung cancer, suggesting that increased levels of CEA and SCC antigen in patients with ADC could be potential predictors of ASC. Nevertheless, pathology on surgically resected gross specimen is considered the most effective means to make an adequate diagnosis of ASC. Mordant et al¹⁰ have reviewed 141 ASC cases and have found that only three patients (2%) were diagnosed with ASC before surgery, while more than half of the patients had no available diagnosis until operation.

According to different proportions of the two components, ASC is further subdivided into three subtypes: ADC-predominant ASC (the proportion of ADC $\geq 60\%$ of tumor), SCC-predominant ASC (the proportion of SCC $\geq 60\%$ of tumor) and structure-balanced ASC (the proportion of ADC and SCC is between 40% and 60%).^{11,15} Zhao et al¹⁸ and Gawrychowski et al¹⁵ have found that structure-balanced ASC had a better prognosis compared to other types. It is generally accepted that radiographic features of ASC are non-specific in comparison with other types of lung cancer. However, some studies have shown that ASC has its own characteristics in iconography (Table 2). With regard to

Table 2 Clinical characteristics of ASC

Clinical factors	Characteristics
Morbidity	0.4%–4% of all lung carcinomas ⁶
Sex	Mainly males ^{8,12–14}
Average age at the time of diagnosis of ASC	68.7 years ¹²
Smoking history	Most patients with ASC have smoking history ^{9,10,12,15}
Location in CT findings	Peripheral types more than central ⁹
Pathological subtype	
ADC-predominant	Mainly peripheral located; ^{9,19,20} peripheral GGO can be a predictive marker ²¹
SCC-predominant	Mainly central located ^{9,19,20}
Structure-balanced	Has a better prognosis compared to other types ^{15,18}

Abbreviations: ADC, adenocarcinoma; ASC, adenosquamous carcinoma of the lung; CT, computed tomography; GGO, ground-glass opacity; SCC, squamous cell carcinoma.

computed tomography (CT) findings, ASC is more likely to be manifested as peripheral than central.⁹ Previous studies have also indicated that central ASC squints are SCC-predominant, while peripheral ASC squints tend to be ADC-predominant.^{9,19,20} In a retrospective study, Lee et al²¹ have identified a larger central ASC compared to peripheral types (5.7 ± 1.2 cm and 3.4 ± 1.8 cm, respectively), while the foci with diameter >5 cm were considered poor prognostic predictors.⁹ Furthermore, the study suggested that peripheral ground-glass opacity (GGO), as seen on CT, could be one of the predictive markers of AC-predominant ASC, especially in cases where a diagnosis of SCC with peripheral GGO is based on a biopsy specimen. CT imaging revealed that spiculate was more frequent in peripheral tumors than in central ones.²¹ In addition, centrally located ASCs tended to reveal inflammatory changes surrounding the foci ($P<0.005$), which predicted a poor prognosis, and it was irrelevant to the component that was dominant in the tumor.⁹

Histogenesis

Histopathology and molecular pathology have verified that distinct subtypes of lung cancer have different cell origins. Classic theory presumed that ADC arises from type II alveolar epithelial cells (AT II), while SCC originates from basal cells in more proximal bronchus.²²⁻²⁴ However, it still remains unclear whether ASC is a simple patchwork of ADC and SCC. Many studies have shown that at the molecular level, ASC is more complex than previously assumed. Shimoji et al²⁵ have divided 21 postoperative ASCs into four groups based on their expression of thyroid transcription factor-1 (TTF-1) and p63: TTF-1+/- and p63+/- . CEA expression was found in each ASC. Nonetheless, its staining intensity differed among distinct areas, various ADC components and a higher expression in SCC's as well as the strongest immunoreactivity present in solid carcinoma nest centers and especially necrotic parts, and thus suggesting that ASC is a heterogeneous tumor. Bastide et al²⁶ have made transcriptomics analyses on primary rat lung carcinomas that were induced by radon progeny inhalation. In 19 lung cancer tissue specimens, five were ADCs, five were SCCs and the others were ASCs. The results showed that there were 72 differently expressed genes between ADCs and SCCs (39 genes differentiated ADCs from ASCs and 40 genes discriminated between SCCs and ASCs). Moreover, ASC tended to be a "pure" hybrid type of ADC and SCC, because ASCs were classified as intermediate between ADC and SCC, since the portion of ASC resembled ADC and others were more similar to

SCC. Nonetheless, it is noteworthy that some genes with an important role in tumorigenesis were observed in ASC, including abnormal expression of genes involved in extra-cellular regulated protein kinases (ERK) activation pathway and neuroendocrine differentiation, which could partly explain the relatively high invasiveness ability of ASC.²⁶ Shu et al²⁷ have retrospectively investigated the thymidylate synthase (TS) expression by immunohistochemistry (IHC) in surgically resected ADCs ($n=121$), SCCs ($n=17$) and ASCs ($n=19$) and have found that the average H-score of TS expression in ASC roughly equaled that of SCC, but significantly exceeded that of ADC. Furthermore, in ASC samples, there was no prominent difference in TS expression between squamous components and glandular components. Also, higher levels of TS expression frequently presaged poorer efficacy of pemetrexed.²⁸ Meanwhile, Shu et al have found two mutations, ie, epidermal growth factor receptor (EGFR) mutations and six harboring kirsten rat sarcoma 2 viral oncogene homolog (KRAS) mutations, respectively, in 19 ASC specimens, with mutations present in both components.²⁷ Similar results have also been observed by Tochigi et al.²⁹ To sum up, based on these data, we could conclude that ASC is not a hybrid of ADC and SCC, but a cancer with more complicated histogenesis at the molecular level.

Based on histogenesis, theories related to the possible histogenic pathways of ASC can be roughly divided into three categories: bipotential undifferentiated cell origin, transitional state and "collision".

Bipotential undifferentiated cell origin

Large-scale sequencing analyses of solid tumors have confirmed that extensive heterogeneity exists in solid cancers between individual tumors, and intratumoral heterogeneity has also been identified in gene,³⁰ including in lung cancer. Occurrence of intratumoral gene mutations of monoclonal origin can be compared to growth of the trees, which in the beginning only have trunks and then branches continue to constantly grow out.³⁰ Driver mutations tend to be in the trunk of neoplastic evolutionary tree, whereas passenger mutations in the branch. This theory implies that ASC derives from a bipotential undifferentiated cell and then differentiates into ADC and SCC. Vassella et al²² have analyzed the mutational profile in each component among 16 Caucasian ASC samples by laser capture microdissection (LCM), fluorescence in situ hybridization (FISH) as well as next-generation sequencing (NGS). The results revealed a higher prevalence of EGFR and PI3K pathway-concerned mutations (31.25% and 25%, respectively) in contrast with classic Caucasian ADC and

SCC, and the same EGFR mutations were contained in both components, while no KRAS mutations were observed. Moreover, this study showed centralization of drive mutations in the trunk and a high incidence of branch mutations in ASC, suggesting that ASC arose from a common precursor cell, which was in line with findings obtained in other studies,^{29,31,32} while the separation of ADC and SCC components may have taken place very early during the proceeding of ASC.²² According to Niho et al,³³ clonal analyses have been carried out on both components of ASC tissues based on the human androgen receptor gene (*HUMARA*), an X-chromosome-linked polymorphic marker. All four cases exhibited either “long pattern” or “short pattern” and each component had same monoclonal pattern, except for one in which loss of heterozygosity (LOH) in *HUMARA* locus was found only in SCC component. Amplification of *HUMARA* in SCC component did not occur after methylation-sensitive restriction enzyme HpaII digestion, indicating identical pattern to ADC component. Mather et al³⁴ have isolated specific cancer stem-like cells (CSLC) co-expressing cytokeratin 5 and 7 (CK5, CK7) from patients with ASC and cultured them in vitro, which were then implanted in immune-deficient mice. Original ASC morphology was rebuilt, and xenograft cells expressed majority of CK5+/CK7-, CK5-/CK7+ or CK5-/CK7-, supporting a common origin of a single cell that had the potential to differentiate into either ADC-like or SCC-like carcinoma of ASC. Additionally, markers of basal cells, Clara cells, bronchial epithelial cells, pneumocytes and neuroendocrine cells were found in xenografts derived from ASC-CSLC, suggesting that the single cell may be a bi- or multi-potential lung stem cell instead of a stem cell located on the border of basal cells and alveolar epithelial cells.

A transitional state between ADC and SCC

Some studies have suggested that ASC is a transitional stage between ADC and SCC, which is not in conflict with the theory that each component of ASC is of monoclonal origin. Kanazawa et al³⁵ have compared gene status of p53 and KRAS, chromosome abnormalities at 9p21 and 9q31-32, and immunohistochemical profiles between each component of 12 ASCs. Briefly, these data indicated that p53 overexpression was found in both components as well as in the transitional area of five samples with p53 immunoreactivity; also, no significant difference in p53 expression was found in distinct tumor areas. Moreover, chromosome abnormalities at 9p21 and 9q31-32 were coincident in both components. Interestingly, no KRAS mutations were detected in any of the tumor components, which was inconsistent with KRAS

mutation frequency in classical ADC in copious reports.^{36,37} Besides, higher expression of SCC-related antigen and lower expression of Mucin 1 (MUC1), an antigen predominantly expressed in ADC, were found in ADC component.³⁵ These results strongly indicated that squamous differentiation was the primary lesion in these ASCs. On the other hand, Han et al²⁴ have observed that Lkb1-deficient ADC can progressively transdifferentiate into SCC in mouse models, suggesting that ASC is an intermediate step for the process of lung ADC to SCC. Furthermore, Tshako et al³⁸ have detected human papillomavirus (HPV) in 23 surgically resected ASC samples. Under a light microscope, the cytoplasm of ADC cells adjacent to the SCC components expanded, and these larger cells revealed immunoreactivity for high molecular weight cytokeratin (HMC) and involucrin and contained HPV DNA, conjecturing ADC transiting to SCC in ASC.

A collision resulted from mingling of ADC and SCC

This viewpoint stated that ASC was the product of an “encounter” between separate independent foci of ADC and SCC. Hammond et al³⁹ have established a lung cancer hamster model and have shown that each component appears more spatially discrete with smaller diameters and exhibits distinct biological characteristics, whereas mingling of both components is more obvious with larger diameters. Hammond et al suggested that the two components originate from different cells, respectively, but concomitantly, and collision occurs as two neoplasms encounter each other. Nevertheless, whether the observations from this study can be applied to humans remains unclear. Additionally, a case report by Kitamura et al⁴⁰ of a man who had primary ADC and SCC in the right upper lobe may support this explanation.

Treatment

Surgery is the preferred treatment option for ASC patients. Lobectomy with lymphadenectomy is considered a standard treatment, while sublobar resection can be applied for early-stage lung cancers or in patients with low pulmonary function.⁴¹ Mordant et al¹⁰ have retrospectively compared postoperative ASCs with contemporaneous ADCs and SCCs; patients with ASC underwent pneumonectomy roughly as often as patients with SCC, but more frequently compared to patients with ADC; these data were in accordance with the study by Maeda et al.¹² Relatively speaking, ASC has a more advanced postoperative stage and a more frequent lymph nodal invasion compared to ADCs and SCCs.⁸ Kong et al⁴² retrospectively analyzed status of lymph node metastasis in 1,156 patients with surgically resected lung cancer by IHC

and H&E staining. Of 49 ASCs, 26 cases were diagnosed as metastatic lymph node, and there was a higher frequency of N2 stage lymph node metastasis in ASC (40.5%) than in ADC (18.7%) and in SCC (21.6%). In the study by Maeda et al,¹² the 5-year survival rate in all stage patients with ASC is 23.3%, while it is 40.8% for SCC and 58.0% for ADC. Also, larger survival differences between ASC and ADC were found in earlier stages. For p-stage IA tumors, the 5-year survival rates were 42.0% for ASC, 81.8% for ADC and 63.4% for SCC; statistical difference was observed between ASC and ADC ($P=0.0005$).¹² Shimoji et al have shown that 3-year recurrence-free survival rate for postoperative ASC patients is 56% and 69% in p-stage I cases.⁶ Furthermore, Gawrychowski et al¹⁵ have analyzed the data from 96 ASC patients revealing that the cumulative postoperative survival rates at 5 and 10 years are 25.4% and 19.2%, respectively, as compared to 42.5% and 39.1% of contemporaneous ADC cases. In summary, ASC has a much more aggressive nature compared with ADC and SCC, and thus early detection, diagnosis and surgery are essential for curing ASC.

Platinum-based postoperative adjuvant chemotherapy has been accepted as the standard treatment for stage II–III NSCLC.^{43,44} A retrospective review including 2,157 lung cancer patients after surgery was carried out by Filosso et al. Stage I–II and stage III–IV patients underwent platinum-based postoperative adjuvant chemotherapy.⁸ The survival curve revealed a longer survival in patients receiving adjuvant chemotherapy compared to those who did not receive adjuvant chemotherapy ($P=0.02$), and thus adjuvant therapy was revealed to be an independent positive prognostic factor for p-stage IA–IIIB patients with ASC.¹² Feng et al⁴⁵ have collected data from 181 patients with ASC and have found that platinum-based postoperative adjuvant chemotherapy significantly improved the survival in stage III patients, and there was a significant correlation between the cycles of chemotherapy and survival rates. Furthermore, 3 and 5-year survival rates for patients undergoing at least four chemotherapeutic cycles were 43.4% and 31%, respectively, which was significantly higher compared to patients treated with neoadjuvant chemotherapy or 1–3 chemotherapeutic cycles. In case of a more aggressive biological behavior of ASC which in turn causes more frequent brain metastases, a postoperative prophylactic cranial irradiation might be necessary.⁸

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) can be used as first-line therapy for advanced EGFR-mutant NSCLC.^{46–49} As ASC is a relatively rare type of NSCLC, the data on efficacy of EGFR-TKIs for patients with ASC are limited. Wang et al⁵⁰ have determined mutational status of EGFR in postoperative specimens of

ASC using PCR. Of 76 ASCs, the frequency of EGFR mutations is 31.6% (24/76), which is lower than that in ADC but higher than that in SCC, and it is consistent with some other studies.^{31,51} A significantly higher rate of EGFR mutations occurred in nonsmokers (51.5% vs 16.3%; $P=0.001$) and in tumors larger than 3 cm (41.3% vs 16.7%; $P=0.024$).⁵⁰ Song et al⁵² have retrospectively reviewed 49 patients with ASC, who received erlotinib or gefitinib treatment. Among these cases, stable disease (SD) was observed in 19 cases, partial response (PR) in 13 cases, while the disease control rate was 65.3%. Moreover, the median progression-free survival (PFS) and median survival time were 4.3 and 17.6 months, respectively. While comparing the data with contemporaneous cohort of SCC and ADC, statistical differences in PFS among three types were observed, ie, 4.3 months for ASC, 4.2 months for ADC and 1.9 months for SCC (all $P<0.05$). In addition, this study revealed higher efficacy of EGFR-TKIs for EGFR-positive patients with ASC than that for EGFR-negative ones.⁵² Similar results are shown in another retrospective study by Fan et al,⁵³ in which 27 EGFR-mutant patients with recurrent ASC after resection who received EGFR-TKIs treatment were enrolled. Accounted for by 9 PR and 11 SD, the disease control rate is 74.1% (20/27). Median PFS and median postoperative OS reach 15 and 39 months, respectively. Tamura et al⁵⁴ have reported a female EGFR-mutant patient with ASC, who successfully underwent a second-line rechallenge with afatinib after failure of first-line gefitinib. Another case of ASC, which acquired resistance to afatinib as a result of T790M-positive status, was reported by Ricciuti et al.⁵⁵ Detection for EGFR mutation in advanced patients with ASC should be a routine testing, and EGFR-TKI therapy for EGFR-positive ASC patients is recommended.

NSCLC patients with anaplastic lymphoma kinase (ALK) rearrangements are sensitive to ALK inhibitors. Wang et al⁵⁰ reported four ALK fusions (5.3%) in 76 patients with ASC. In a case report by Chaft et al,⁵⁶ a male postoperative ASC patient with ALK rearrangement was first treated with chemotherapy. Recurrence was observed 2 years later, and then the crizotinib treatment was administered. Tumor continuously shrunk over 13 months, while lymph nodes remained stable. Mesenchymal–epithelial transition factor (MET) is a potential therapeutic target in NSCLC, while the significant efficacy of crizotinib for NSCLC patients with ROS proto-oncogene 1 (ROS1) rearrangements has been confirmed.⁵⁷ In a study analyzing 16 Caucasian ASC samples by NGS,²² no MET mutation and ROS1 rearrangement were detected. Further studies are needed to determine whether ALK inhibitors may be effective for MET-mutant or ROS1 rearrangements in patients with ASC.

Immune checkpoint blockade therapies have earned its spurs in the treatment of malignant tumors in recent years.⁵⁸ Key immunological checkpoint proteins include programmed death 1 (PD-1) and its ligand PD-L1. Shi et al⁵⁹ have evaluated the expression of PD-L1 in patients with ASC using IHC and in situ hybridization. The rate of PD-L1 expression was similar in ADC components of ASC and ADC (11.1% and 13.5%, respectively), as well as the SCC components and SCC (38.89% and 28.9%, respectively). PD-L1 inhibitor may be a potential treatment choice for ASC patients with high PD-L1 expression; nonetheless, these observations need to be further verified by larger studies.

Conclusion

To summarize, ASC is a special subtype of NSCLC, different from ADC and SCC. Fibrobronchoscope brush biopsy, trans-bronchial needle aspiration biopsy (TBNA) and CT-guided biopsy are not reliable means for diagnosing ASC. Compared with ADC and SCC, it has higher grade malignancy, stronger lymph nodal invasiveness, more frequent brain metastases and poorer prognosis. Even though the most effective chemotherapy regimen for patients with ASC remains unclear, platinum-based doublet chemotherapy should be considered as standard treatment option, which needs to be verified by larger studies. Detection of EGFR mutation in advanced patients with ASC should be a routine testing, and EGFR-TKIs can be an effective treatment for EGFR-positive patients with ASC. Crizotinib may be a potential choice for advanced ALK-rearrangement ASC patients. Immune checkpoint blockade therapies are important issues nowadays, and it may be feasible to recommend PD-L1 testing in patients with ASC.

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Disclosure

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