Received: 14 October 2023 | Accepted: 7 December 2023

DOI: 10.1111/1759-7714.15202

ORIGINAL ARTICLE

WILEY

Primary pulmonary adenoid cystic carcinoma: A clinicopathological study of 64 patients

Xiang Tan[1,2,3] | Tao Xu[4] | Wang Shen[2,5] | Cheng Ai[6] | Weilin Zhang[5,7] | Xiaojun Tang[2,5] | Feng Luo[1,2] | Qinghua Zhou[2,5]

[1]Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

[2]Lung Cancer Center, West China Hospital, Sichuan University, Chengdu, China

[3]Department of Thoracic Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, China

[4]Department of Thoracic Surgery, the Affiliated Hospital of Southwest Medical University, Luzhou, China

[5]Lung Cancer Center, West China Tianfu Hospital, Sichuan University, Chengdu, China

[6]Department of Cardiothoracic Surgery, Bishan Hospital of Chongqing Medical University, Chongqing, China

[7]Rehabilitation Medicine Center, West China Hospital, Sichuan University, Chengdu, China

Correspondence
Feng Luo and Qinghua Zhou, Lung Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China.
Email: luofeng66666@sina.com and qinghuazhou1016@126.com

Abstract

Background: This study aimed to investigate the clinicopathological features and prognostic indicators of primary pulmonary adenoid cystic carcinoma (PACC).

Methods: Clinical data were collected from 64 primary PACC patients and analyzed retrospectively at the Tianjin Medical University General Hospital, the West China Hospital of Sichuan University, the First Affiliated Hospital of Guangxi Medical University, and the Bishan Hospital of Chongqing Medical University from January 2003 to August 2023. The 64 patients (28 males and 36 females) were aged from 20 to 73 years, with a median age of 49 years and an average age of 49.3 years.

Results: Immunohistochemical staining showed that the tumors expressed CK7, S-100 protein, CK5/6, CD117, and p63. Seven patients underwent fluorescence in situ hybridization (FISH) testing and three were found to have myeloblastosis (MYB) gene translocation. In total, 53 patients underwent surgery, among whom 31 received only surgery and 22 received both surgery and postoperative chemoradiotherapy. In addition, 10 patients received chemoradiotherapy only, while one patient underwent treatment with traditional Chinese medicine. The overall survival rates in the first, third, and fifth years were 98.4%, 95.3%, and 87.5%, respectively.

Conclusion: Prognostic analysis revealed that age, tumor size, lymph node metastasis status, margin status, and choice of treatment modality significantly influenced the patients' prognosis.

KEYWORDS
lung cancer, pathology, primary pulmonary adenoid cystic carcinoma

INTRODUCTION

According to the World Health Organization (WHO) classification of lung cancer, primary salivary gland-type tumors of the lung (PSGT) are a distinct category of lung tumors.[1] Pulmonary adenoid cystic carcinoma (PACC) is one of the major types of PSGT lung cancers, although accounting for only 0.04%–0.2%.[2] PACC arises from the bronchial gland and is characterized by slow growth and low-grade malignancy. Furthermore, the tumor typically exhibits infiltrative characteristics.[3,4] However, its clinicopathological features, demographics, treatment, prognosis, and long-term survival have not been fully elucidated due to its rare and unique nature. Therefore, a retrospective analysis of the clinical characteristics of 64 patients with PACC was conducted.

METHODS

Data from 64 patients pathologically diagnosed with PACC were collected from four tertiary hospitals: Tianjin Medical University General Hospital, West China Hospital of Sichuan University, the First Affiliated Hospital of Guangxi Medical University, and Bishan Hospital of Chongqing Medical University. The data were collected from January 2003 to August 2023 with authorization from the respective

Xiang Tan and Tao Xu contributed equally to this study.

Institutional Ethics Committees and Review Boards. These patients had no history of salivary gland tumors and no tumors were found in the salivary gland imaging examination. Among the patients, 53 underwent surgical resection procedures such as lobectomy, pneumonectomy, bronchial sleeve resection, or resection and reconstruction of the tracheal carina and main bronchus. Among them, 22 patients received postoperative adjuvant therapy (chemotherapy or radiotherapy). In contrast, another 10 patients received chemoradiotherapy alone.

Tumor tissue samples were obtained by surgical resection or biopsy. If the lesion was extensively infiltrated and unsuitable for surgical resection, a biopsy was performed to confirm the pathological condition. The pathological diagnosis was confirmed by two pathologists, combining clinical and imaging data in order to ensure result accuracy. All tumors were classified using the International eighth edition TNM staging system. All patients were followed up through the outpatient system, inpatient system, and telephone return visits. The last follow-up time was August 31, 2023.

Statistical analysis

The distribution of individual and clinical characteristics of patients was demonstrated by employing descriptive statistical methods. The overall survival (OS) rates at 1-, 3-, and 5-years were calculated utilizing the Kaplan–Meier method, while statistical comparisons were conducted through the log-rank test. Influences of various variables on OS was evaluated by multivariate Cox proportional hazard regression models. IBM SPSS Ssatistics version 23.0 (IBM Corporation) was used for statistical analysis in this study. Two-sided p-values < 0.05 were considered statistically significant.

TABLE 1 The clinical characteristics of 64 patients with pulmonary adenoid cystic carcinoma (PACC).

Characteristics	*n*
Gender	
Male	28
Female	36
Smoking history	
Yes	25
No	39
Tumor location	
Main bronchi and bronchi	51
Lobe	13
TNM stage	
Stage I	40
Stage II	6
Stage III	12
Stage IV	6
Tumor sizes (cm)	
≤3	46
>3	18
Lymph node metastasis	
Yes	14
No	50
Treatment	
Radical surgery	31
Radical surgery + postoperative chemoradiotherapy	22
Chemoradiotherapy	10
Others	1
R status	
R0	30
R1	23

RESULTS

The 64 patients with primary PACC included 28 males (43.8%) and 36 females (56.2%). Their ages ranged from 20 to 73 years, with a median age of 49 years and an average age of 49.3 years. In total, 25 patients (39.1%) had a history of smoking or secondhand smoke exposure, while 39 cases (60.9%) had no such history (Table 1). Cough without apparent cause was the initial symptom in 58 cases, including three cases with hemoptysis, nine cases with sputum production (four containing blood streaks), seven cases with chest pain, and three cases with chest tightness/discomfort. Additionally, four cases initially presented with chest tightness/discomfort, while one case first exhibited fever, and one case was detected during routine physical examination. The tumors were predominantly distributed in central areas such as the trachea or main bronchi in 51 patients (79.7%), whereas pulmonary lobe tumors were found in 13 patients (20.3%). Surgical resection was performed in 53 individuals (82.8%), among whom 30 underwent R0 resection (56.6%) and 23 underwent R1 resection (43.4%). After histological confirmation, lymph node metastasis was found in nine individuals (17%), while 44 individuals showed no evidence of lymph node metastasis (83%). According to the eighth edition of the global clinical TNM staging classification, 40 patients were classified as stage I, six patients as stage II, 12 as stage III, and six patients as stage IV. A total of 11 patients (17.2%) received conservative treatment due to locally advanced disease or unresectable late-stage disease (Table 1).

Gross pathological examination revealed smooth-surfaced endobronchial bulging masses without intact mucosal coverage. They ranged in size from $0.8 \times 0.6 \times 0.5$ cm to $6 \times 5 \times 1.2$ cm and appeared as grayish-white, solid masses of medium texture upon cross-sectioning. Some cases showed mucus secretion and blurred borders. Furthermore, microscopic observation revealed that the extent of tumor infiltration often exceeded the boundaries visible to the naked eye due to diffuse infiltration along the bronchial wall and perineural invasion.[4] Microscopically,

infiltrative growth of pulmonary adenoid cystic carcinoma (PACC) was identified beneath the bronchial mucosa. Based on histological features and cellular arrangement, PACC can be classified into three types, including tubular tumor (grade I), sieve-shaped tumor (grade II), and solid-type mass (grade III).[5,6] The cytological examination revealed cells of uniform size and morphology. The samples were characterized by sparse cytoplasm, small nuclei, and deep staining. Nuclear division was infrequent. Lymphocyte infiltration with neuroinvasive phenomena was also observed in the interstitium. Notably, the mass displayed a structure resembling sieves, glands, cords, or solid nests surrounded by a mucinous basement membrane-like material that was homogeneous and transparent. Internally, dilated pseudocysts were also visible. The sieve and tubular types were more common whereas the solid type was less frequent. Moreover, the solid variant displayed a more malignant propensity with fenestrated periphery, an increased likelihood of blood vessel invasion, and bronchial wall penetration or even tracheal cartilage rupture into the lungs.[7,8] These changes increase the risk of skip metastases and disease progression.

CD117 expression was positively detected in 96.5% (55/57) of cases, CK7 was found in all patients (56/56), P63 was detected in 98.2% of cases (56/57), S-100 demonstrated a positivity rate of 94.3% (50/53) and CK5/6 displayed a positivity rate of 97.9% (48/49). Next-generation sequencing revealed wild-type exons 18, 19, 20, and 21 for EGFR, ALK, and ROS1 in eight patients. Furthermore, fluorescence in situ hybridization (FISH) testing for the MYB gene was performed on seven patients, with only three cases (42.8%) showing MYB gene translocation (Figure 1).

Treatment modalities

Complete mass resection was performed in 53 of the 64 patients, including bronchial sleeve resection (4 patients), lobectomy (24 patients), and tracheal bifurcation and main bronchotomy reconstruction (25 patients). Additionally, 22 patients received postoperative radiotherapy based on tumor margin resection status (R0/R1), TNM staging (stage II–IV), and lymph node metastasis status. Radiotherapy was also given to 10 patients with extensive locally advanced invasion, while one case received conservative treatment with traditional Chinese medicine.

The follow-up time for the 64 patients ranged from 6 to 180 months, with an average duration of 58.2 months. Among them, 14 patients died. The OS rates in the first, third, and fifth years were 98.4%, 95.3%, and 87.5%, respectively. In our study, univariate analysis showed that the 3-year survival rate was 100% in TNM stage I patients compared to 86.3% in TNM stage II–IV patients, while the 5-year survival rate was 93.4% in TNM stage I patients compared to only 61.6% in TNM stage II–IV patients ($p < 0.001$). The 5-year survival rate for patients with positive lymph node metastases was only 63.8%, significantly lower than that in patients with negative lymph node metastases (86.9%, $p = 0.001$). Furthermore, age, tumor size, treatment and R status were also significantly correlated with the 5-year survival of these patients in the univariate analysis (Table 2, Figure 2).The results of the multivariable Cox proportional hazards regression model indicated that tumor size and treatment methods had a significant impact on survival (all $p < 0.05$) (Figure 2).

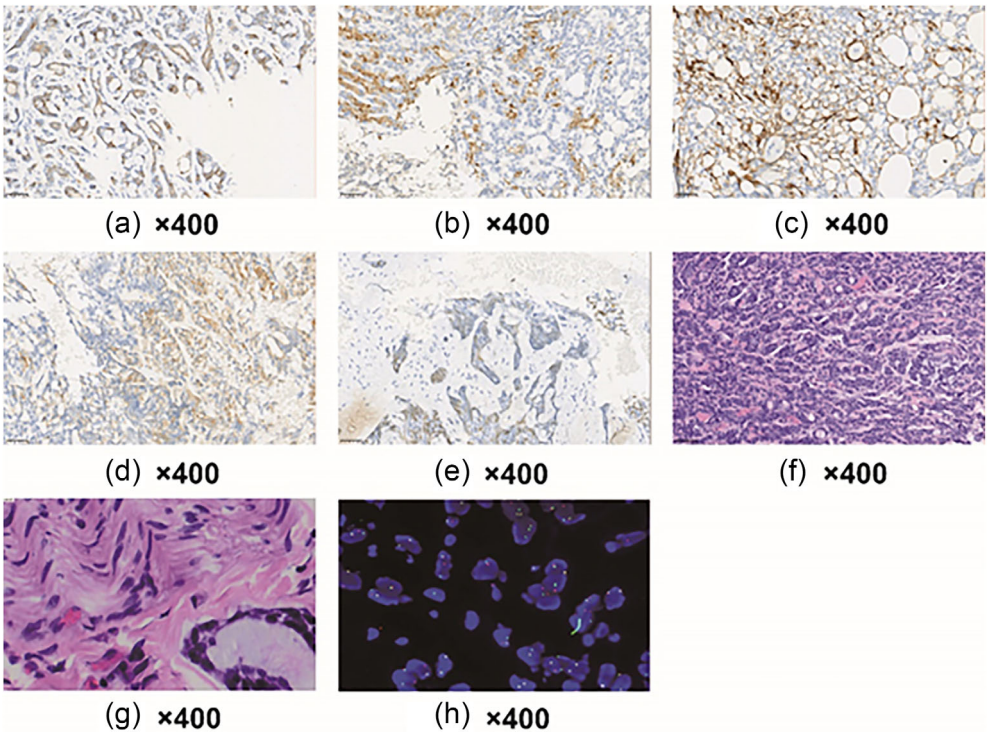

FIGURE 1 (a) CD117 was patchy positive in some tumor cells. (b) S-100 was positive in peripheral myoepithelial cells. (c) CK5/6 was patchy positive in some tumor cells. (d) CK7 was positive in the ductal cells. (e) P63 was positive in the nuclei of peripheral myoepithelial cells. (f) Cribriform and tubular type patterns of adenoid cystic carcinoma are seen (hematoxylin & eosin [H&E]). (g) Nerve invasion by tumor cells. (h) Fluorescence in situ hybridization (FISH) for myeloblastosis (MYB) break-apart assay showed separate red and green signals in more than 20% of tumor cells.

TABLE 2 Univariate analysis of survival rates of 64 cases with pulmonary adenoid cystic carcinoma (PACC).

Characteristics	*n*	Survival rate (%)			χ^2	*p*
		1-year	3-year	5-year		
Gender					1.084	0.298
Male	28	100	96 (92.1–99.9)	90.9 (84.7–97.1)		
Female	36	97.2 (94.5–99.9)	94.4 (90.6–98.2)	76.7 (68.8–84.6)		
Age (year)					4.11	0.043
≥45	47	100	93.3 (86.9–99.7)	66 (51.9.80.1)		
<45	17	97.9 (95.8–100)	95.6 (92.6–98.6)	86.9 (81.3–92.5)		
Smoking history					1.127	0.288
Yes	25	100	95.7 (91.4–100)	90.3 (83.8–96.8)		
No	39	97.4 (94.9–99.9)	94.8 (91.2–98.4)	76.9 (69–84.8)		
TNM stage					16.015	<0.001
Stage I	40	100	100	93.4 (88.9–97.9)		
Stage II + III + IV	24	95.7 (91.4–100)	86.3 (78.9–93.7)	61.6 (49.7–73.5)		
Tumor location					0.745	0.388
Main bronchi and bronchi	51	98 (96–100)	93.8 (90.3–97.3)	83.8 (78.1–89.5)		
Lobe	13	100	100	88.9 (78.4–99.4)		
Tumor sizes (cm)					13.543	<0.001
>3	18	94.7 (89.6–99.8)	89.2 (82–96.4)	57.3 (43.5–71.1)		
≤3	46	100	97.7 (95.4–100)	92 (96.5–87.5)		
Lymph nodes metastasis					10.218	0.001
Yes	14	92.9 (86–99.8)	76.6 (64.7–88.5)	63.8 (48.5–79.1)		
No	50	100	100	86.9 (81.4–92.4)		
Treatment					11.665	0.001
Radical surgery	31	100	100	91.7 (83.7–99.7)		
Radical surgery + Postoperative chemoradiotherapy	22	100	95.2 (90.6–99.8)	58.4 (45–71.8)		
Chemoradiotherapy	10	90 (80.5–99.5)	90 (80.5–99.5)	67.5 (46.8–88.2)		
Others	1	0	0	0		
R status					6.455	0.011
R0	30	100	96 (92.1–99.9)	87.4 (80.6–94.2)		
R1	23	100	95.2 (90.6–99.8)	75.7 (64.9–86.5)		

DISCUSSION

PACC is a rare malignant tumor originating from the salivary gland and is most commonly found centrally in the trachea and main bronchus.[3] It is characterized by slow progression and late metastasis. The clinical manifestations of PACC are nonspecific and mainly depend on the location of the tumor and distal obstruction.[9] In the early stages, most patients show no obvious symptoms and only present with an irritating dry cough. Respiratory system symptoms such as wheezing, dyspnea, fever, obstructive pneumonia, and hemoptysis typically appear when the lumen is already half-blocked by the tumor. These manifestations are difficult to differentiate from common respiratory diseases such as chronic obstructive pulmonary disease and asthma.[10]

In this study, tumors located in the trachea and main bronchi accounted for 81.3% of the cases. Due to the overlap of mediastinal and skeletal shadows over the trachea, this lesion is hard to diagnose accurately on traditional chest x-rays.[8] Therefore, high-resolution computer tomography (HRCT) is advised for accurate imaging.[8,11] In CT images, PACC is commonly observed as a central type with uneven or uniform wall thickening. The growth pattern can be classified into three types: intraluminal, extraluminal, and transmural.[11] Among them, intraluminal growth refers to the tumor being attached to the inner wall and protruding into the lumen, while extraluminal growth involves a tumor attached to the outer wall and extending into the mediastinal area. Simultaneously, thickened wall segments infiltrating both inside and outside of the lumen can be observed.[11] Additionally, PACC also extends over 3 cm longitudinally and infiltrates over half of the luminal circumference.[12] Notably, PACC is characterized by submucosal and perineural spread.[13] Even in advanced PACC patients, bronchoscopy can be used to determine tumor morphology, size, and intraluminal invasion. This assists in treatment

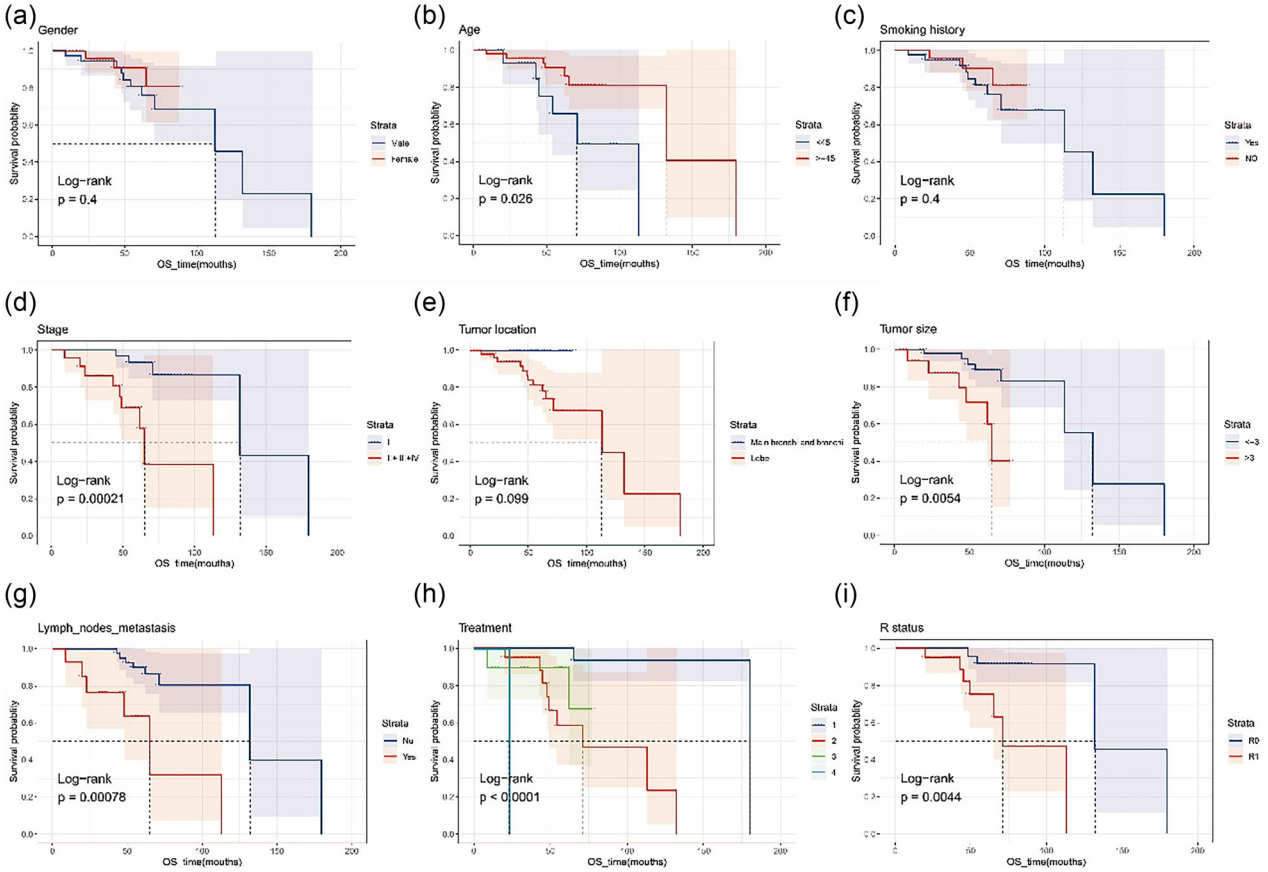

FIGURE 2 Prognostic factors of primary pulmonary adenoid cystic carcinoma.

planning and guides neoadjuvant therapy through biopsy confirmation for patients who are not eligible for R0 resection surgery.[14]

Among the 64 cases of PACC, there were more female patients than male patients (ratio of 1.29:1). This finding was consistent with a previous study.[7] The disease is frequently observed in middle-aged and elderly individuals, with an average age of 49.2 years.[15] The current research revealed that patients over the age of 45 exhibited poor 5-year survival rates (Table 2, Figure 3). Nonsmokers constituted the majority of the patients (60.9%), suggesting that smoking may not be significantly associated with tumor occurrence and development ($p > 0.05$).[16] According to the literature, the rate of lymph node metastasis in patients with PACC ranged from 18.2% to 35.3%, exhibiting a negative correlation between lymph node metastasis and survival.[17] Among the 64 patients included in this study, lymph node metastasis was observed in 14 cases (21.9%), which was consistent with previous reports.[17] Additionally, some PACC patients have hematogenous metastasis and may exhibit long-term asymptomatic manifestations. The lungs are the most common site of metastasis, while it is also frequently observed in the brain, bones, liver, and kidneys.[18] However, the factors influencing the prognosis of PACC remain controversial. The present study demonstrates that patients with stage I tumors, tumors smaller than 3 cm, without lymph node metastasis, negative surgical margins, and early surgery have better survival rates. Using a multivariable Cox proportional hazards model, the results indicated that tumor size and treatment method were the main factors influencing survival in PACC patients.

Surgical resection is currently the primary therapeutic strategy in the treatment of PACC. Surgical approaches include lobectomy or pneumonectomy with bronchoplasty, sleeve resection with end-to-end anastomosis, local excision of intraluminal tumor with electrocauterization of the tumor base, and others. Among the 64 PACC patients, 53 underwent surgical resection. Age, clinical stage, margin status, and lymph node involvement were significantly correlated with treatment modality and the 5-year survival rate. A 5-year survival rate of 93.4% was observed in the 31 early-stage patients treated solely by surgery. In the largest case reports to date, the 5- and 10-year mortality rates ranged from 65% to 97.6% and 53.0% to 86.7%, respectively. Our findings are consistent with these studies.[3,19]

However, due to its slow growth and infiltrative patterns such as submucosal spread and perineural invasion, PACC is prone to recurrence and metastasis, as shown by the failure of R0 resection in 23 patients in our study (Table 2, Figure 3). Additionally, this type of cancer may exhibit longitudinal growth along with circumferential wall thickening and transmural growth. Such growth patterns lead to a large

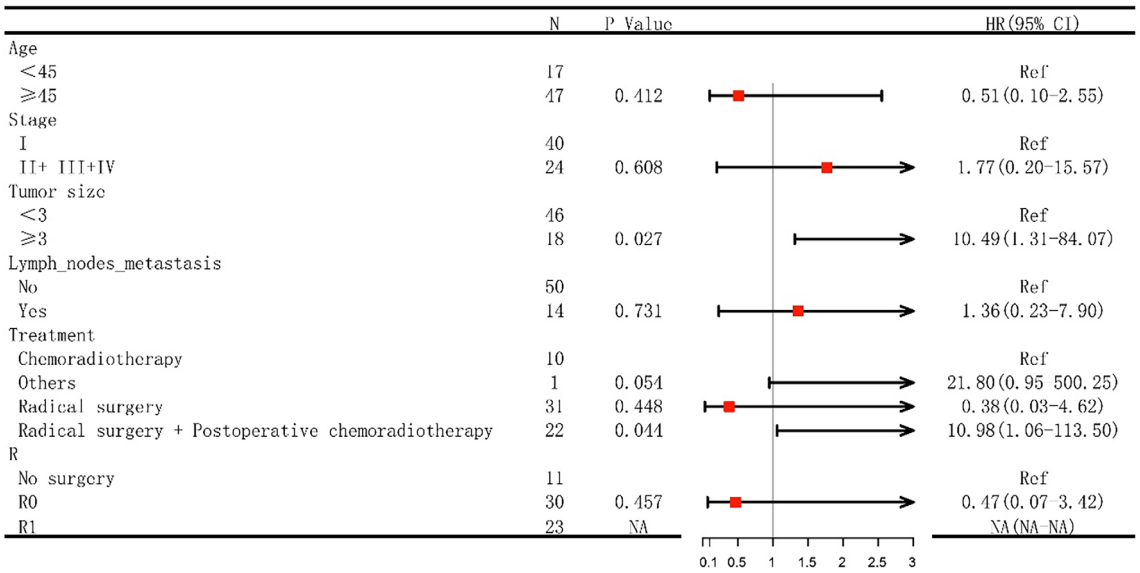

FIGURE 3 Overall survival curves stratified by clinical characteristics. (a) Gender, (b) age, (c) smoking history, (d) TNM stage, (e) tumor location, (f) tumor size (cm), (g) lymph node metastasis, (h) treatment and (i) R status.

tumor volume and unfavorable location, including the distal trachea and carina, but has a lesser impact on lung parenchyma. Due to the risks of functional limitations, poor resection anastomosis, and inadequate surgical access, surgical removal becomes challenging and often cannot be fully completed.[20,21] Incomplete resection was identified by intraoperative frozen pathology, displaying the tumor's unstable invasion pattern, which resulted in a higher rate of positive surgical margins and consequently increased the risk of recurrence and metastasis.[22,23] In this study, a poorer prognosis was observed in the 23 patients who underwent R1 resection, which was in line with previous reports.[24] In certain cases, R1 resection surgery was performed to avoid extensive loss of trachea circular cartilage. The patients fully recovered after the operation and achieved longer OS following adjuvant therapy. These research findings indicate that incomplete resection combined with adjuvant therapy may be an acceptable and effective option for patients who cannot undergo complete resection or are at high risk.[25] Nevertheless, the 5-year survival rate of patients with R1 resection plus chemoradiotherapy was not significantly higher than patients who received only chemoradiotherapy. This may be attributed to the limited number of cases included in this study or the complications resulting from concurrent radiotherapy and chemotherapy after relapse, thus accelerating disease progression. In this study, one patient with postoperative recurrence underwent radiotherapy and chemotherapy, which resulted in the development of a tracheoesophageal fistula and eventual death within only 9 months. Chemotherapy remains one of the main treatment strategies for advanced PACC patients. The platinum-based doublet regimen recommended by the NSCLC guidelines is considered the primary chemotherapy option for PACC, which includes carboplatin and cisplatin in combination with pemetrexed, as well as paclitaxel and gemcitabine.[24] Adjuvant radiotherapy is frequently recommended; however, its effectiveness has not been confirmed and there is a lack of consensus regarding its efficacy. Synchronous combined radiotherapy has also shown promising results.[26] In this study, 10 patients who received concurrent chemoradiotherapy achieved an average survival of 50.1 months. Additionally, one patient underwent traditional Chinese medicine treatment with a survival time of only 23 months. This indicates that synchronous chemoradiotherapy can improve the prognosis for advanced PACC patients.

Relevant studies have focused on immunohistochemical markers such as CD117, p63, S-100, CK7, and CK5/6, elevated expression levels may be used as diagnostic markers for PACC.[8] In contrast, napsin A is highly expressed in primary lung adenocarcinoma and is rarely expressed in PACC, which facilitates the differentiation between primary lung adenocarcinoma and PACC.[10] CD117 positivity in diseased myoepithelial cells may indicate low myoepithelial cell differentiation, which is associated with a poor prognosis.[8] Generally, CD117 can help differentiate PACC from common lung cancer subtypes such as lung adenocarcinoma. However, it cannot be used alone for the differential diagnosis of salivary gland tumors since other salivary gland tumors can also express CD117 to varying degrees.[27] Furthermore, coexpression of CD117 and S-100 may be used to differentiate between PACC and mucoepidermoid carcinoma of the lung.[28] Notably, CD117 positivity plays a crucial role in the diagnosis of PACC when CD117 binds to the MYB protein due to a PACC-specific MYB chromosomal translocation.[29] This MYB gene translocation (t[6;9] [q22-23; p23-24]) occurs in approximately 80% of ACC; the differentiation of PACC from other salivary gland tumors

mainly relies on histopathology and its specific gene fusion mutations.[15] The incidence of MYB gene translocation in PACC is only about 40%, with the MYB positivity rate in this study being 42.8% (3/7), which generally aligns with previous studies.[28,30] The MYB gene is expected to be a hotspot for PACC-targeted therapy, which deserves further study. In addition, next-generation sequencing analysis was performed on eight patients in this study, which revealed that the *EGFR*, *ALK*, and *ROS1* genes were all wild-type. These findings suggest that PACC currently does not benefit from targeted agent treatment, consistent with previous studies.[31] However, further validation with larger sample sizes is still required. Immunohistochemical testing for PD-L1 was conducted on eight patients and indicated a low tumor mutational load, as well as negative or low PD-L1 expression. This implies that immune checkpoint inhibitors alone may not be suitable for PACC patients, but may be beneficial when combined with radiotherapy.[8]

Nevertheless, the limitations of this study should be acknowledged. First, the data were collected from different platforms across four hospitals, and the collection and follow-up were limited. Additionally, some data were only obtained from patients' outpatient medical records and telephone follow-ups. Second, although PACC shows a high 5-year survival rate, the long-term survival rate remains low. Furthermore, the follow-up time for some patients in this study had not yet reached 5 years, which may have affected the conclusions. Finally, the sample size was small, and the lack of precise statistical information may have impacted the results of the study. Prospective studies conducted in multiple large centers are required to further explore optimal treatment strategies for PACC.

In conclusion, PACC is a rare primary malignant lung tumor with atypical clinical symptoms. Early surgery or adjuvant radiotherapy after surgery remains the most effective treatment option. Age, tumor size, lymph node metastasis status, margin status, and choice of treatment modality are independent prognostic factors that affect survival. Longer follow-up and further studies are necessary.

AUTHOR CONTRIBUTIONS

Xiang Tan and Tao Xu analyzed data, Wang Shen wrote the paper; Feng Luo and Qinghua revised the manuscript; Cheng Ai, Xiaojun Tang and Weilin Zhang collected literatures.

CONFLICT OF INTEREST STATEMENT

No authors report any conflict of interest in this work.

ORCID

Wang Shen https://orcid.org/0000-0002-9211-2901
Xiaojun Tang https://orcid.org/0000-0001-8757-0927

REFERENCES

1. Nicholson AG, Tsao MS, Beasley MB, Borczuk AC, Brambilla E, Cooper WA, et al. The 2021 WHO classification of lung tumors: impact of advances since 2015. J Thorac Oncol. 2022;17:362–87.
2. Krifa M, Bdioui A, Lajmi Z, Missaoui N, Hmissa S, Mokni M. Primary adenoid cystic carcinoma of the lung: a case report and literature review. Heliyon. 2021;7:e06206.
3. Molina JR, Aubry MC, Lewis JE, Wampfler JA, Williams BA, Midthun DE, et al. Primary salivary gland-type lung cancer: spectrum of clinical presentation, histopathologic and prognostic factors. Cancer. 2007;110(10):2253–9.
4. Garg PK, Sharma G, Rai S, Jakhetiya A. Primary salivary gland-type tumors of the lung: a systematic review and pooled analysis. Lung India. 2019;36(2):118–22.
5. Gao F, Zang L, He J, Xu W. A case of solid variant of adenoid cystic carcinoma from trachea: a case report and review of literature. Onco Targets Ther. 2021;14:1997–2002.
6. Seethala RR. An update on grading of salivary gland carcinomas. Head Neck Pathol. 2009;3(1):69–77.
7. Elnayal A, Moran CA, Fox PS, Mawlawi O, Swisher SG, Marom EM. Primary salivary gland-type lung cancer: imaging and clinical predictors of outcome. AJR Am J Roentgenol. 2013;201(1):W57–63.
8. Chen Z, Jiang J, Fan Y, Lu H. Pulmonary adenoid cystic carcinoma: molecular characteristics and literature review. Diagn Pathol. 2023;18(1):65.
9. Huo Z, Meng Y, Wu H, Shen J, Bi Y, Luo Y, et al. Adenoid cystic carcinoma of the tracheobronchial tree: clinicopathologic and immunohistochemical studies of 21 cases. Int J Clin Exp Pathol. 2014;7(11):7527–35.
10. Qing S, Zhou K, Liu X, Li X, Deng F, Ma Y. Primary pulmonary adenoid cystic carcinoma: clinicopathological analyses of 12 cases. Int J Clin Exp Pathol. 2015;8(6):7619–26.
11. Wang SC, Yin LK, Zhang Y, Xue LM, Ye JD, Tao GY, et al. CT diagnosis and prognosis prediction of tracheal adenoid cystic carcinoma. Eur J Radiol. 2021;140:109746.
12. Li X, Yi W, Zeng Q. CT features and differential diagnosis of primary pulmonary mucoepidermoid carcinoma and pulmonary adenoid cystic carcinoma. J Thorac Dis. 2018;10(12):6501–8.
13. Bhatia K, Ellis S. Unusual lung tumours: an illustrated review of CT features suggestive of this diagnosis. Cancer Imaging. 2006;6(1):72–82.
14. Kramer T, Annema JT. Advanced bronchoscopic techniques for the diagnosis and treatment of peripheral lung cancer. Lung Cancer. 2021;161:152–62.
15. Li MA-O, Zhao BR, Liu SQ, An J, Deng PB, Han-Zhang H, et al. Mutational landscape and clonal diversity of pulmonary adenoid cystic carcinoma. Cancer Biol Ther. 2018;19(10):898–903.
16. Moersch HJ, Clagett OT, Ellis FH Jr. Tumors of the trachea. Med Clin North Am. 1954;38:1091–6.
17. Wo Y, Li S, Wang Y, Lu T, Qin Y, Sun X, et al. Predictors of nodal metastasis and prognostic significance of lymph node ratio and total lymph node count in tracheobronchial adenoid cystic carcinoma. Cancer Manag Res. 2018;10:5919–25.
18. Junejo NN, Almusalam L, Alothman KI, Ai Hussain TO. An unusual case report of pulmonary adenoid cystic carcinoma metastasis to the kidney. Case Report and Literature Review. Urol Case Rep. 2019;27:100927.
19. Pandey D, Garg PK, Jakhetiya A, Pandey R, Bhoriwal S, Nath D, et al. Surgical experience of primary salivary gland tumors of lung: a case series. Int J Surg. 2015;21:92–6.
20. Hsu AA, Tan EH, Takano AM. Lower respiratory tract adenoid cystic carcinoma: its management in the past decades. Clin Oncol (R Coll Radiol). 2015;27(12):732–40.
21. Suzuki T. What is the best management strategy for adenoid cystic carcinoma of the trachea? Ann Thorac Cardiovasc Surg. 2011;17(6):535–8.
22. Choudhury BK, Barman G, Singh S, Ahmed K. Adenoid cystic carcinoma of the upper trachea: a rare neoplasm. J Clin Imaging Sci. 2013;3:39.
23. Kawashima O, Hirai T, Kamiyoshihara M, Ishikawa S, Morishita Y. Primary adenoid cystic carcinoma in the lung: report of two cases and therapeutic considerations. Lung Cancer. 1998;19(3):211–7.
24. Zhao Y, He G, Zhai Y, Zhou Z, Bi N, Mao Y, et al. Adenoid cystic carcinoma of lobar bronchial origin: 20-year experience at a single

institution. Ann Surg Oncol. 2022;29:4408–16. https://doi.org/10.1245/s10434-022-11590-5
25. Ning YA-O, He W, Bian D, Xie D, Jiang G. Tracheo-bronchial adenoid cystic carcinoma: A retrospective study. Asia Pac J Clin Oncol. 2019;15(4):244–9.
26. Levy A, Omeiri A, Fadel E, Le Péchoux C. Radiotherapy for tracheal-bronchial cystic adenoid carcinomas. Clin Oncol (R Coll Radiol). 2018;30(1):39–46.
27. Roden AC. Recent updates in salivary gland tumors of the lung. Semin Diagn Pathol. 2021;38(5):98–108.
28. Thierauf J, Ramamurthy N, Jo VY, Robinson H, Frazier RP, Gonzalez J, et al. Clinically integrated molecular diagnostics in adenoid cystic carcinoma. Oncologist. 2019;24(10):1356–67.
29. Andersson MA-O, Mangiapane G, Nevado PT, Tsakaneli A, Carlsson T, Corda G, et al. ATR is a MYB regulated gene and potential therapeutic target in adenoid cystic carcinoma. Oncogenesis. 2020;9(1):5.
30. Roden AC, Greipp PT, Knutson DL, Kloft-Nelson SM, Jenkins SM, Marks RS, et al. Histopathologic and cytogenetic features of pulmonary adenoid cystic carcinoma. J Thorac Oncol. 2015;10(11):1570–5.
31. Huo Z, Wu H, Li S, Liang Z. Molecular genetic studies on EGFR, KRAS, BRAF, ALK, PIK3CA, PDGFRA, and DDR2 in primary pulmonary adenoid cystic carcinoma. Diagn Pathol. 2015;10:161.

How to cite this article: Tan X, Xu T, Shen W, Ai C, Zhang W, Tang X, et al. Primary pulmonary adenoid cystic carcinoma: A clinicopathological study of 64 patients. Thorac Cancer. 2024;15(5):386–93. https://doi.org/10.1111/1759-7714.15202