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Research Article

Prognostic Factors and Treatment Outcomes in Pulmonary Adenoid Cystic Carcinoma

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Abstract

Objectives: Pulmonary adenoid cystic carcinoma (PACC) is a rare primary tumor of the lung, representing less than 1% of all pulmonary malignancies. There is no strong evidence for cryotherapy, radiotherapy, and adjuvant chemotherapy in patients with PACC.

Methods: Data from patients who underwent surgery for pulmonary adenoid cystic carcinoma between January 2009 and November 2024 were retrospectively analyzed. Clinical data, surgical approaches, markers at the time of diagnosis, and adjuvant therapies were included in the analysis. Prognostic factors potentially affecting recurrence-free survival and overall survival were analyzed using Cox regression analysis.

Results: A total of 45 patients were included in the study. The median age was 61 years (range: 24–81), and 26 patients (57.8%) were male. Tumors were most commonly located in the lung lobes (n=29, 64.4%), and the most frequent histological subtype was the mixed type (n=19, 42.2%). Among mixed subtypes, the most prevalent pattern was a combination of cribriform and solid architecture (n=12). The median recurrence-free survival (RFS) for the entire cohort was 82.8 months (95% CI: 53.4–112.1), and the median overall survival (OS) was 145.5 months (95% CI: 76.9–214.0). The 5-year OS rate was 84.4% (n=7 deaths), and the 10-year OS rate was 73.3% (n=12 deaths). Lymph node metastasis (HR: 4.19, 95% CI: 1.82–9.63, p=0.001) and increased Ki-67 expression (HR: 1.06, 95% CI: 1.02–1.09, p=0.001) were significantly associated with shorter RFS. Radiotherapy did not demonstrate a statistically significant impact on recurrence-free survival (HR: 0.56, 95% CI: 0.25-1.24, p=0.149). No other clinical or pathological factors were found to be significantly associated with RFS. In the analysis of factors associated with OS, receiving adjuvant radiotherapy was found to be a favorable prognostic factor (HR: 0.27, 95% CI: 0.10-0.71, p=0.008). In contrast, lymph node metastasis (HR: 3.71, 95% CI: 1.33–10.39, p=0.012) and elevated Ki-67 index (HR: 1.04, 95% CI: 1.00–1.08, p=0.031) were identified as negative prognostic markers. No statistically significant difference in OS was observed between patients undergoing surgical resection and those treated with cryotherapy (HR: 2.56, 95% CI: 0.89–7.38, p=0.083).

Conclusion: Adjuvant radiotherapy was associated with improved overall survival, whereas lymph node metastasis and elevated Ki-67 expression were identified as unfavorable prognostic indicators. Adjuvant chemotherapy did not appear to provide a survival benefit. Although cryotherapy yielded comparable survival outcomes to surgical resection in this limited cohort, the difference was not statistically significant. Therefore, cryotherapy may be considered a feasible alternative for patients who are medically inoperable or unsuitable for surgery. Larger multicenter and prospective studies are needed to validate these findings and to optimize treatment strategies for this rare malignancy.

Keywords: Adenoid Cystic Carcinoma, Cryotherapy, Lung Cancer, Prognostic, Radiotherapy

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Pulmonary Adenoid Cystic Carcinoma (PACC), historically referred to as cylindroma or cribriform carcinoma, is a high-grade malignant epithelial tumor that most commonly arises from the salivary glands in the head and neck region.[1] Rarely, it can originate from the submucosal glands of the central airways, such as the trachea and main bronchi.[2] Primary pulmonary adenoid cystic carcinoma (PACC) is an extremely rare neoplasm, accounting for less than 1% of all primary lung malignancies.[3] Due to the denser distribution of submucosal glands in the central bronchi compared to the segmental bronchi, PACC typically presents as a centrally located tumor, while peripheral lung involvement is uncommon.[3] Histopathologically, primary PACC comprises three main histological subtypes: cribriform, tubular, and solid. Among these, the cribriform pattern is the most frequently observed, while the solid pattern is the least common but is considered the most aggressive histological variant.[4] Solid areas are composed of nests of tumor cells lacking luminal structures and may demonstrate higher mitotic activity. Immunohistochemically, PACC typically shows low proliferative activity; however, the Ki-67 proliferation index may range from 2% to 35% positivity, with higher values more frequently observed in solid areas compared to the other subtypes.[5] PACC is characterized by a longer survival compared to both small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). However, 5-year survival rates vary widely (50–85%) depending on tumor stage, surgical margin status, and histological subtype.[6,7] The primary treatment for non-metastatic PACC is surgical resection, and depending on the tumor's location and extent, surgical options may include tracheal resection, lobectomy, pneumonectomy, and segmental resection.[8] However, since the tumor usually progresses by submucosal spread along the airway wall, complete resection (R0) may be difficult to achieve or surgery may not be possible due to its location being close to the main bronchi. While 5-year survival rates reach 87.5% in patients suitable for surgery, survival rates for patients not suitable for surgery drop to 12% to 27%.[6,9] Cryotherapy is a technique that induces cell death by exposing the target tissue to controlled low temperatures (ranging from -20°C to -196°C), leading to the crystallization of intra- and extracellular fluids. This process disrupts cell membrane integrity and triggers cell necrosis.[10] For patients who are either unsuitable for surgery or exhibit positive surgical margins postoperatively, cryotherapy and radiotherapy are among the available treatment options; however, due to the rarity of the disease, prospective randomized data are lacking.[8,11] Adjuvant chemotherapy is also an option for systemic therapy, although it remains unclear whether chemotherapy alters the natural history of most metastatic salivary gland tumor histologies, particularly ACC.[12] In this study, we aimed to present single-center data on pulmonary adenoid cystic carcinoma patients followed at our institution and to evaluate the impact of adjuvant chemotherapy, radiotherapy, cryotherapy, and surgical treatments on survival.

Methods

Study Design and Patient Selection

In this retrospective study, a total of 45 patients diagnosed with pulmonary adenoid cystic carcinoma, who received outpatient treatment between January 2009 and November 2024, were included. Patients were eligible if they met the following criteria: 1) were at least 18 years old; 2) underwent surgery (surgical excision or cryotherapy after the diagnosis); and 3) had no evidence of distant organ metastasis confirmed by computed tomography, magnetic resonance imaging, or other imaging modalities. Patients with concomitant or prior malignancy, a history of salivary gland disease, or tumors detected on salivary gland imaging were excluded. Tumor tissue samples were obtained either through surgical resection or biopsy. When lesions were extensively disseminated and not amenable to surgical resection, a biopsy was performed to confirm the pathological diagnosis. The diagnosis was verified by two pathologists in conjunction with clinical and imaging data. Radiotherapy was administered using the Linear Accelerator (LINAC) device at a dose of 60-70 Gy in a conventionally fractionated (1.8-2 Gy per fraction) fashion. All tumors were categorized according to the 8th edition of the International TNM Classification system.[13] Transthoracic cryotherapy was applied to patients who were not suitable for surgery (patients with large vessel invasion, high surgical co-morbidity, main bronchus compression, inadequate pulmonary function test) or in patients who were inoperable during intraoperative surgery. Transthoracic cryotherapy was performed under general anesthesia and sterile operating room conditions. A 16-gauge cryoprobe was inserted into the targeted lung nodule using an argon-based cryosurgical device. The tumor tissue was cooled to approximately -160°C, creating ice bubbles around it. This freezing process was performed in three consecutive cycles, each lasting 8–10 minutes, followed by an 8–10-minute thawing cycle with helium. Finally, cryotherapy was completed with an adrenaline injection into the tumor area to control bleeding during the procedure.

Statistical Analysis

Statistical analyses were performed using SPSS 24 (SPSS Inc., Chicago, IL). Categorical variables are presented as numbers and percentages. Survival analyses were con-

ducted using the Kaplan-Meier method, with group comparisons made using the Log-Rank test. Univariate analyses of factors affecting survival were performed using the Cox Regression Model, with hazard ratios (HR) and the corresponding 95% confidence intervals (95% CI) reported. The multivariate Cox-regression model was applied using the Forward:LR method. Recurrence-free survival (RFS) and overall survival (OS) were calculated from the date of the first surgery to the date of the first event or death, or to the last follow-up in cases without an event. Statistical significance was defined as $p<0.05$.

Results

A total of 45 patients meeting the inclusion criteria were enrolled in the study. The median age was 61 years (range: 24–81), and 26 patients (57.8%) were male. Tumors were most commonly detected in the lung lobes (n=29, 64.4%), and the most frequent histological subtype was the mixed type (n=19, 42.2%). Among the mixed types, the most common pattern was a combination of cribriform and solid architectures (n=12). At the time of study completion, 27 patients (60%) had experienced recurrence, and 18 patients (40%) had died due to cancer-related causes. The median recurrence-free survival (mRFS) for all patients was 82.8 months (95% CI: 53.4–112.1), and the median overall survival (mOS) was 145.5 months (95% CI: 76.9–214.0). The 5-year OS was 84.4% (n=7 deaths) and the 10-year OS was 73.3% (n=12 deaths). The patients' baseline characteristics and histopathological data are presented in Table 1. In the univariate analysis to identify factors associated with recurrence-free survival (RFS), the presence of lymph node metastasis (HR: 4.19, 95% CI: 1.82–9.63, p=0.001) and increased Ki-67 expression (HR: 1.06, 95% CI: 1.02–1.09, p=0.001) were significantly associated with RFS. Radiotherapy did not show a statistically significant difference in terms of recurrence duration (HR: 0.56, 95% CI: 0.25-1.24, p=0.149). No significant association was detected between RFS and other factors (Table 2). For overall survival (OS), the analysis revealed that receiving adjuvant radiotherapy was a favorable prognostic factor (HR: 0.27, 95% CI: 0.10-0.71, p=0.008). In contrast, the presence of lymph node metastasis (HR: 3.71, 95% CI: 1.33–10.39, p=0.012) and higher Ki-67 levels (HR: 1.04, 95% CI: 1.00–1.08, p=0.031) were identified as negative prognostic indicators. There was no significant difference in OS between surgical resection and cryotherapy (HR: 2.56, 95% CI: 0.89–7.38, p=0.083) (Table 3). In the multivariate Cox-regression analysis (including lymph node and Ki-67) for RFS, lymph node metastasis (HR: 3.52, 95% CI: 1.49–8.30, p=0.004) and Ki-67 (HR: 1.05, 95% CI: 1.01–1.09, p=0.009), and in the multivariate Cox-regres-

Table 1. Clinicopathological features of the patients

Patients characteristics	N	%
Age		
<65	33	73.3
≥65	12	26.7
Sex		
Male	26	57.8
Female	19	42.2
Smoking history		
Yes	31	68.9
No	14	31.1
Comorbidity		
Yes	24	53.3
No	21	46.7
Stage		
1	7	15.6
2	20	44.4
3	12	26.7
4a	6	13.3
Histological Type		
Cribriform	7	15.6
Tubular	6	13.3
Solid	13	28.9
Mixed	19	42.2
Tumor Location		
Main bronchi and bronchi	16	35.6
Lobe	29	64.4
Primary Tumor Size		
≤3 cm	20	44.4
>3 cm	25	55.6
Lymph node Status		
Positive	19	42.2
Negative	26	57.8
Surgery Type		
Lobectomy	16	35.6
Pneumonectomy	4	8.9
Wedge resection	5	11.1
Cryotherapy	20	44.4
Radiotherapy		
Yes	30	66.7
No	15	33.3

Table 1. Continue

Patients characteristics	N	%
Adjuvant Chemotherapy		
Yes	25	55.6
No	20	44.4
Lymphovascular Invasion		
Yes	12	26.7
No	13	28.9
Unknown	20	44.4
Perineural Invasion		
Yes	12	26.7
No	13	28.9
Unknown	20	44.4
Margin		
Positive	24	53.3
Negative	21	46.7

sion analysis (including lymph node, radiotherapy, and Ki-67) for OS, lymph node metastasis (HR: 8.10, 95% CI: 2.32–28.30, p=0.001) and radiotherapy (HR: 0.12, 95% CI: 0.04–0.41, p=0.001) constituted a prognostic model. Kaplan–Meier analysis was used to generate survival curves. The corresponding mOS values according to radiotherapy were 184.2 months (95% CI: 103.9–264.5) for patients who received radiotherapy versus 81.3 months (95% CI: 24.0–138.6) for those who did not (Log-rank p=0.004) (Figure 1). No statistical difference was found in terms of both RFS and OS in patients who underwent cryotherapy (p=0.177, p=0.693, respectively) (Fig. 2).

Discussion

In this study, the clinical and laboratory data, as well as the prognostic and treatment options, of 45 patients with pulmonary ACC were evaluated. It was concluded that lymph node metastasis and increased Ki-67 are poor prognostic markers, whereas age, lymphovascular invasion, and perineural invasion were not prognostically significant for PACC. The findings suggest a limited role for adjuvant chemotherapy in terms of survival, while radiotherapy may represent a valuable component of local disease control and overall treatment strategy. Furthermore, overall survival in patients who underwent cryotherapy was found to be similar to that of those who received surgical resection. PACC is a disease with late recurrences and despite the potential for metastasis, its 5-year survival rate is 73–79% and its 10-year survival rate is 45–57%.[14,15] Zhao et al. detected lymph node metastasis in approximately 20% of patients with metastatic pulmonary ACC and found that increased lymph node involvement was associated with

Table 2. Univariate Cox regression analysis for survival times

		Recurrence-Free Survival (RFS)		Overall Survival (OS)	
Variable	**Category**	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Sex	Male/Female	0.85 (0.38-1.87)	0.679	0.74 (0.28-1.93)	0.539
Age	<65/≥65	0.97 (0.42-2.24)	0.933	1.08 (0.40-2.92)	0.880
Smoking	No/Yes	0.72 (0.29-1.79)	0.474	0.63 (0.20-1.93)	0.415
Comorbidity	No/Yes	0.62 (0.28-1.37)	0.237	0.93 (0.37-2.38)	0.886
Stage	1/≥2	1.72 (0.51-5.81)	0.382	0.90 (0.25-3.22)	0.876
Histological Type	Solid/ Others	1.55 (0.65-3.73)	0.327	1.55 (0.55-4.43)	0.410
Tumor Location	Bronchi/Lobe	1.38 (0.60-3.18)	0.450	1.99 (0.65-6.06)	0.227
Tumor Size	3cm≤/>3cm	1.47 (0.66-3.26)	0.348	0.56 (0.21-1.49)	0.248
Lymph node	Negative/Positive	4.19 (1.82-9.63)	**0.001**	3.71 (1.33-10.39)	**0.012**
Surgery Type	Cryotherapy/Others	1.72 (0.78-3.82)	0.182	2.56 (0.89-7.38)	0.083
Radiotherapy	No/Yes	0.56 (0.25-1.24)	0.149	0.27 (0.10-0.71)	**0.008**
Chemotherapy*	No/Yes	0.61 (0.27-1.39)	0.237	0.93 (0.36-2.44)	0.888
LVI	No/Yes	0.91 (0.33-2.52)	0.852	0.82 (0.23-2.92)	0.760
Ki-67	Continuous	1.06 (1.02-1.09)	**0.001**	1.04 (1.00-1.08)	**0.031**
Margin	Negative/Positive	1.57 (0.70-3.54)	0.277	2.16 (0.76-6.12)	0.148

[s]Significant values are indicated in bold. * Adjuvant Chemotherapy
LVI: Lymphovascular Invasion; HR: Hazard Ratio; CI: Confidence Interval.

Table 3. Multivariate cox-regression model for factors affecting recurrence-free survival and overall survival

		Recurrence-Free Survival (RFS)		Overall Survival (OS)	
Variable	**Category**	**HR (95% CI)**	***P****	**HR (95% CI)**	***p****
Lymph node	Negative/Positive	3.52 (1.49-8.30)	0.004	8.10 (2.32-28.30)	0.001
Radiotherapy	No/Yes			0.12(0.04-0.41)	0.001
Ki-67	Continuous	1.05 (1.01-1.09)	0.009		

Multivariate cox-regression modeling, including lymph node and ki-67 for RFS and lymph node, radiotherapy and ki-67 for OS were analyzed
*The multivariate model was established using the Forward:LR method. HR: Hazard Ratio.

a reduction in disease-free survival.[11] Gu et al. reported that lymph node metastasis did not have an impact on prognosis.[16] In our study, lymph node metastasis was ob.. served in 42.2% of patients, and it was identified as a poor prognostic indicator (For RFS: HR: 4.19, 95% CI: 1.82–9.63, p=0.001; For OS: HR: 3.71, 95% CI: 1.33–10.39, p=0.012). In patients with PACC, distant metastases are rare; however, local progression contributes to mortality, making the achievement of local control vitally important. Sharma et al. reported in a study of 12 patients that radiotherapy might be beneficial in reducing local recurrence.[17] In our study, 66.7% (n=30) of patients received radiotherapy, and these patients exhibited significantly longer overall survival compared to those who did not receive radiotherapy (HR: 0.27, 95% CI: 0.10–0.71, p=0.008). In patients receiving postoperative adjuvant therapy or with positive surgical margins, there is a lack of robust evidence regarding the efficacy of radiotherapy and the optimal doses to be administered. Je et al. conducted a study with 22 patients and observed that PACC patients who received 50 Gy of thoracic radiotherapy achieved improved survival.[18] Levy et al. reported that patients receiving adjuvant radiotherapy in the range of 45–65 Gy or definitive radiotherapy in the range of 66–70 Gy exhibited better prognoses.[19] At our center, patients were treated with radiotherapy doses ranging from 60 to 70 Gray. Cryosurgery, which initiates cell necrosis through cyclic freezing and thawing of the target tissue, has emerged as a minimally invasive treatment option for lung cancer. It is used as a safe method in selected cases of central lung cancers and rare lung cancer subtypes.[10,20,21] Reported cases of cryotherapy in PACC patients have been documented.[3] In our study, cryotherapy was administered to 44% of the patients instead of surgical techniques, and the survival outcomes were similar to those observed with surgery (HR: 2.56, 95% CI: 0.89–7.38, p=0.083). Based on our literature review, studies comparing cryotherapy and surgery are limited. TNM staging is commonly used for lung cancer, with lymph node metastases categorized as N1 or N2 influencing the

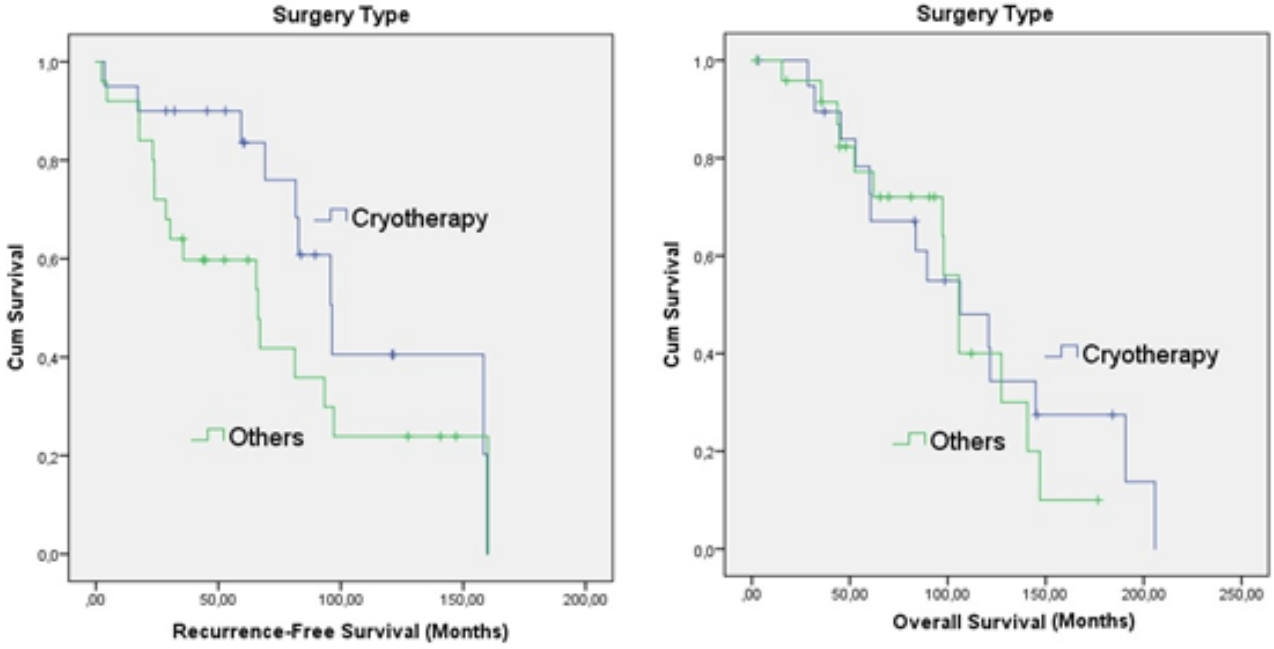

Figure 1. OS and RFS survival curve for all patients, OS curve by radiotherapy status.

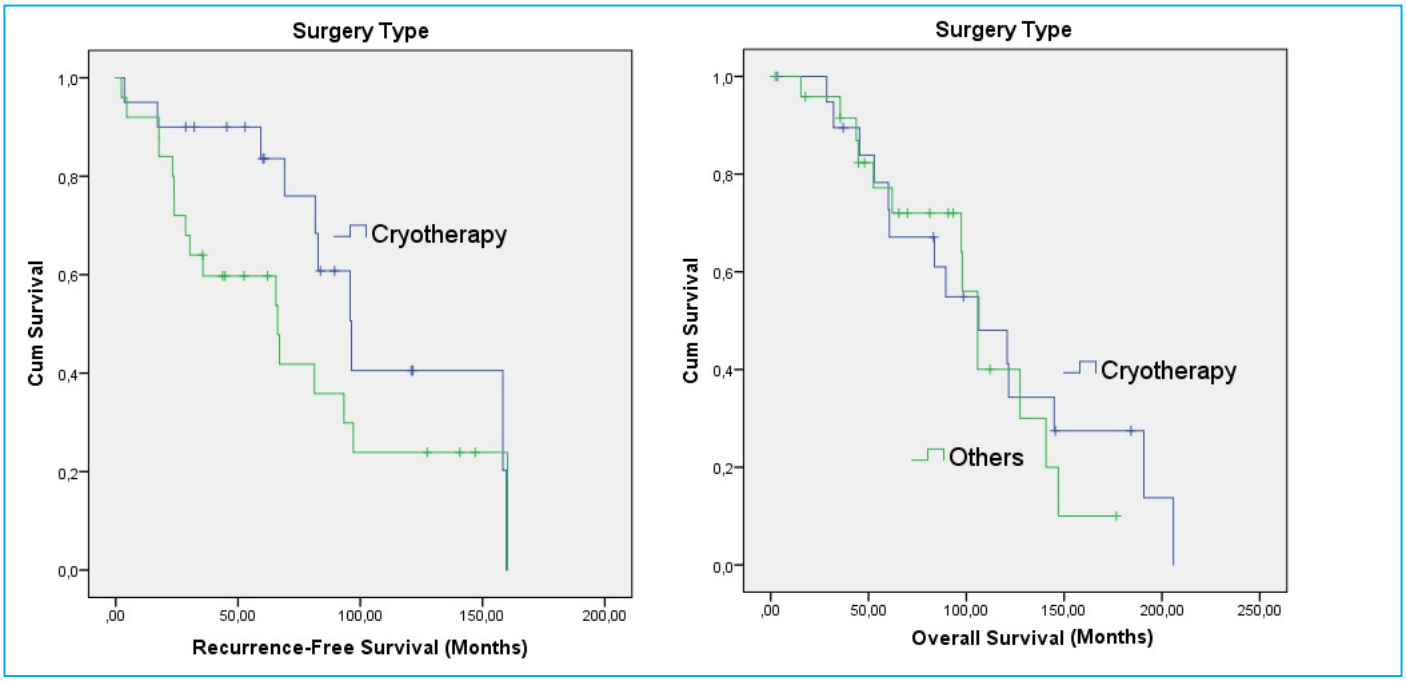

Figure 2. RFS and OS curve by surgery type.

stage. However, there is no specific staging system for pulmonary ACC.[13] In our study, when patients were grouped according to the lung TNM system, no prognostic differences were observed between stage I and stages II–IVa, and similarly, tumor size did not have a prognostic impact. This suggests that treatment decisions should be made independently of tumor size. In a recent multicenter study analyzing 64 patients, lymphovascular invasion and solid histology were identified as independent indicators of recurrence.[6] In our study, however, neither lymphovascular invasion nor solid histology was found to affect prognosis. The present study has several limitations. First, due to the rarity of pulmonary adenoid cystic carcinoma, the sample size was relatively small, which may have limited the statistical power of certain subgroup analyses. Consequently, the absence of statistically significant associations for some clinicopathological variables does not necessarily exclude their potential prognostic relevance. Larger, multicenter studies are needed to validate these findings.

Conclusion

In conclusion, our study demonstrated that in ACC patients, adjuvant chemotherapy does not appear to impact overall survival, and radiotherapy is the most important determinant of survival. Cryotherapy may be a treatment option for ACC patients, but it should be considered as a treatment option due to the lack of patient time. Additionally, we showed that lymph node metastasis at diagnosis and Ki-67 expression may serve as prognostic markers. Future studies should aim to standardize treatment protocols, investigate optimal radiotherapy dosing, and include prospective randomized trials.

Disclosures

Ethics Committee Approval: This retrospective study was approved by the local ethics committee of Ankara Etlik City Hospital (Approval No: AEŞH-BADEK1-2025-038, Date: 06 May 2025).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Authors' contributions: Concept – EZ, SK; Design – EZ, SK; Supervision – EZ, NG, TE; Data collection &/or processing – EZ, NG, TE; Analysis and/or interpretation – EZ, AK, SÇ; Literature search – EZ, AK, SÇ; Writing – EZ; Critical review – EZ.

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