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# Survival Outcomes and Prognostic Factors in Head and Neck Adenoid Cystic Carcinoma Following Curative Surgery

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## ABSTRACT

**Objective:** Adenoid cystic carcinoma (ACC) is a rare malignancy characterized by indolent progression and a high-risk of local recurrence and distant metastasis. This study aimed to identify predictors of recurrence, distant metastasis, and survival among patients with head and neck ACC who underwent primary curative surgery.

**Material and Methods:** We conducted a retrospective analysis of patients with head and neck ACC diagnosed between January 2005 and December 2023. The clinical and pathological parameters were assessed to identify prognostic factors.

**Results:** Among the 125 patients included in the study, recurrence occurred in 73 patients (58.4%) and distant metastasis was detected in 46 patients (36.8%). The estimated 5-year, 10-year, and 15-year recurrence-free survival (RFS) rates were 49%, 27%, and 19%, respectively. The estimated overall survival rates at 5, 10, and 15 years were 86%, 78%, and 55%, respectively. Multivariate analysis revealed that male gender was an independent poor prognostic factor for RFS [hazard ratio (HR): 2.11, 95% confidence interval (CI): 1.15-3.86] and for distant-metastasis-free survival (HR: 2.79, 95% CI: 1.41-5.56). Despite aggressive treatment, more than one-third of patients experience distant recurrence during follow-up.

**Conclusion:** Our study identified male gender as an independent predictor of poor prognosis in patients who underwent primary curative surgery.

**Keywords:** Adenoid cystic carcinoma; head and neck cancer; male gender; prognostic factors; recurrence; salivary gland tumors

## INTRODUCTION

Adenoid cystic carcinoma (ACC) is a rare tumor that originates in secretory glands. ACC is the most common malignant tumor of the minor salivary glands (30%) and the second most common in the major salivary glands (10%).[1] However, ACC may originate from other sites in the head and neck region. ACC predominantly affects women, accounting for approximately 60-70% of cases and being most common in the 5th or 6th decades of life.[2] ACC shows a slow growth pattern, often demonstrating extensive local infiltration and perineural invasion. Most of the time, the symptoms are vague and caused by the mass effect of the primary tumor. Because the tumor grows slowly, diagnosis is often delayed and challenging.

The initial treatment of ACC is surgery; however, achieving clear surgical margins is relatively difficult as the true extent

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of ACC tumors is often underestimated.[3] Surgery is generally followed by external radiation therapy, as ACC appears to be sensitive to radiotherapy (RT), with postoperative RT increased the local control rates.[3,4] Despite aggressive local therapy, typically involving surgery and RT, the majority of ACC patients eventually develop recurrent or metastatic disease. In some studies, the 10-year recurrence rate exceeds 60%.[5,6] Chemotherapy is generally the first-line treatment in the metastatic setting for patients without a targetable mutation who need systemic therapy. Upon disease progression, anti-vascular endothelial growth factor tyrosine kinase inhibitors may be considered.[7-9] The long-term prognoses remain poor, with an estimated overall survival (OS) rate of less than 70% over a 10-year period.[10-12] The rarity of ACC, along with its tendency for late recurrence and the need for prolonged follow-up periods, makes the identification of prognostic markers particularly challenging. In this study, we aimed to evaluate survival outcomes and prognostic factors in patients with head and neck ACC who underwent primary surgery.

## MATERIAL AND METHODS

We conducted a retrospective cohort study involving patients diagnosed with ACC of the head and neck who were treated and followed up at two tertiary hospitals in Ankara, Türkiye, between January 2005 and December 2023. The study included patients who had a diagnosis of ACC of the head and neck, were older than 18 years of age, and underwent primary curative surgery. The study excluded patients with metastatic disease at diagnosis and those with incomplete data required for survival analysis.

We extracted demographic information (e.g., age, gender), Eastern Cooperative Oncology Group (ECOG) performance status, pathological characteristics (e.g., histological subtype, perineural invasion), presence of adjuvant treatment, date of recurrence, date of the last follow-up, and mortality status. Surgical margin positivity is defined as the presence of tumor cells at the resected margin or within ≤5 mm. The primary endpoints of the study were recurrence-free survival (RFS) and factors affecting RFS. Secondary endpoints were distant metastasis-free survival (DMFS) and OS. RFS was defined as the time from surgery to recurrence or death. DMFS was defined as the time from surgery to the date of distant metastasis or death. OS was defined as the time from surgery to the date of death.

The study was approved by the Ankara University Faculty Ethics Committee (date: 10/02/2025, application number: 2025000051-2) and it was carried out in accordance with the Code of Ethics of the World Medical Association also known as a declaration of Helsinki.

### Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Mac, version 24.0 (IBM Corp., Armonk, NY). Continuous variables were expressed as medians with interquartile ranges, while categorical variables were presented as percentages. Categorical variables were compared using the chi-square test, and continuous variables were compared using either the Mann-Whitney U test or the Student's t-test. Survival outcomes were estimated using the Kaplan-Meier method. Multivariate analyses were performed using variables with a p-value of ≤0.10 in the univariate analyses. Multivariable Cox regression analysis was employed to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). All p-values were two-sided, with statistical significance defined as $p<0.05$.

## RESULTS

A total of 152 patients with ACC of the head and neck were identified. Among them, 22 patients were excluded due to metastatic disease at diagnosis, and 5 were excluded due to lack of follow-up and incomplete data for survival analysis. A total of 125 patients were included in the study. The median age was 47 years (range, 19.8-79.8 years). Among the patients, 72 (57.6%) were female, and 77 (63.1%) had an ECOG performance status of 0. Of the primary tumor sites, 40 (32%) originated from the major salivary glands, 40 (32%) from the oral cavity and hypopharynx, and 19 (15.2%) from the nasal sinuses. Other tumor locations are detailed in Table 1. The most common histologic types were cribriform (41.4%) and mixed (41.4%). Among the 114 patients with available clinical T stage data, 16 (14.0%) had T1 disease, 39 (34.2%) had T2, 37 (32.5%) had T3, and 22 (19.3%) had T4. Regarding nodal status (n=115), 97 patients (84.3%) were node-negative, while 18 (15.7%) were node-positive. Only 24 patients (20.9%) underwent surgery resulting in negative surgical margins. A total of 99 patients (79.2%) received adjuvant treatment, of whom 69 (69.7%) underwent RT and 30 (30.3%) received chemoradiotherapy (CRT). Among the 30 patients treated with CRT, 23 received concurrent cisplatin, 2 received carboplatin, and 1 received doxorubicin; the concurrent chemotherapy agent was unknown for the remaining 4 patients.

The median follow-up time was 71.7 months (95% CI: 54.5-88.9). Recurrence occurred in 73 patients (58.4%). Median RFS was 59.9 months (95% CI: 44.4-75.5) (Figure 1A). The 5-year, 10-year, and 15-year RFS were 49%, 27%, and 19%, respectively. By recurrence type, 35 patients (47.9%) experienced only locoregional recurrence, 27 (37.0%) experienced distant recurrence, and 11 (15.1%) experienced both locoregional and distant recurrence. Treatment for the first recurrence is given in Table 2. Multivariate Cox regression analysis showed

**TABLE 1: Baseline characteristics of patients.**

| Variables | | n=125 |
|---|---|---|
| Age, years (median, range) | | 47.01 (19.8-79.8) |
| Age, years (n=125) | <55 | 88 (70.4) |
| | ≥55 | 37 (29.6) |
| Gender (n=125) | Female | 72 (57.6) |
| | Male | 53 (42.4) |
| ECOG-PS (n=122) | 0 | 77 (63.1) |
| | 1 | 42 (34.4) |
| | 2 | 3 (2.5) |
| Primary location (n=125) | Parotid | 16 (12.8) |
| | Submandibular-sublingual gland | 24 (19.2) |
| | Oral cavity-hypopharynx | 40 (32) |
| | Nasopharynx | 7 (5.6) |
| | Nasal sinuses | 19 (15.2) |
| | Maxilla | 9 (7.2) |
| | Mandibula | 1 (0.8) |
| | Orbital | 4 (3.2) |
| | Larynx | 5 (4) |
| Histologic subtype (n=70) | Tubular | 5 (7.1) |
| | Cribriform | 29 (41.4) |
| | Solid | 7 (10) |
| | Mixed | 29 (41.4) |
| T stage (n=114) | 1 | 16 (14) |
| | 2 | 39 (34.2) |
| | 3 | 37 (32.5) |
| | 4 | 22 (19.3) |
| Nodal status (n=115) | N - | 97 (84.3) |
| | N + | 18 (15.7) |
| Surgical margin (n=113) | Negative | 24 (20.9) |
| | Positive | 91 (79.1) |
| Solid component (n=80) | No | 47 (58.8) |
| | Yes | 33 (41.3) |
| PNI (n=93) | No | 20 (21.5) |
| | Yes | 73 (78.5) |
| Adjuvant treatment (n=125) | No | 26 (20.8) |
| | Yes | 99 (79.2) |
| Type of adjuvant treatment (n =99) | RT | 69 (69.7) |
| | CRT | 30 (30.3) |

CRT: Chemoradiotherapy; ECOG: Eastern Cooperative Oncology Group; PNI: Perineural invasion; PS: Performance status; RT: Radiotherapy.

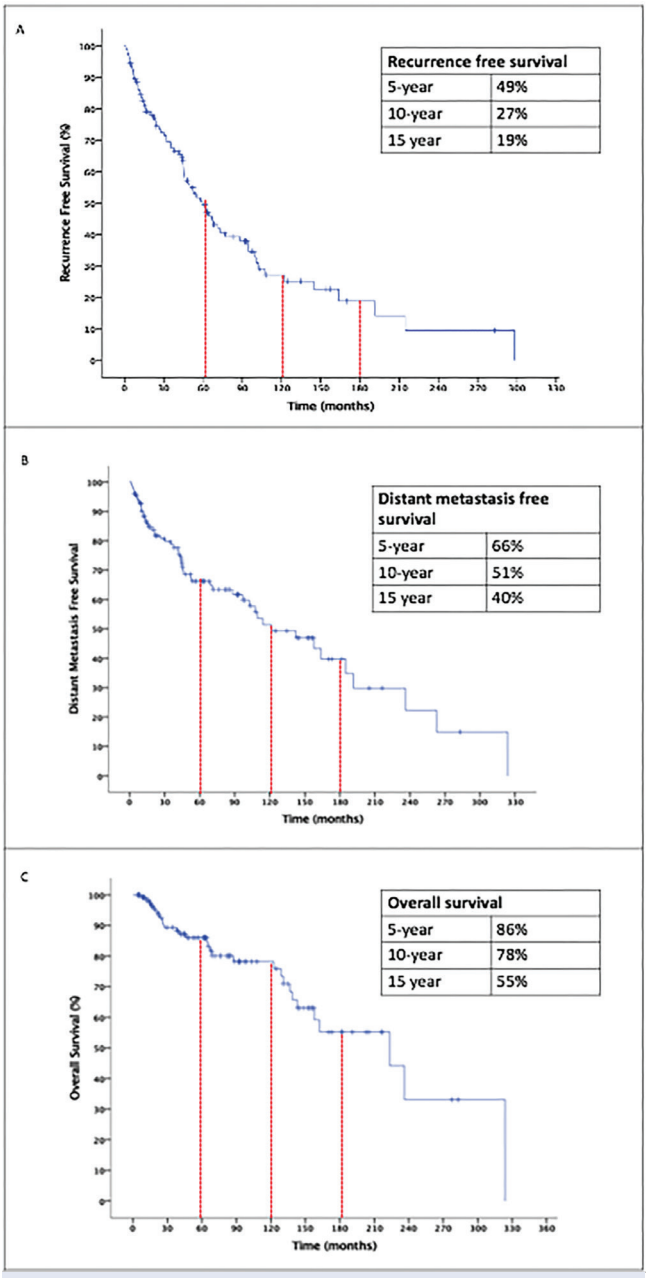


**FIGURE 1:** Kaplan-Meier curve for recurrence free survival (A), distant metastasis free survival (B) and overall survival (C).

that male gender was an independent predictor of RFS (male vs. female HR: 2.11, 95% CI: 1.15-3.86; p=0.016) after adjusting for confounding factors such as primary tumor location, T stage, nodal status, surgical margin, and type of adjuvant treatment (Table 3).

Distant metastasis occurred in 46 (36.8%) patients. The median DMFS was 121.4 months (95% CI: 72.9-169.9) (Figure 1B). Five-year, 10-year, and 15-year DMFS rates were 66%, 51%, and 40%, respectively. The most common metastatic site was the lung (82.6%), followed by non-regional lymph nodes (41.3%), bone (19.6%), and liver (13%) (Table 4). Multivariate

Cox regression analysis showed that male gender was an independent predictor of DMFS (male vs. female HR: 2.79, 95% CI: 1.41-5.56; p=0.003) after adjustment for confounding factors such as primary tumor location, surgical margin, and type of adjuvant treatment (Table 5).

**TABLE 2: Characteristics of first recurrence (n=73).**

| | | |
|---|---|---|
| Type of recurrence | Locoregional | 35 (47.9) |
| | Distant | 27 (37) |
| | Locoregional + distant | 11 (15.1) |
| Type of treatment | Surgery | 21 (28.8) |
| | Surgery + RT | 8 (10.9) |
| | Surgery + CRT | 4 (5.5) |
| | RT | 6 (8.2) |
| | CRT | 3 (4.1) |
| | Systemic treatment | 19 (26) |
| | No treatment | 12 (16.4) |

CRT: Chemoradiotherapy; RT: Radiotherapy.

Thirty (24%) patients died during follow-up. The median OS was 223.3 months (95% CI: 96.6-349.9) (Figure 1C). The 5-year, 10-year, and 15-year OS rates were 86%, 78%, and 55%, respectively. No variables were found to be predictors of OS in the univariate analysis; therefore, multivariate analysis was not performed (Supplementary Table 1).

## DISCUSSION

ACC accounts for only about 1% of all head and neck cancers, and its rarity has limited the availability of high-quality clinical evidence. Because of this, research on ACC is limited. Its prolonged clinical course, initially slow growth, and subsequent progression pose clinical challenges. Due to these factors, real-world data on this disease is generally limited. In our study, we report patient characteristics and prognostic factors associated with this disease, based on a relatively large patient cohort. Our study demonstrated that male gender was an independent prognostic factor for the RFS and DMFS, but did not impact the OS. The 5-year RFS, DMFS, and OS rates were 49%, 66%, and 86%, respectively, while the 15-year RFS,

**TABLE 3: Univariate and multivariate analyses for recurrence free survival.**

| Variable | | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | HR (95% CI) | p | HR (95% CI) | p |
| Age | <55 | 1 | | - | |
| | ≥55 | 1.12 (0.67-1.91) | 0.642 | - | - |
| Gender | Female | 1 | | 1 | |
| | Male | 1.58 (0.99-2.51) | 0.054 | 2.11 (1.15-3.86) | **0.016** |
| ECOG-PS | 0 | 1 | | - | |
| | 1 | 1.33 (0.82-2.16) | 0.247 | - | - |
| Primary location | Major salivary gland | 1 | | 1 | |
| | Other | 2.07 (1.21-3.56) | **0.008** | 1.17 (0.80-3.65) | 0.166 |
| T stage | T1-2 | 1 | | 1 | |
| | T3-4 | 1.56 (0.94-2,58) | 0.083 | 0.97 (0.50-1.86) | 0.917 |
| Nodal status | N - | 1 | | 1 | |
| | N + | 2.02 (1.11-3.66) | **0.021** | 1.74 (0.87-3.48) | 0.116 |
| Surgical margin | Negative | 1 | | - | |
| | Positive | 1.66 (0.93-2.62) | 0.085 | 1.75 (0.79-3.85) | 0.165 |
| Solid component | No | 1 | | - | |
| | Yes | 1.05 (0.57-1.92) | 0.883 | - | - |
| PNI | No | 1 | | - | |
| | Yes | 0.87 (0.43-1.75) | 0.694 | - | - |
| Adjuvant treatment | No | 1 | | - | |
| | Yes | 0.79 (0.45-1.41) | 0.434 | - | - |
| Type of adjuvant treatment | RT | 1 | | 1 | |
| | CRT | 1.35 (1.02-1.79) | **0.037** | 1.28 (0.67-2.42) | 0.455 |

CI: Confidence interval; CRT: Chemoradiotherapy; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; PNI: Perineural invasion; PS: Performance status; RT: Radiotherapy.

DMFS, and OS rates were 19%, 40%, and 55%, respectively. These findings support the indolent but persistent nature of ACC, with a high tendency for late recurrence and metastasis.

RFS, DMFS, and OS rates at landmark time points vary across different studies.[1,10,13,14] A Swedish study involving 142 patients treated with curative intent reported the following survival outcomes: 5-year disease free survival (DFS) of 64.9%, 10-year DFS of 49.6%, and 15-year RFS of 37.7%, while 5-year OS was 83.5%, 10-year OS was 59.4%, and 15-year OS was 42.5%.[15] The study demonstrated that adjuvant treatment prolonged both RFS and OS; however, no significant difference was observed between RT and CRT. The percentage use of adjuvant therapy and the types of adjuvant therapy were similar to those in our study. However, compared with this study, our study observed lower RFS rates but higher OS rates. On the other hand, a large surveillance, epidemiology, and end results program (SEER) database study including 1555 patients diagnosed between 1993 and 2007—including metastatic patients—found 5-year, 10-year, and 15-year OS rates of 85%, 73%, and 67%, respectively.[12] The variability in survival rates across studies is likely attributable to differences in patient demographics, disease stage, histopathological characteristics, and treatment strategies.

In our study, male sex was the only independent poor prognostic factor for recurrence and distant metastasis; however, it was not prognostic for OS. SEER database analysis,

**TABLE 4: Characteristics of distant metastasis (n=46).**

| | | |
|---|---|---|
| Metastasis sites | Non-regional LN | 19 (41.3) |
| | Lung | 38 (82.6) |
| | Liver | 6 (13) |
| | Bone | 9 (19.6) |
| | CNS | 5 (10.9) |
| | Kidney | 1 (2.2) |
| | Adrenal gland | 1 (2.2) |
| Type of treatment | Surgery | 5 (10.9) |
| | Systemic treatment | 30 (65.2) |
| | No treatment | 11 (23.9) |

LN: Lymph node.

**TABLE 5: Univariate and multivariate analyses for distant metastasis free survival.**

| Variable | | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | HR (95% CI) | p | HR (95% CI) | p |
| Age | <55 | 1 | | - | |
| | ≥55 | 1.63 (0.88-2.99) | 0.118 | - | - |
| Gender | Female | 1 | | 1 | |
| | Male | 2.20 (1.24-3.91) | **0.007** | 2.79 (1.41-5.56) | **0.003** |
| ECOG-PS | 0 | 1 | | | |
| | 1 | 1.23 (0.72-2.09) | 0.443 | - | - |
| Primary location | Major salivary gland | 1 | | 1 | - |
| | Other | 1.97 (1.02-1.97) | **0.045** | 1.19 (0.88-4.42) | 0.098 |
| T stage | T1-2 | 1 | | - | |
| | T3-4 | 1.38 (0.75-2.53) | 0.303 | - | - |
| Nodal status | N - | 1 | | - | |
| | N + | 1.54 (0.73-3.22) | 0.257 | - | - |
| Surgical margin | Negative | 1 | | 1 | |
| | Positive | 2.34 (1.08-5.07) | **0.030** | 1.44 (0.64-3.26) | 0.376 |
| Solid component | No | 1 | | - | |
| | Yes | 1.36 (0.64-2.92) | 0.425 | - | - |
| PNI | No | 1 | | - | |
| | Yes | 2.62 (0.79-8.63) | 0.113 | - | - |
| Adjuvant treatment | No | 1 | | - | |
| | Yes | 1.91 (0.76-4.82) | 0.171 | - | - |
| Type of adjuvant treatment | RT | 1 | | 1 | |
| | CRT | 1.49 (1.08-2.07) | **0.014** | 1.51 (0.73-3.09) | 0.266 |

CI: Confidence interval; CRT: Chemoradiotherapy; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; PNI: Perineural invasion; PS: Performance status; RT: Radiotherapy.

including more than 3000 patients, showed OS significantly shorter in male patients with head and neck ACC (HR: 0.73; 95% CI: 0.65-0.8[2]).[12] Also, another SEER database analysis by Lloyd et al.[10] demonstrated that overall and cancer specific survival was shorter in male patients. Furthermore, a recent meta-analysis including 17.497 patients showed that male gender was associated with poor DMFS and OS.[16] Although these results suggest a potential hormonal influence on the biological behavior of ACC, the prognostic impact of male gender remains uncertain, as studies have yielded conflicting results.[17,18] Estrogen receptor β expression has been demonstrated in ACC, and experimental data suggest that estrogen signalling may impact differentiation; however, the clinical relevance of these observations remains uncertain, and any sex-related hormonal contribution to outcomes should be considered hypothesis-generating.[19,20] Additional, possible explanations for the observed female advantage include greater health and body awareness, which may facilitate earlier symptom recognition, timelier presentation to care, and consequently earlier diagnosis.[21]

In univariate analysis, tumor location other than the major salivary gland was associated with shorter RFS and DMFS. Tumors originated from major salivary glands, especially from the parotid gland, and a more favorable prognosis was found in patients who were treated with curative intent.[2] While some cohorts have shown similar findings, not all studies have reported a significant impact of the subsite on disease prognosis.[1,10,13,22,23] ACCs located in the nasal sinuses or nasal cavity are often diagnosed at a later stage than those in the major salivary glands, which may adversely affect prognosis. Although study results are conflicting, considering several studies have indicated, prognosis may worsen with advancing T stage.[1,2,6,24] In our cohort, 91 patients (79.1%) had positive surgical margins. Even in early-stage ACC patients, positive surgical margins are common, and tumor size, location, and the surgeon can influence the likelihood of positive surgical margins. ACC arising near the skull base (nasopharynx, nasal cavity, and paranasal sinuses) is associated with a higher risk of local recurrence, largely because clear margins are difficult to achieve due to involvement of critical structures such as the skull base, dura, cranial nerves, and carotid artery, which limits the extent of resection.[3] Even within the same anatomic location, positive surgical margins are more frequent in ACC than in other histologic types, potentially owing to its marked tendency for perineural spread and infiltrative growth. Positive surgical margin and perineural invasion are other factors that have been identified as predictors of poor outcomes in head and neck ACC.[3,23,25] However, findings regarding prognostic markers remain conflicting, with studies yielding inconsistent results.[26] Moreover, the interrelationships among these defined prognostic markers further complicate their interpretation.

In our cohort, neither the receipt of adjuvant therapy nor the adjuvant modality was associated with survival outcomes. This may be attributable to the vast majority of patients receiving adjuvant treatment, thereby limiting meaningful between-group comparisons. Although postoperative RT with or without concurrent chemotherapy is commonly recommended after resection for head and neck ACC, there are no randomized or prospective trials definitively establishing its benefit. In a retrospective study of 319 patients with non-metastatic head and neck ACC, postoperative RT was associated with improved local recurrence–free survival, but not with DMFS, DFS, or OS.[27] These results align with several other studies showing that postoperative RT primarily impacts local control.[28-30] Since these studies are retrospective, treatment allocation was likely influenced by baseline risk factors, which should be taken into account when interpreting the findings, given the potential for selection bias and confounding by indication.

### Study Limitations

Our study has several limitations. First, its retrospective design is subject to inherent biases, including selection bias and missing data, which may have influenced the outcomes; in particular, several pathological variables were not consistently available across all cases, including histologic subtype, presence of a solid component, PNI, exact surgical margin distance. Second, the relatively low number of death events limited the statistical power of OS analyses, potentially reducing our ability to detect prognostic associations and precluding robust multivariable modeling for OS. Additionally, there are no standardized guidelines for adjuvant treatment in ACC, and treatment approaches are heterogeneous, potentially influencing survival outcomes. Lastly, the impact of molecular biomarkers on prognosis could not be assessed, as molecular testing data were not available for this cohort.

## CONCLUSION

ACC is a rare head and neck tumor characterized by late relapses. Despite aggressive treatment, more than one-third of patients experience distant recurrence during follow-up. Our study identified male gender as an independent poor prognostic factor in patients who underwent primary curative surgery. In the future, prospective multi-institutional studies with larger sample sizes, extended follow-up periods, and molecular marker integration will be needed to further elucidate the prognostic factors for ACC.

### Ethics

**Ethics Committee Approval:** The study was approved by the Ankara University Faculty Ethics Committee (date: 10/02/2025, application number: 2025000051-2) and it was carried out in accordance with the Code of Ethics of the World Medical Association also known as a declaration of Helsinki.

**Informed Consent:** Retrospective study.

### Footnotes

#### Authorship Contributions

Surgical and Medical Practices: H.B., S.Y., S.D.B., İ.H.G., M.K.G., S.A., H.A.Y., Concept: H.B., S.A., H.A.Y., Design: H.B., H.A.Y., Data Collection or Processing: H.B., M.K., T.K.Ş., O.T.D., H.A.Y., Analysis or Interpretation: H.B., H.A.Y., Literature Search: H.B., H.A.Y., Writing: H.B., M.K., T.K.Ş., O.T.D., S.Y., S.D.B., İ.H.G., M.K.G., S.A., H.A.Y.

**Conflict of Interest:** Sercan Aksoy MD is editor-in-chief in Journal of Oncological Sciences. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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