

## Local Recurrence and Survival in Patients with Adenoid Cystic Carcinoma of Head and Neck

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Please cite this article as: Farhan F, Kazemian A, Jafari F, Karimi Hosseini D, Samiee F, Esmati E, et al. Local recurrence and survival in patients with adenoid cystic carcinoma of head and neck. Middle East J Cancer. 2022;13(3):507-14. doi: 10.30476/mejc.2022.87963.1454.

### Abstract

**Background:** Adenoid cystic carcinomas is a rare tumor occurring in major salivary glands. Despite definitive treatment, these aggressive cancers often recur and metastasize with no known effective chemotherapy regimen. The present study aimed to evaluate the recurrence and survival rates of head-and-neck adenoid cystic carcinoma and assess the prognostic factors related to the patients' local recurrence and survival.

**Method:** A retrospective study was conducted on 54 patients with adenoid cystic carcinoma. Demographic data, operative factors of patients before, during, and after surgery were reviewed and finally calculated using the Kaplan-Meier method.

**Results:** Among the 54 patients, 61.1% were female, and 38.9% were male with an average age of  $46.00 \pm 14.52$  years. The survival rate at 12, 24, 36, 60, 84, 100 and 120 months post-surgery were 100, 93.3, 84.4, 48.9, 24.4, 20.0 and 13.3%, respectively. Both the marital status ( $P = 0.002$ ) and the type of surgery ( $P = 0.045$ ) were significantly related to the overall survival of the patients, and the local recurrence significantly correlated with overall survival ( $P = 0.027$ ).

**Conclusion:** According to the findings, marital status, type of surgery, metastases, histological staging, and local recurrence rate were related to the overall survival of the patients. Hence, it is of utmost importance to pay attention to these factors in health centers. It is recommended to opt for case-control and prospective studies with more samples for further investigation in the future.

**Keywords:** Carcinoma, Adenoid cystic, Survival, Local recurrence, Salivary glands

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### Introduction

Salivary gland neoplasms are important types of clinically and mor-

phologically diverse neoplasms.<sup>1</sup> Although these neoplasms grow slowly, they tend to invade the blood

vessels or peripheral nerves early, leading to high incidences of local recurrence and distant metastases (such as bone and lung).<sup>2-4</sup> The salivary gland neoplasm represents 3% of head and neck neoplasms<sup>5</sup> and it is the second main malignant tumor of the salivary glands.<sup>6</sup> It accounts for approximately 1% of all malignancies in the head and neck.<sup>1</sup> Due to the local recurrence of glands in the nerve pathway, physicians, pathologists, and surgeons often face significant diagnostic and management challenges.<sup>7</sup>

Although ACC develops mainly in the salivary glands, it can also occur at other sites such as the trachea, external ear, lacrimal gland, breast, and oropharyngeal nasopharyngeal spaces.<sup>8</sup> Surgery remains to be the main treatment approach for localized ACC.<sup>9</sup>

Poor prognostic factors that affect the outcomes following surgery in resectable cases include perineural invasion, positive margins, and lymph node status.<sup>8</sup> In cases where surgery is impossible, radiotherapy is an alternative method, and systemic therapy may, to a lesser extent, affect ACC patients, which needs further investigations.<sup>8</sup> Since ACC is an uncommon condition, almost all reports are case series using very few sample sizes.<sup>10</sup> Besides, scarce reports exist on population-based ACC and these reports addressed the ACCs' clinical behaviors only at a single anatomic location and not between different locations.<sup>10</sup>

Therefore, the present study aimed to evaluate the recurrence and survival rates in patients suffering from head-and-neck ACC and assess the prognostic factors related to local recurrence and the survival of patients.

## Materials and Methods

This retrospective study was carried out on 54 patients with adenoid cystic carcinoma (ACC) referred to our university hospital, Tehran, Iran, between September 2005 and January 2011. The subjects were identified by a pathology registry review, coded by histologic diagnoses.

This study was performed in concordance with the World Medical Association Declaration of Helsinki, and approved by the Ethics Committee of Tehran University of Medical Sciences (93-

03-51-26688). All participants signed informed consent that their medical records would be used for research.

### *Patients and their demographic data*

The study included patients with pathologically proven ACC and aged 10-90 years. The exclusion criteria were not suffering other malignant diseases than ACC and not being metastatic. Demographic data and the operative factors of patients before, during, and after surgery were reviewed. The duration of treatment, death, surgery, chemotherapy, and radiotherapy was further determined. The staging was done based on the TNM system. The disease-specific survival was also specified and finally analyzed.

### *Statistical analysis*

Data were analyzed using SPSS (ver. 20) statistical analysis software using Chi 2, ANOVA, and t-tests. Patients' survival rate was determined by the univariate Kaplan-Meier test. Hazard ratios (HR) were used to estimate the relationship between clinical and pathological features of interesting outcomes and the significance of the relationships was determined using 95% confidence intervals (CIs). Variables with  $P < 0.10$  on univariate analysis were involved in the multivariate model.  $P < 0.05$  was considered as statistically significant.

## Results

Among 54 patients, 33 (61.1%) were female, and 21 (38.9%) were male with a mean age of  $46.00 \pm 14.52$  years. The sites most commonly involved were the maxillary sinus tumor 15 (27.8%), submandibular gland 11 (20.4%), lingual gland 4 (7.4%), parathyroid 4 (7.4%), lips 4 (7.4%), buccal 3 (5.6%), hard plate 3 (5.6%), and soft plate 1 (1.9%). The diagnosis of all patients was approved by an expert pathologist. In one patient (1.9%), the primary tumor was observed in the nose area and in eight patients (14.8%), in other areas (Table1). The radiotherapy dose and schedule was the same among all patients, and 60 Gy was delivered during six weeks.

As shown in table 2, the T1 stage was observed in 7 patients (13%). In 8 (14.8%) and 10 patients (18.5%) the T2 and T3 stages were detected,

respectively. The T4 tumor was observed in 10 patients (18.5%) and it was unknown in 19 (35.2%) of the patients. Among the therapeutic methods, 15 (27.8%) received chemotherapy. Also, in 39 (72.2%) of the patients, radiotherapy was done during the treatment course (Table 2).

As shown in table 3, lymph node status was negative in 9 (16.7%) and positive in 8 (14.8%) patients, respectively. In 37 (68.5%), lymph node status was unknown. In 10 patients (18.5%), the extracapsular extension was negative, while it was positive in 3 (5.6%). In 41 (75.9%) of the patients, the extracapsular extension was unknown (Table3).

Among 54 patients, 13 (24.1%) had a negative tumor margin and 25 (46.3%) had a positive tumor margin. In 16 of them (29.6%), the tumor margin was unknown (Figure 1).

The perineural invasion was negative in 3 (5.6%) and positive in 25 (46.3%). In 26 patients (48.1%), the perineural invasion was not reported. According to table 4, the local recurrence of the tumor was observed in 31 (57.4%) of the patients, while in 22 (40.7%), local recurrence was not detected. In this study, metastasis was observed in 13 patients (24.1%), while in 39 (72.2%), there was no metastasis and it was unknown in two patients.

Figure 2 demonstrates the results of survival rates according to the variables of disease and treatment type with a median 36 months of follow-

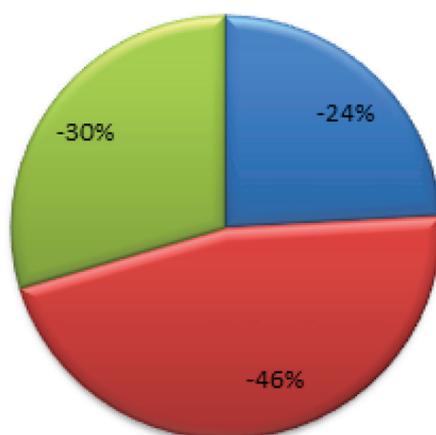
**Table1.** Patients and disease characteristics

Characteristic	Value
<b>Patients (n)</b>	54
<b>Mean age (years)</b>	46.00 ± 14.52
<b>Sex [n (%)]</b>	
Women	33 (61.1%)
Men	21 (38.9%)
<b>Common sites [n (%)]</b>	
Maxillary sinuous tumor	15 (27.8%)
Submandibular gland	11 (20.4%)
Lingual gland	4 (7.4%)
Parathyroid	4 (7.4%)
<b>Lips</b>	4 (7.4%)

up period (ranging from 2 to 185 months); the survival rate after 12, 24, 60, 84, 100, and 120 months was 100, 93.3, 84.4, 48.9, 24.4, 20, and 13.3 %. As shown in figure 2, based on the Kaplan-Meier test, those who were single had a significantly lower survival compared with married couples ( $P = 0.002$ ). The patients who underwent surgical resection showed significantly higher survival rates in comparison with those who were merely biopsied ( $P = 0.045$ ). There was no correlation between the primary tumor site at the time of diagnosis and the patients' survival rate based on the ANOVA t-test ( $P = 0.64$ ). Metastatic patients had a lower survival rate than others, but the difference was not statistically significant ( $P = 0.08$ ).

The multivariate analysis results are presented in table 5. According to the results, tumor relapse

■ negative tumor ■ positive tumor ■ margin was unknown



**Figure 1.** This figure shows the tumor margin in patients undergoing surgical resection due to ACC.  
ACC: Adenoid cystic carcinoma

was the only variable that became statistically significant in this analysis ( $P = 0.027$ ). No significant differences were found based on metastasis ( $P = 0.93$ ), surgery ( $P = 0.96$ ), and marriage ( $P = 0.98$ ).

**Discussion**

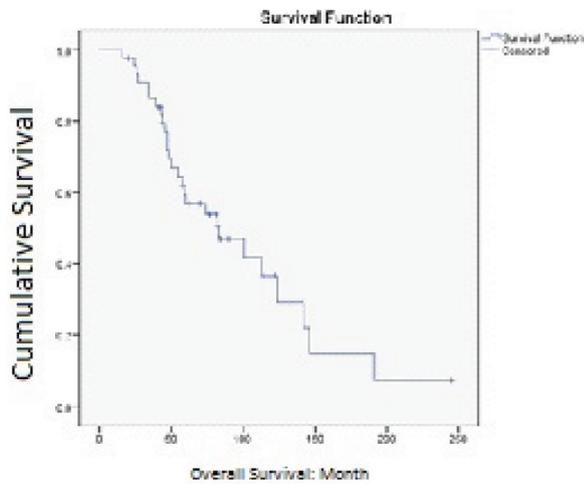
The aim of the present study was to evaluate the recurrence and survival rates of head-and-neck ACC and assess the prognostic factors related to the patients’ local recurrence and survival.

**Table 2.** Patients’ stage and disease characteristics

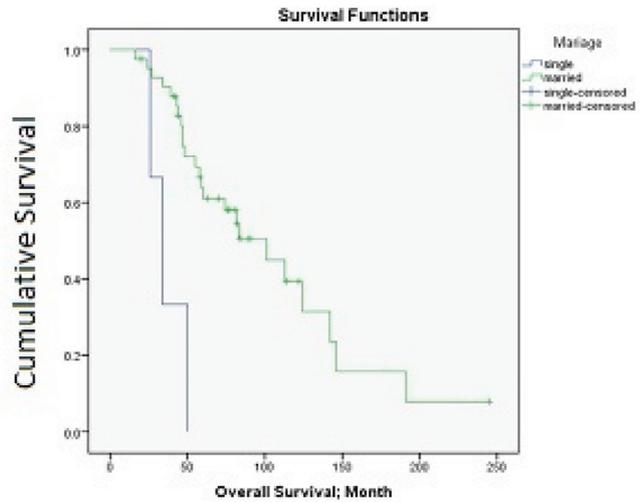
Characteristic stage [n (%)]	Value
T1	7 (13%)
T2	8 (14.8%)
T3	10 (18.5%)
T4	10 (18.5%)
<b>Treatment [n (%)]</b>	
Radiotherapy	39 (72.2%)
chemotherapy	15 (27.8%)

Both the marital status ( $P = 0.002$ ) and the type

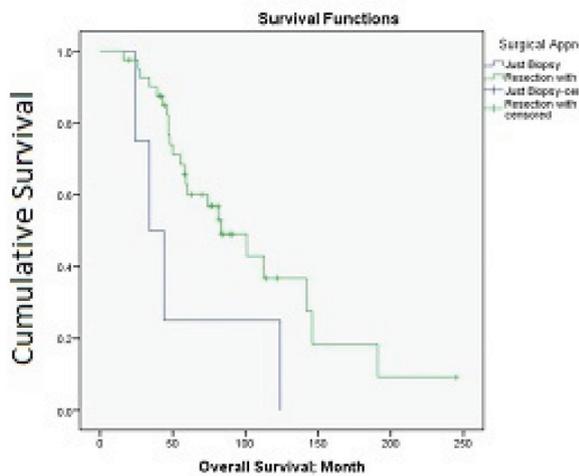
survival rate of the patients



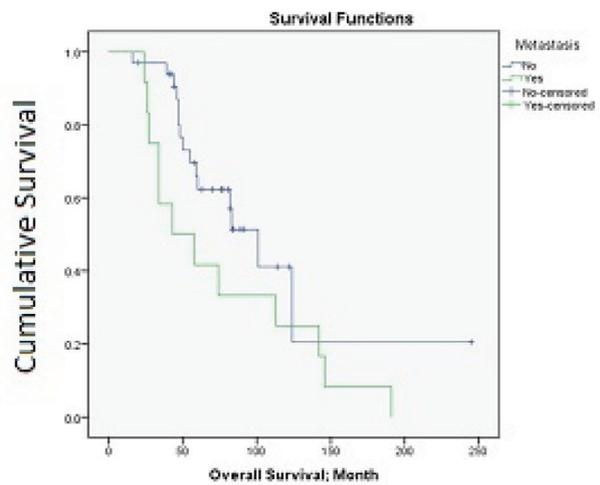
marriage



surgical approach



Metastatic patients



**Figure 2.** This figure shows the disease-survival rate of the patients suffering from salivary gland ACC. ACC: Adenoid cystic carcinoma

**Table 3.** Patients' nodal status and capsular extension characteristics

Characteristic	Value
<b>Nodal status [n (%)]</b>	
Negative	9 (16.7%)
Positive	8 (14.8%)
Unknown	37(68.5%)
<b>Capsular extension [n (%)]</b>	
Negative	10 (18.5%)
Positive	3 (5.6%)
Unknown	41 (75.9%)

of surgery ( $P = 0.045$ ) were significantly related to the overall survival of the patients, and the local recurrence significantly correlated with the overall survival ( $P = 0.027$ ).

The ACC is a tumor with relentless growth that is described based on perineural involvement and many local recurrences. Metastases of the regional lymph node are normally rare. However, they may remain undetectable because of the cervical metastases that are potentially occult and clinically undetectable, with unusual neck dissections and the absence of detailed pathological evaluations of lymph nodes.<sup>11</sup> According to our findings, among the 54 patients, the perineural invasion was negative in 5.6% and positive in 46.3%. In 48.1% of the patients, the perineural invasion was not reported.

In a similar study, combined treatment resulted in an 85% locoregional release from recurring, and the survival rates of disease at 5, 10, and 15 years were 89, 67.4, and 39.6%, respectively. Distant metastases were found in 35 patients (21.9%) as the only involved site. Positive margins at surgery, perineural involvement of major nerves, and solid histological characteristics were reported to have a direct association with increased rates of treatment failure.<sup>12</sup> Due to the high risks associated with local recurrence and distant metastasis, the perineural invasion has been reported as an indicator of poor prognosis in several studies.<sup>9,13-15</sup>

In our study, 24.1% had a negative tumor margin, while 46.3% had a positive tumor margin. In 16 patients (29.6%), the tumor margin was unknown. Resection was not performed in 79 patients (67%) because of the tumor length, distant

**Table 4.** Patients' perineural invasion characteristics

Characteristic	Value
<b>Perineural invasion [n (%)]</b>	
Yes	3(5.6%)
No	25(46.3%)
Unknown	26 (48.1%)
<b>Local recurrence [n (%)]</b>	
Detected	31 (57.4%)
Not detected	22 (42.6%)
<b>Metastasis [n (%)]</b>	
Yes	13 (24.1%)
No	39 (72.2%)

metastasis (7%), regional extent (24%), or other causes (2%). The overall rate of operative mortality was 7.3%, with an improved rate of 21% to 3% over the course of ten years. Lymph node metastasis was present in 19.4% of the resected patients and 40% had tumors in airway margins (ACC 59% versus squamous cell carcinoma 18%). The overall survival rate of 5 and 10 years was 52% and 29% in resected ACC.<sup>16</sup> In a study on six cases with the ACC of head and neck, five patients were treated with surgery followed by radiotherapy; furthermore, four cases had no recurrences or distant metastases after regular follow-up. Only in one case, lung metastasis developed after two years.<sup>17</sup>

Based on our results, the most commonly involved sites were the maxillary sinus tumor, submandibular gland, lingual gland, and parathyroid. Besides, the T1 tumor was observed in seven patients (13%). In 14.8% and 18.5%, the T2, T3, and T4 tumors were detected, respectively. As shown in related studies in salivary glands, the major glands were affected in 20 individuals, the minor glands in 50, while in eight, the maxillary sinus glands gave rise to ACC. The lacrimal glands were affected in six patients. Reclassified TNM-stage at the time of diagnosis varied.<sup>18</sup>

Although several studies have reported a strong relationship between the origin site and prognosis, it remains unclear if the major or minor salivary glands yield a more miserable clinical result.<sup>3,13,19,20</sup>

In another study, the primary tumor location in 56 cases was the hard palate and submandibular

**Table 5.** The results of the multivariate analysis

	P-Value	Hazard ratio	95.0% CI for Exp (B)	
			Lower	Upper
Metastasis	0.933	0.000	0.000	3.869E + 112
Surgery	0.965	115008.328	0.000	2.391E + 233
Marriage	0.988	36833.023	0.000	-
local recurrence	0.027	0.293	0.099	0.871

CI: Confidence interval

region,<sup>17</sup> cases in the parotid gland, and 16 cases in the oral cavity excluding palate. The overall survival rates at 1, 5, and 10 years were 94.6, 60.5, 41.6%, respectively, for all patients.<sup>21</sup>

A multivariate survival analysis of patients diagnosed with the localized disease showed that the risk of mortality was higher in patients developing ACC of major salivary glands compared with those with the ACC of breast or skin.<sup>10</sup> Tumor location is reported as a significant predictor of patients' survival in localized cases of ACC.<sup>19</sup> The head-and-neck ACC occurs with a higher rate in minor salivary glands, skin, lacrimal, and thyroid glands. Distant metastasis was reported in 52% of the patients and can happen with no local relapse. Even in the case of recurrence, patients may survive for several years; in one study 5-year disease-free survival was not different in patients treated with radiotherapy from those treated with surgery alone.<sup>10</sup> Another study revealed that 14% of all disease recurrences happened beyond five years following definitive treatment.<sup>22</sup> A 5-year survival rate of 75% was reported in patients undergoing surgery and post-op radiotherapy for ACC of the minor salivary glands.<sup>23</sup>

Of note, prolonged time or improved local recurrence rate can improve patients' survival, but this has not been well established in the research, even those with a large population.<sup>20</sup> The main prognostic factors for poor survival are advanced age, advanced initial stage, location, histologic subtype, and incomplete surgical resection.<sup>21</sup> The most common prognostic factors reported for overall survival are the T and N stages, histology, and age. TNM stage has been shown to have no direct association with overall survival, explaining the need for more evaluations that are exact and revisal of the TNM staging to

reflect better patient survival.<sup>8</sup>

This study suffers from some limitations, including small sample size and the use of heterogeneous paradigms for treatment. The full pathologic characteristics of some patients were unavailable at the time of recurrence. Since recurrences are mostly diagnosed using fine-needle aspiration and/or treated via non-surgical approaches in our institution, the initial surgical specimen slides may sometimes be unavailable. We attempted to update the available pathologic information; however, further studies with full pathologic reviews would be desirable to confirm these findings.

## Conclusion

ACC is a head-and-neck tumor with a low occurrence rate. Recurrence, either local or distant, is a limiting factor in the life of patients with ACC. Therefore, determining prognostic factors associated with local recurrence is very important. In conclusion, according to our findings, marital status, type of surgery, metastases, histological staging, and local recurrence rate were associated with the patients' overall survival; thus, it is certainly important to pay attention to these factors in health centers, and it is recommended that more case-control and prospective studies be done with more samples for further investigation in the future.

## Acknowledgement

We appreciate Dr. Rosario Mazzola for his generous cooperation in the revision process after the peer review of the manuscript.

## Conflict of Interest

None declared.

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