

Adenoid cystic carcinoma of head and neck. A 5-year retrospective study: Experience in a single third-level reference center

Carcinoma adenoide quístico de cabeza y cuello. Un estudio retrospectivo de 5 años. Experiencia en un centro de referencia de tercer nivel

Sergio I. Gamboa-Hoil¹*, Juan C. Silva-Godínez² y José A. Abrego-Vásquez²

¹Departamento de Cabeza y Cuello; ²Departamento de Cirugía. Hospital de Oncología, Centro Médico Nacional Siglo XXI, Instituto Mexicano de Seguridad Social, Ciudad de México, México

Abstract

Introduction: Adenoid cystic carcinoma (ACC) is a rare tumor, with an annual incidence of 3-4.5 cases/million. **Materials and methods:** We conducted a descriptive and retrospective study. We included patients diagnosed with ACC of head and neck of a single third-level referral center, from January 2008 to December 2013. **Results:** A total of 23 patients were included in the study, 10 males (43.5%) and 13 females (56.5%) (F:M ratio 1.3:1). Median age was 52 years. Localization was predominantly observed in the oral cavity (26%) followed by the palate (17.4%). At presentation, 15 patients (65.2%) had clinical Stage II. The most frequent histology was the cribriform type in 10 patients (43.5%). Following resection, positive margins were observed in 15 (65.2%), neural invasion in 8 (34.8%), and lymphovascular invasion in 2 (8.7%) patients. The median time to recurrence in our population was 23 months. Recurrence at 5 years was observed in 15 patients (65%). At 2 years, recurrence was predominantly local in 7 patients (46%); whereas after 2 years, it was predominantly pulmonary 6 patients (40%). Overall, 5 year-survival was 78%. **Conclusions:** Cystic adenoid carcinoma is characterized by a high recurrence rate. Nevertheless, it has a high overall 5-year survival, which justifies an aggressive treatment.

Key Words: Salivary gland. Sinonasal. Rare tumor.

Resumen

Antecedentes: El carcinoma adenoide quístico es un tumor raro, con una incidencia anual de 3-4.5 casos por millón. **Materiales y métodos:** Estudio descriptivo, retrospectivo, que incluyó pacientes con carcinoma adenoide quístico de cabeza y cuello de un centro de referencia de tercer nivel, desde enero de 2008 hasta diciembre de 2013. **Resultados:** Se incluyeron 23 pacientes, 10 hombres (43.5%) y 13 mujeres (56.5%) (relación 1.3:1), con una media de edad de 52 años. Predominó en la cavidad bucal (26%), seguida del paladar (17.4%). Al diagnóstico, 15 pacientes (65.2%) tenían estadio clínico II. La histología cribiforme fue la más frecuente (10 pacientes; 43.5%). Posterior a la cirugía, se observaron márgenes positivos en 15 (65.2%), invasión neural en 8 (34.8%) e invasión linfovascular en 2 (8.7%) pacientes. La media de recurrencia fue de 23 meses. La recurrencia a 5 años se observó en 15 pacientes (65%). A los 2 años predominó la recurrencia local (7 pacientes; 46%); después de los 2 años predominaron las metástasis pulmonares (6 pacientes; 40%). La supervivencia a 5 años fue del 78%.

Correspondencia:

*Sergio I. Gamboa-Hoil

Calle 14, 100f

C.P. 97577, Cuzamá, Yucatán, México

E-mail: sergio_gamboa@hotmail.com

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Conclusiones: *El carcinoma adenoide quístico se caracteriza por una alta tasa de recurrencia. Sin embargo, tiene una alta supervivencia global a 5 años, lo que justifica un tratamiento agresivo.*

Palabras Clave: *Glándula salival. Sinonasal. Tumor raro.*

Introduction

Adenoid cystic carcinoma (ACC) is a rare tumor, with an annual incidence of 3-4.5 cases per million. It represents < 2% of all head and neck malignancies and about 40-50% of the neoplasms of salivary glands. Malignant tumors of the salivary glands represent 2-4% of all cancers of the head and neck^{1,2}.

ACC is mostly observed in the middle age, between the 5th and 6th decades of life³⁻⁵. The incidence rate has been reported in 0.71 and 0.39 cases per 100,000 habitants for males and females, respectively, with an M:F ratio of 1.8:1². Smoking, alcoholism, and human papillomavirus infection have not been shown to constitute risk factors^{6,7}.

The parotid gland is the most frequently affected site (20.6% of cases)⁸. ACC with sinonasal origin displays a broad spectrum of symptoms⁸⁻¹⁰. It presents in earlier stages in minor salivary glands (T1 and T2 lesions)^{11,12}.

Ultrasound has a diagnostic sensitivity between 62% and 84% and a specificity between 88% and 96%¹³. In the evaluation of skull base involvement, computed tomography has a reported sensitivity and specificity of 88 and 89%, respectively, whereas magnetic resonance has a sensitivity of 100% and specificity of 85%^{14,15}. The role of positron emission tomography with 18-fluorodeoxyglucose is to rule out distant disease, with a reported sensitivity and specificity of 85.7% and 96.3%, respectively¹⁶.

Resection surgery, with a 1-2 cm negative margin is the treatment of choice. Elective neck dissection is not routinely indicated^{2,12,17}.

Radiation treatment, indicated as either a single modality or as part of combined treatment with surgery, offers no survival benefit for early-stage lesions^{2,17}. Chemotherapy is controversial due to the slow growth rate observed and lack of response². Recurrences have been reported at 2 years up to 50% of cases, without observing a universal prognostic factor¹⁸.

In the present report, we describe our experience making emphasis on clinical and pathological characteristics in patients with ACC of head and neck, treated at our institution between January 2008 to December 2013.

Materials and methods

We conducted a descriptive, retrospective study including patients diagnosed with ACC of head and neck, treated with surgery at the Head and Neck Department of the Oncology Hospital of the Mexican Social Security Institute during the period from January 2008 to December 2013. This department serves around 13% of all cancer patients referred to this center.

We considered the following variables: age, sex, site of primary tumor, predominant histologic subtype in each case, size of tumor, positive lymph nodes, metastases, clinical-stage, margins, presence of perineural invasion, presence of lymphovascular invasion, capsular rupture, and degree of differentiation and ulceration. In addition, overall survival and recurrence rate was calculated according to the variables aforementioned. Margins were defined as follows: clear margin was considered when no tumor was found in the margin; positive margins were considered when tumor was found in the margin.

Descriptive statistics were used to present the results. To compare nominal variables, Chi-squared test was used, $p < 0.05$ was considered significant. We used SPSS version 25 software to conduct the analyses. We considered the American Joint Committee on Cancer Classification Staging Manual, 8th Edition for Staging purposes¹⁹.

Results

A total of 25 cases were identified. Two cases were excluded from the analyses; one patient did not have a clinical file and one who received follow-up outside our unit. We analyzed data on 23 patients.

Females were more frequently affected (13 patients, 56.5%, female: male ratio 1.3: 1). The median age was 52 years. Six patients (26%) had comorbidities. The demographic characteristics of our population are presented in table 1.

The most frequent presentation site was the oral cavity (6 patients, 26%) followed by the palate (4 patients, 17.4%) and the maxillary sinus (4 patients, 17.4%) (Table 2).

The majority of patients presented with Stage II disease (15 patients, 65.2%). The most frequent histology was cribriform type in 10 patients (43.5%).

Table 1. Characteristics of patients with adenoid cystic carcinoma of head and neck

Characteristics	Measurement scale	Patients = 23 (%)
Diabetes mellitus	Yes	1 (4.3)
Arterial hypertension	Yes	5 (21.7)
Smoking	Yes	8 (34.8)
Alcoholism	Yes	6 (26.1)

Table 2. Sites and subsites for presentation

Sites	Subsites	Patients = 23 (%)
Major salivary glands	Parotid	2 (8.7)
	Submandibular	2 (8.7)
Minor salivary glands	Oral cavity	6 (26)
	Lower lip	1 (4.3)
Oropharynx	Tongue base	2 (8.7)
	Palate	4 (17.4)
Paranasal sinuses	Maxillary	4 (17.4)
	Ethmoidal	1 (4.3)
Eyelid		1 (4.3)

A combination of cribriform type with other histological variants was observed in 10 patients (43.5%). After resection, positive margins were observed in 15 patients (65.2%) and neural invasion in 8 patients (34.8%). Grade II tumors were the most frequent (16/23 patients, 69.6%) (Table 3).

Treatments performed in our population are shown in table 4. One patient with a lesion located in the maxillary sinus was treated with neoadjuvant chemotherapy based on 2,5-fluorouracil cycles followed by surgery and adjuvant radiotherapy; one patient with a lesion located in the oral cavity was treated with neoadjuvant chemotherapy based on 1 cycle of carboplatin and paclitaxel followed by surgery without radiotherapy and one patient with a lesion located in the maxillary sinus was treated with neoadjuvant chemotherapy based on 4 cycles of carboplatin and paclitaxel-doxorubicin followed by surgery, without radiotherapy (Table 4).

We found no difference in recurrence at 5 years when considering tumor site presentation and histopathological characteristics; only the variable age < 60 years showed statistical significance when analyzing 5-year survival ($p = 0.003$). No other variables were found to be significant (Table 5).

We observed a greater recurrence rate in the first 2 years (8 patients, 53%). Local recurrence was more

Table 3. Histopathological characteristics

Characteristics	Measurement scale	Patients = 23 (%)
Histology	Cribriform	10 (43.5)
	Solid	2 (8.7)
	Cribriform tubular	3 (13)
	Cribriform solid	3 (13)
	Cribriform solid tubular	4 (17.4)
	Solid tubular	1 (4.3)
Size	T1	5 (21)
	T2	17 (73.9)
	T3	1 (4.3)
Lymph nodes	Yes	2 (8.7)
Metastases	No	23 (100)
Clinical stage	I	5 (21.7)
	II	15 (65.2)
	III	3 (10)
Positive margins	Yes	15 (65.2)
Neural invasion	Yes	8 (34.8)
Lymphovascular invasion	Yes	2 (8.7)
Capsular rupture	Yes	0 (100)
Grade	I	3 (13)
	II	16 (69.6)
	III	4 (17.4)
Ulceration	Yes	2 (8.7)

Table 4. Treatment performed

Treatment	Patients = 23 (%)
Surgery	13 (57)
QT neo + surgery	2 (9)
Surgery + Rt adjuvant	7 (30)
Qt neo + surgery + RT adjuvant	1 (4)

QT neo: neoadjuvant chemotherapy; Rt: radiotherapy.

common at 2 years follow-up as compared to late recurrence (7 patients, 46% vs. 1 patient, 7%), $p = 0.008$. Lung was the most frequent site of distant recurrent (Table 6).

The median time to recurrence was 23 months (range 4-60 months). Two-year recurrence-free survival was 65%, whereas 5-year recurrence-free survival was 35%. Two-year overall survival was 96% and 5-year overall survival as 78% (Fig. 1).

Table 5. Frequency of recurrence and 5-year survival according to the site of presentation and histopathological characteristics

Characteristics	Measurement scale	Recurrence 15 (65%)	No recurrence 8 (35%)	p-value	Survived 18 (78%)	No survived 5 (22%)	p-value
Age	Minor 40	4 (17)	0 (0)	0.13	1 (4)	3 (13)	0.003
	40-60	8 (35)	6 (26)		14 (61)	0 (0)	
	Greater 60	3 (13)	2 (9)		3 (13)	2 (9)	
Gender	Male	7 (30)	3 (13)	0.51	8 (35)	2 (9)	0.63
	Female	8 (35)	5 (22)		10 (43)	3 (13)	
Sites	Major salivary glands	2 (9)	2 (9)	0.34	2 (9)	2 (9)	0.28
	Minor salivary glands	4 (17)	3 (13)		6 (26)	1 (4)	
	Oropharynx	5 (22)	1 (4)		6 (26)	0 (0)	
	Paranasal sinuses	4 (17)	1 (4)		3 (13)	2 (9)	
	Eyelid	0 (0)	1 (4)		1 (4)	0 (0)	
Histology	Cribriform	9 (39)	4 (17)	0.48	9 (39)	4 (17)	0.25
	Solid	6 (26)	4 (17)		9 (39)	1 (4)	
Size	T1	2 (9)	3 (13)	0.20	4 (17)	1 (4)	0.70
	≥ T2	13 (57)	5 (22)		14 (61)	4 (17)	
Lymph nodes	(+)	1 (4)	1 (1)	0.88	2 (9)	0 (0)	0.60
	(-)	14 (61)	7 (30)		16 (70)	5 (22)	
Clinical stage	I	2 (9)	3 (13)	0.20	4 (17)	1 (4)	0.70
	≥II	13 (57)	5 (22)		14 (61)	4 (17)	
Positive margins	(+)	11 (48)	4 (17)	0.25	11 (48)	4 (17)	0.41
	(-)	4 (17)	4 (17)		7 (30)	1 (4)	
Neural invasion	(+)	6 (26)	2 (17)	0.40	7 (30)	1 (4)	0.41
	(-)	9 (39)	6 (26)		11 (48)	4 (17)	
Lymphovascular invasion	(+)	1 (4)	1 (4)	0.88	2 (9)	0 (0)	0.60
	(-)	14 (61)	7 (30)		16 (70)	5 (22)	
Capsular rupture	(-)	15 (65)	8 (35)		18 (78)	5 (22)	---
Grade	I	2 (9)	1 (4)	0.89	2 (9)	1 (4)	0.48
	II	10 (43)	6 (26)		12 (52)	4 (17)	
	III	3 (13)	1 (4)		4 (17)	0 (0)	
Ulceration	(+)	2 (9)	0 (0)	0.41	2 (9)	0 (0)	0.60
	(-)	13 (57)	8 (35)		16 (70)	5 (22)	

p ≤ 0.05: significant.

Discussion

In our cohort, ACC was more frequent in females (male:female ratio 1:1.3). Our incidence rate and median age at presentation (52 years) are similar to those previously reported by Ouyang et al.⁸ and Monteriro

et al.¹¹, as well as in a national report by Luna-Ortiz et al.³

We observed an overall 5-year survival of 77% in females and 80% in males. Monteiro reported a 72.1% overall survival rate in females, and 62.7 in males. In our study, in the same way as published by Pinakapani

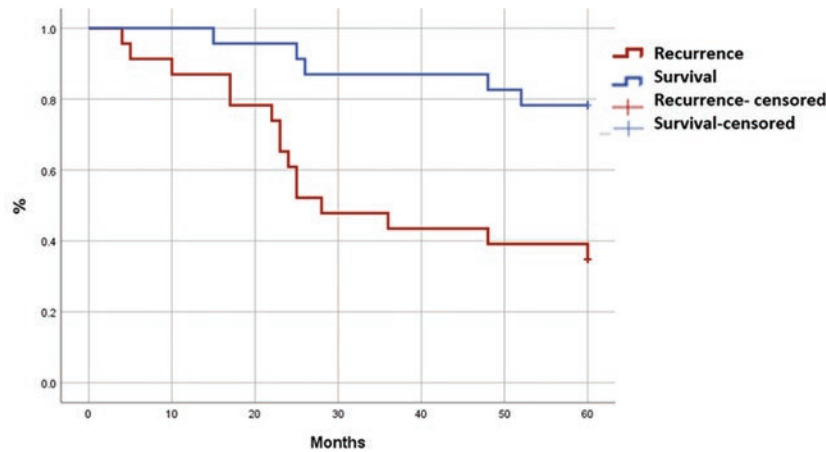


Figure 1. Overall survival and recurrence rate at 2 and 5 years.

Table 6. Local and distance recurrence according to the period of time studied

Time (month)	Local	Local + pulmonary	p-value
≤ 24	7 (46)	1 (7)	0.008
> 24	1 (7)	6 (40)	

p ≤ 0.05: significant.

et al.⁹, there are not significant differences in survival related to gender. Like Ouyang, we found not an association between age and survival. In opposition, Chang et al.² found an association between age and local recurrence. This association was not observed in our study.

We observed a greater frequency of lesions in the oral cavity followed by the palate and maxillary sinus. In comparison, Ouyang and Monteiro reported a higher frequency in the palate (29.4%) followed by submandibular lesions (19.3%). While this contrasts with previous reports, we grouped oral cavity lesions that involved floor of the mouth, trigone, jugal mucosa, and the malar area. In Pinakapani's report, the palate is the most frequent intraoral site, whereas the parotid is the most frequent among the major salivary glands.

In addition, we observed a predominance of female patients affected with the nasal cavity and paranasal sinuses lesions. Maxillary sinus was more frequently involved (80%) followed by ethmoidal sinus (20%). Lupinetti et al.¹² and Miller et al.⁶ reported a greater frequency in the maxillary sinus from 29.5% to 52% followed by the nasal cavity and the ethmoidal sinus.

With respect to lesion size, we found a greater frequency of T2 tumors (73.9%) with an average tumor

size of 3.1 cm (range 1.0-7.0 cm), in concordance with the report by Luna, and similar to the series of da Cruz et al.⁴, who reported an average size of 3.1-4.3 cm. In contrast, Lupinetti reports T4 lesions in 65% of the cases, whereas Guntinas-Lichius et al.¹⁰ observed T2 in 60%. In our cohort, we observed a 80% survival rate in patients with T1-T2 lesions in contrast to Amitt et al.²⁰, who observed a 5-year overall survival of 51%.

We observed positive margins in 65.2% of our cases, in contrast to Luna who reported margins positive in 32.6% of cases. We believe that our high rate of positive margins is due to the fact of tumor site presentation, which is in accordance to Lupinetti, who reported negative margins after resections in 36.4% of their cohort and Bradley, who discusses that tumor location, particularly in the nasal cavity and paranasal sinuses, has a worse prognosis due to the technical difficulty in achieving adequate margins of the tumor¹⁸. In this regard, Amit et al.²¹ described positive margins as a prognostic factor for overall survival (HR 2.68 p = 0.04) in comparison to negative or close margins (< 5 mm, HR 1.1, p = 0.23), that is, it had an equal impact on overall survival. It is important to consider that several studies consider positive and close margins together in the evaluation of survival, which reflects different results. In addition, other authors have reported that negative margins do not seem to improve survival, but local control⁹.

Considering lymph node affection, 8.7% of our cases presented with positive lymph nodes, similar to the rate observed by other reports. Similar to Luna, we did not observe a difference in survival in patients with positive lymph nodes. In addition, we did not observe

patients with metastases at the time of diagnosis; however, an incidence of 4.4-8.5% has been reported^{1,4,8}.

About 57% of our patients received only surgery as treatment, whereas 30% received adjuvant radiotherapy and an additional 13% received neoadjuvant chemotherapy. In both local and international reports surgery followed by adjuvant radiotherapy is reported as the most frequent treatment²⁻⁴. As Monteiro, we did not observe significant differences in treatment modality and 5-year survival.

The use of chemotherapy is controversial, with a limited and poorly defined role, used in most cases as palliative management. However, Amit et al.²¹, on the other hand, consider that the small number of patients treated with primary chemoradiation with curative intent limits any significant analysis.

In our series, cribriform histology was the most frequent (43.5%), while solid histology was present in 8.7%. Cribriform type is reported as the most frequent histology (44.1-70.7% of cases) followed by solid histology (20.6-29.3%)^{3,4,8}. When addressing survival, according to histology, we did not observe a significant difference. However, da Cruz found solid histology to be a prognostic factor in survival. In contrast, both Lupinetti et al., and Wang²² reported a significant difference in the specific survival of disease in favor of cribriform histology.

We observed perineural invasion (presence of viable tumor in the perineural space) in 34.8% of our cases, in contrast to other studies that report up to 48.3% with lymph node involvement². In our study, accordance with Chang and Luna, significant statistical differences between perineural invasion and survival were not found. Pinakapani considers perineural invasion as a prognostic factor, due to the inherent risks of neural propagation, but results have not been clear^{2,3,9}.

Ouyang reported T3-T4 lesions, positive lymph nodes, and lymphovascular invasion as risk factors for local recurrence. For metastases, he added positive margins. Monteiro reported age > 50 years as a prognostic factor for overall, as well initial stage and the perineural invasion. Amit et al.²⁰ reported age as prognostic factors the age over 70, nodal involvement, metastasis, free margins, and tumors located in the nasal cavity and paranasal sinuses; however, in another report²¹, he found no statistical differences between perineural invasion and overall survival or disease-specific survival.

We observed a median time to local or distant recurrence observed of 23 months, similar to that

reported by da Cruz of 27.2 months. We observed a 5-year recurrence rate of 65%. Local recurrences were observed in 53% and distant recurrences in 40%, which combined local recurrence plus metastasis in 47 %. In the same manner, as to risk factors, recurrence rates vary according to the author. Monteiro et al. reported a recurrence rate of 34.7%, while da Cruz reported 55%. Local recurrences have been described from 10.3% to 74% and metastases from 17.2% to 68.5%^{2,4,8,11,23}.

We observed that lung was the most frequent site of metastasis (100% of our cases) with a median time to distant recurrence of 28.5 months. Females were more prone to develop a distant recurrence (57.2%). Girelli et al. reported the lung as the most frequent site of recurrence, with the majority of lesions appearing after 36 months of follow-up. However, Girelli observed a greater frequency in males (58%)²⁴. Spiro²⁵ suggested that the incidence of metastases to other anatomical sites is probably higher than previously recognized, because once the lung metastases are detected no further investigations are made.

Five-year overall survival observed in our cohort was 78%, which agrees with that reported by Luna of 57.6% and other authors. In our study, 5-year survival in patients without recurrence was 100%, while in patients with recurrences, this dropped to 66%. In contrast, Ouyang reported a 5-year overall survival in patients without recurrence of 86.1%, and in patients with recurrence of 81.2%, and Lupinetti observed a 5-year survival in patients nasal cavity and paranasal sinuses tumors of 62.9% and recurrence in 56.2% (30.5% local and 38.1% distant, 67% with lung metastases).

As pointed out by Coca-Pelaz et al. and Bradley, due to the tumoral behavior and the possibility of late recurrences and distant metastasis after many years, it is important to have longer surveillance periods^{1,18}.

Conclusions

The cystic adenoid carcinoma is characterized by a high frequency of recurrences but with a high overall survival at 5 years, which justifies an aggressive surgical treatment.

Conflicts of interest

The authors declare not having any conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments have been conducted on humans or animals for this research.

Confidentiality of the data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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