Adenoid Cystic Carcinoma in a Mexican Population

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Abstract

Objective To analyze the demographic data, clinical behavior, management (surgery/radiotherapy), disease-free survival (DFS) and overall survival (OS) in Mexican Mestizos with adenoid cystic carcinoma (ACC).

Material and Methods A retrospective study comprising all cases with histologic diagnosis of ACC of the head and neck treated from 1986 to 2012.

Results There were 101 cases (69 women and 32 men), with a mean age of 50 years; mean evolution time before diagnosis was 25 months (range 1–180 months). Most tumors involved maxillary sinus (25.8 %), followed by hard palate (15.9 %) and parotid gland (10.9 %). Surgery was the treatment in 81 cases (80.2 %), radiotherapy alone in 3 cases (3 %), chemo-radiotherapy in 4 cases (4 %) and 13 cases (12.9 %) did not receive any treatment. Post-surgery adjuvant radiotherapy was used in 58 cases (57.4 %); 6 cases (5.9 %) had adjuvant chemo-radiotherapy after surgery and 37 (36.6 %) cases did not receive any adjuvant treatment. Mean follow-up time was 52 months (range 1–288 months). Histologic patterns were cribriform (50.5 %), solid (28.7 %), and tubular (11.9 %) types. OS

was 57.6 % and 42.3 % at 5 and 10 years respectively. DFS was 57.8 % at 5 years and 49.7 % at 10 years.

Conclusions Initial management in most cases within this series was surgery followed by radiotherapy. There is more to learn about real benefits of molecular therapies. There were no significant differences in DFS and OS depending on site of involvement. OS did not show statistically significant differences amongst patients with positive and negative lymph nodes.

Keywords Adenoid cystic carcinoma · Head and neck · Salivary glands · Surgery

Introduction

Salivary gland tumors may arise from parotid, submandibular, sublingual, or any of the intraoral salivary glands located throughout the oral mucosa and pharynx, the seromucous glands of the nasal passages, sinuses, larynx, and also from ectopic salivary gland tissue. Adenoid cystic carcinoma (ACC) is a malignant neoplasm characterized by a slow, indolent growth; it frequently produces perineural invasion and distant metastasis, mainly to the lung and bones, followed, in decreasing order, by brain, liver and omentum [1, 2]. Several indicators of bad prognosis have been recognized, such as advanced clinical stage, solid histologic subtype, increased p53 expression, positive surgical margins after resection, and perineural invasion [1].

Surgery of the primary tumor remains as initial treatment of choice for ACC, and frequently it is complemented by neck dissection, whose value is still under discussion in the literature [2] and this is usually followed by postoperative radiotherapy; however, there has not been established

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yet an effective systemic management for recurrent or metastatic ACC, and it is not known if systemic therapy impacts on the course of the disease [3]. The aim of our study is to analyze the demographic data, clinical behavior, surgical management of the primary tumor and neck management of adenoid cystic carcinoma (ACC), as well as to describe the adjuvant treatment with radiation therapy, disease free survival and survival in Mexican Mestizos.

Materials and Methods

In a retrospective study from 1986 to 2012 we retrieved information from those patients with primary ACC of the head and neck treated at a single cancer institution in Mexico City, and reviewed their clinical files considering the following variables: age, sex, evolution time previous to diagnosis, site of primary tumor, initial and adjuvant treatments, predominant histologic subtype in each case, presence of perineural invasion, recurrences and metastases. Additionally, general overall survival and disease-free survival figures were calculated and the tumor distribution according to site (major salivary glands, intraoral, or extraoral minor salivary glands) was recorded. Margins were defined as follows: *Clear* margin was considered when tumor-free margins were ≥ 5 mm; *close* margin when tumor-free margins were between >1 and <5 mm; *positive* margins were considered when tumor was ≤ 1 mm [4]. Histological grades were defined according to Perzin et al. [5] as: Grade I, a predominantly tubular pattern, without a solid component. Grade II: a predominantly cribriform pattern with a maximum of 30 % of solid pattern. Grade III: more than 30 % of solid pattern. Descriptive statistics of nominal variables and a bivariate analysis were performed to compare variables related with recurrence; significant variables were included in a multivariate analysis. Overall survival and disease free survival curves were analyzed with Kaplan–Meier. For this purpose we used SPSS version 20.0 software.

Results

A total of 101 cases of adenoid cystic carcinoma of the head and neck region were included for demographic analysis. Of these, 16 lacked follow-up and did not receive treatment. Table 1 shows the site of origin of the tumors, with most cases developing from extraoral glands (41.6 %), followed by intraoral minor salivary glands (35.6 %) and major salivary glands (22.8 %). Eighty-five cases were included for long term follow-up. Thirty-two cases (31.7 %) were men and there were 69 (68.3 %)

Table 1 Location of ACC in the present series

Site	N (%)
Intraoral minor salivary glands	36 (35.6 %)
Hard palate	16 (15.9)
Tongue	7 (6.9)
Gum	4 (3.9)
Floor of mouth	3 (2.9)
Oral mucosa	5 (4.9)
Lip	1 (0.9)
Major salivary glands (all)	23 (22.8)
Parotid	11 (10.9)
Submandibular	9 (8.9)
Sublingual	3 (2.9)
Extraoral minor salivary glands	42 (41.6)
Maxillary sinus	26 (25.8)
Nasal cavity	4 (3.9)
Orbitary region (glandula lagrimal)	10 (9.9)
Nasopharynx	1 (0.9)
Larynx	1 (0.9)
Total	101(100)

women, with a men to women ratio of 1:2.4, a mean age at presentation of 50 years (range 18–91 years), and a mean time of evolution prior to diagnosis of 25 months (range 1–180 months). Ninety cases (89.1 %) had negative cervical lymph nodes at the time of diagnosis. Lymph node dissection was performed in 16 of these cases, 9 of which had metastasis. There were 11 cases (10.9 %) with positive lymph nodes at initial diagnosis, 6 of which had evidence of metastasis; however, overall survival did not show statistically significant differences among patients with positive and negative lymph nodes (Fig. 1). Six cases (5.9 %) had distant metastasis at initial diagnosis and 23 additional cases were diagnosed during the follow-up period. Lung was the most frequent site for metastases.

Surgery was the initial treatment in 81 cases (80.2 %); radiotherapy alone was used in 3 cases (3 %) deemed unresectable. Chemo-radiotherapy alone was employed in 4 cases (4 %) and 13 cases (12.9 %) did not receive any treatment. Post-surgical adjuvant radiotherapy was applied in 58 cases (57.4 %); 6 cases (5.9 %) had adjuvant post-surgical chemo-radiotherapy, and 37 (36.6 %) cases did not receive any adjuvant treatment (Table 2). Disease free survival and overall survival was significantly longer ($p = 0.000$) in patients receiving adjuvant radiation therapy than in those who did not (Fig. 2 a, b). Cribriform was the predominant histologic pattern observed in this series (50.5 %), followed by solid (28.7 %), and tubular (11.9 %) types. Multivariate analysis (Table 3) showed that only two of the documented variables were statistically significant: pulmonary metastases

Fig. 1 N+ versus N– overall survival at diagnosis according to Kaplan–Meier

Table 2 Treatment modalities employed in the present series

	N (%)
<i>Treatment</i>	
Surgery	81 (80.2)
Treatment out of our hospital and follow up	2 (2.3)
Radiotherapy	3 (3)
Chemotherapy + radiotherapy	4 (4)
Without treatment	13 (12.9)
<i>Adjuvant therapy</i>	
Radiotherapy ^a	58 (57.4)
Chemotherapy/radiotherapy ^a	6 (5.9)
None	37 (36.6)
Total	85/101 (100)

^a Patients treated by surgery followed by radiotherapy

($p < 0.0001$) and adjuvant radiotherapy. Patients who did not receive adjuvant radiotherapy had a lower frequency of recurrence as compared to those who did receive it ($p = 0.055$). In addition, no significant differences were found in disease-free survival and overall survival according to subsite location in major salivary glands, intraoral and extraoral minor glands, as shown in Fig. 3a, b. Mean follow-up time was 52 months (range 1–288 months). Disease-free survival was 57.8 and 49.7 % at 5 and 10 years respectively (Fig. 4a), while overall-survival was 57.6 and 42.3 % at 5 and 10 years respectively (Fig. 4b).

Discussion

ACC is a malignant neoplasm characterized by slow, indolent growth; surgery remains the treatment of choice, followed by radiotherapy. Prognostic factors include: age, tumor site, histologic subtype, duration of symptoms (which are closely related to its location), clinical stage, treatment modalities employed, the presence of positive surgical margins following resection, and vascular or perineural invasion [1–3, 6, 7]. In the present study, ACC was more frequently found during the fifth decade of life; however, this finding did not appear to be a relevant prognostic factor for survival. Although some series have reported lower survival rates in patients older than 45 years. In addition, we found a female predominance in our series, which contrasts with studies that report a male predominance. Nevertheless, gender does not represent a factor of prognostic significance for survival [1, 8] (Table 3). Although cribriform and solid histologic subtypes are the most frequently identified patterns in this and other studies' their significance as prognostic factors does not enjoy a widely spread consensus [9]. Nevertheless, a multivariate analysis performed by Da Cruz Perez et al. [1], found that solid type was a significant prognostic factor and, similarly, Van Weert et al. [10] confirmed that the solid type or Grade III is related to a significantly worse outcome, possibly because it is a higher grade tumor with a more aggressive growth pattern and a tendency for early development of distant metastasis. It is interesting to note that, contrary to these results, we agree with other studies [11] that have found that histological grade does not seem to influence the clinical course.

According to previous studies, ACC is located mainly in intraoral minor salivary glands, followed by extraoral minor glands and by major salivary glands; however, we had a predominance of cases originating in extraoral minor glands, as maxillary sinus was the most frequently affected region [1, 6]. The sites reported as those with the worse prognosis are nasal cavity and larynx, possibly because in these areas tumors have attained a larger size at diagnosis and are more complex for surgical management and to get free margins [7]; however, in this study differences in location was not found as a prognostic factor [8].

Although clinical stage has been mentioned in some reports as an important factor for predicting survival, in the present study this could not be evaluated because more than a half of the patients had been previously treated and they could not be staged, and the vast majority of the remaining cases were in stages II and IV at diagnosis [1]. Even though some studies consider clinical stage as the most important prognostic factor [12], this is a controversial issue, since some institutions assess these tumors in

Fig. 2 **a** Disease free survival in patients treated with or without radiotherapy, according to Kaplan–Meier, **b** overall survival in patients treated with or without radiotherapy

a similar way they assess squamous cell carcinoma; however, it is important to note that the value of T is the one with the higher weight as prognostic factor, followed by M, while N is more difficult to evaluate and does not seem to clearly influence on survival, as it has been found in this and other studies, like the one by Duberge et al. [13]. This situation opens to debate whether an elective neck dissection is warranted, in the absence of clinical suspicion of N+. This problem is illustrated in the study of Amit et al. [7], in which one may consider that there was overtreatment in a significant number of cases, as only 29 out of 38 patients who had N1 at diagnosis were histopathologically positive when they performed 272 neck dissections considered as therapeutic and elective procedures. Despite this, the authors claim that these were justified. On the opposite end of the argument are studies such as the one from Cruz et al. [1], which state that elective neck dissections should not be performed in most cases. Only 5.6 % of our cases had positive adenopathy at surgery. Recent reports [7, 14] have shown no survival advantage for patients undergoing elective neck dissection for ACC.

Positive margins are also considered a prognostic factor for recurrence. In our study, 53.5 % (46 cases) were reported as negative and only 32.6 % (28 cases) were reported as positive. In addition, it has not been defined precisely which is the size (measured in millimeters) to be considered as an ideal free surgical margin adjacent to this type of tumor [1, 15, 16]. In this respect, studies like that of da Cruz Perez et al. [1] and the one by Duberge et al. [13] have demonstrated differences when comparing cases with free margins, macroscopic margins, and microscopic

margins. Da Cruz Perez et al. [1] found a 5-year survival of 58, 42 and 0 %, respectively. The microscopic margins are those in which radiotherapy plays a more important role. However, recurrences after radiotherapy have been reported at around 12 %, increasing only the disease-free period, with the possibility of distant metastasis being higher than that of local recurrence [4, 12]. The same is said for perineural invasion, a very frequent finding in ACC, which, according to Garden et al. [4], is associated with a reduction in local control of the neoplasm. However, it has not been associated with a worse prognosis in terms of overall survival. It remains to determine whether perineural invasion is indeed associated with positive margins and recurrence, or if it is an independent focal phenomenon, but some results suggest that the tendency of a tumor to disseminate along nerves is not associated with its ability for local invasion and proliferation, but is rather associated with positive margins [7]. These facts were also found in our analysis, where perineural invasion had no impact on survival, a finding which we consider was because worse prognosis is not due to local recurrence, but due to metastatic disease, and this is particularly important when the lung is the preferred site, which has significant prognostic value, as has been previously reported in the literature [1, 7, 15, 17].

Undoubtedly, surgery remains, when it is possible, the initial and gold standard for treatment of ACC, and it is usually followed by radiotherapy, due to the above mentioned factors. In the multivariate analysis that is presented in Table 3 it is shown that patients who received this therapeutic modality had a lower recurrence rate as

Table 3 Clinical, pathologic and treatment characteristics

Variable n (%)	No recurrence (n = 50)	Recurrence (n = 36)	P
<i>Gender</i>			
Male	14 (16.3)	15 (17.4)	P = 0.186
Female	36 (41.9)	21 (24.4)	
<i>Location</i>			
Major SG	12 (14)	9 (10.5)	P = 0.610
Intraoral minor SG	15 (17.4)	14 (16.3)	
Extraoral minor SG	23 (26.7)	13 (15.1)	
<i>Clinical stage</i>			
I	5 (5.8)	4 (4.7)	P = 0.836
II	14 (16.3)	7 (8.1)	
III	4 (4.7)	5 (5.8)	
IV	15 (17.4)	12 (14)	
Unknown	12 (14)	8 (9.3)	
<i>Grade</i>			
I	8 (9.3)	3 (3.5)	P = 0.570
II	28 (32.6)	19 (22.1)	
III	12 (14)	11 (12.8)	
Unknown	2 (2.3)	3 (3.5)	
<i>Histologic pattern</i>			
Solid	14 (16.3)	11 (12.8)	P = 0.640
Tubular	8 (9.3)	3 (3.5)	
Cribiform	26 (30.2)	19 (22.1)	
Unknown	2 (2.3)	3 (3.5)	
<i>Surgical margins</i>			
Negative	22 (25.6)	24 (27.9)	P = 0.105
Positive	19 (22.1)	9 (10.5)	
Unknown	9 (10.5)	3 (3.5)	
<i>Perineural invasion</i>			
No	36 (41.9)	30 (34.9)	P = 0.220
Yes	14 (16.3)	6 (7)	
<i>Vascular invasion</i>			
No	42 (48.8)	34 (39.5)	P = 0.136
Yes	8 (9.3)	2 (2.3)	
<i>Treatment</i>			
Surgery	42 (48.8)	35 (40.7)	P = 0.214
Radiotherapy	3 (3.5)	0 (0)	
Chemotherapy/radiotherapy	3 (3.5)	1 (1.2)	
No treatment	2 (2.3)	0 (0)	
<i>Adjuvant</i>			
Radiotherapy	32 (37.2)	25 (29.1)	P = 0.035
Chemo/radiotherapy	1 (1.2)	5 (5.8)	
None	17 (19.8)	6 (7)	
<i>Liver metastases</i>			
No	50 (58.1)	33 (38.4)	P = 0.038
Yes	0 (0)	3 (3.5)	
<i>Lung metastases</i>			
No	47 (54.7)	12 (14)	P < 0.0001
Yes	3 (3.5)	24 (27.9)	
SG salivary glands

Fig. 3 **a** Disease free survival and **b** overall survival for subsite in major salivary glands, intraoral and extraoral minor according to Kaplan–Meier

Fig. 4 General **a** disease free survival and **b** overall survival for ACC according to Kaplan–Meier

compared to those who did not receive it ($p = 0.035$); however, Fig. 2 a, b shows that overall survival and disease free period were higher for those who had radiotherapy ($p < 0.000$) which is also in accordance with other series. Silverman et al. [18], did not find statistically significant differences with respect to survival, local control and distant control at 5 and 10 years, in a study of 129 patients who received or not post-operative radiotherapy, did not find statistically significant differences with respect to

survival, local control and distant control at 5 and 10 years, concluding that T stage and microscopic margins are the most important factors for defining the need of postoperative radiotherapy in head and neck ACC, and that radiotherapy may not be necessary for patients in early stages of T and negative surgical margins. Survival in the present series was 57.6 and 42.3 % at 5 and 10 years respectively, similar to other figures found in the international literature [6, 11, 13, 16, 19], which may be due to the fact that, at the

present time, there is no systemic treatment suitable for the management of the metastatic disease. Expectations have been put on irinotecan, at least for selected patients. However, this drug has not yet demonstrated a valid effect for ACC, except on isolated case reports.

Conclusions

Adenoid cystic carcinoma is an infrequent neoplasm whose initial treatment is surgery, usually followed by radiotherapy; use of conventional chemotherapy is still controversial and there is much more to learn about a real benefit of molecular therapies. According to site of presentation, we found no significant differences in disease-free survival and overall survival according to subsite location in major salivary glands, intraoral and extraoral minor glands. Overall survival did not show statistically significant differences among patients with positive and negative lymph nodes at the time of diagnosis.

Compliance with Ethical Standards

Conflict of interest None.

References

1. da Cruz Perez DE, de Abreu Alves F, Nobuko Nishimoto I, de Almeida OP, Kowalski LP (2006) Prognostic factors in head and neck adenoid cystic carcinoma. *Oral Oncol* 42:139–146
2. van der Wal JE, Becking AG, Snow GB, van der Waal I (2002) Distant metastases of adenoid cystic carcinoma of the salivary glands and the value of diagnostic examinations during follow-up. *Head Neck* 24:779–783
3. Kim KH, Sung MW, Chung PS, Rhee CS, Park CL, Kim WH (1994) Adenoid cystic carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 120:721–726
4. Garden AS, Weber RS, Morrison WH, Ang KK, Peters LJ (1995) The influence of positive margins and nerve innervation in adenoid cystic carcinoma of the head and neck treated with surgery and radiation. *Int J Radiat Oncol Biol Phys* 32:619–626
5. Perzin KH, Gullane P, Clairmont AC (1978) Adenoid cystic carcinoma arising in salivary gland; a correlation of histologic features and clinical course. *Cancer* 42:265–282
6. Kokemuller H, Eckardt A, Brachvogel P, Hausamen JE (2004) Adenoid cystic carcinoma of the head and neck: a 20 years experience. *Int J Oral Maxillofac Surg* 33:25–31
7. Amit M, Binenbaum Y, Trejo-Leider L, Sharma K, Naomi R, Ilana R et al (2015) International collaborative validation of intraneural invasion as a prognostic marker in adenoid cystic carcinoma of the head and neck. *Head Neck* 37:1038–1045
8. Khafif A, Anavi Y, Haviv J, Fienmesser R, Calderon S, Marshak G (2005) Adenoid cystic carcinoma of the salivary glands: a 20-year review with long term follow-up. *Ear Nose Throat J* 84:662–667
9. Marcinow A, Ozer E, Teknos T, Wei L, Hurtuk A, Old M, Agrawal A, Carrau R, Iwenofu OH (2013) Clinicopathologic predictors of recurrence and overall survival in adenoid cystic carcinoma of the head and neck: a single institutional experience at a tertiary care center. *Head Neck* 36:1705–1711
10. van Weert S, Bloemena E, van der Waal I, de Bree R, Rietveld DH, Kuik JD, Leemans CR (2013) Adenoid cystic carcinoma of the head and neck: a single-center analysis of 105 consecutive cases over a 30-year period. *Oral Oncol* 49:824–829
11. Spiro RH, Huvos AG, Strong EW, Adenoid cystic carcinoma of salivary origin (1974) A clinicopathologic study of 242 cases. *Am J Surg* 128:512–520
12. Spiro RH, Huvos AG (1992) Stage means more than grade in adenoid cystic carcinoma. *Am J Surg* 164:623–628
13. Dubergé T, Bénézy K, Resbeut M, Azria D, Minsat M, Ellis S, Teissier E, Zaccariotto A, Champetier C, Cowen D (2012) Adenoid cystic carcinoma of the head and neck: a retrospective series of 169 cases. *Cancer Radiother* 16:247–256
14. Amit M, Na'ara S, Sharma K, Ramer N, Ramer I, Agbetoba A (2015) Elective neck dissection in patients with head and neck adenoid cystic carcinoma: an international collaborative study. *Ann Surg Oncol* 22:1353–1359
15. Dodd RL, Slevin NJ (2006) Salivary gland adenoid cystic carcinoma: a review of chemotherapy and molecular therapies. *Oral Oncol* 42(759):69
16. Khan AJ, DiGiovanna MP, Ross DA, Sasaki CT, Carter D, Son YH, Haffti BG (2001) Adenoid cystic carcinoma: a retrospective clinical review. *Int J Cancer* 96:149–158
17. Guarney TA, Eisele DW, Weinberg V, Shin E, Lee N (2005) Adenoid cystic carcinoma of the major salivary glands treated with surgery and radiation. *Laryngoscope* 115:1278–1282
18. Silverman DA, Carlson TP, Khuntia D, Bergstrom RT, Saxton J, Esclamado RM (2004) Role for postoperative radiation therapy in adenoid cystic carcinoma of the head and neck. *Laryngoscope* 114:1194–1199
19. Rapids AD, Givalos N, Gakiopoulou H, Faratzis G, Stavrianos SD, Vilos GA, Douzinas EE, Patsouris E (2005) Adenoid cystic carcinoma of the head and neck: clinicopathological analysis of 23 patients and review of the literature. *Oral Oncol* 41:328–335