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Adenoid Cystic Carcinoma of the Head and Neck: Epidemiology and Predictors of Prognosis

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ABSTRACT

Objectives: The biologic behavior of the adenoid cystic carcinoma (ACC) and the factors predicting outcome for these tumors are still poorly understood. Our objective is to analyze the predicting factors and the value of different treatment possibilities, since none sole treatment has been standardized. **Methods:** A retrospective analysis of the epidemiologic, clinical and histologic aspects of ACC, as well as treatment options and other prognostic factors of all the cases of ACC of the head and neck treated at this Institution were analyzed. From 1974 until 2011, 152 patients were diagnosed with ACC and treated at the Portuguese Institute of Oncology (Porto Centre). Main outcome measures: overall survival, local recurrence and distant metastasis were calculated by the Kaplan-Meier method. Factors predictive of outcome were identified by univariate and multivariate analysis. **Results:** The mean age at diagnosis was 55.8 years (range, 19 - 83 years). Incidence was higher in the female population, with a female to male ratio of 1.7:1 respectively. The primary tumor location was hard palate and submandibular region in 56 cases, 28 in each location (24.6%), parotid gland (17 cases, 14.9%) and oral cavity excluding palate (16 cases, 14%).Distributions according to T stage were: T1 (29.8%); T2 (30.7%); T3 (17.5%); T4 (22%). The overall 1-year, 5-year and 10-year survival for all patients were 94.6%, 60.5%, 41.6%, respectively. **Conclusions:** Univariate survival analysis revealed that age older than 60 years ($p = 0.002$), solid histologic subtype ($p = 0.042$), advanced clinical stage ($p < 0.001$) and the presence of perineural invasion ($p = 0.036$) were correlated with a poor survival. Multivariate analysis confirmed that age and advanced clinical stage were worst independent predicators of overall survival as well as perineural invasion for local recurrence and distant metastasis. In our analysis, radiotherapy did not have a relevant impact on survival, except in cases of solid histologic subtype. To analyze distant metastatic capacity, long term follow-up was necessary, since distant metastasis way occurs even after 10 years, which has the case with 4 patients.

Keywords: Adenoid Cystic Carcinoma; Head and Neck Cancer; Prognostic Factors

1. Introduction

Adenoid cystic carcinoma (ACC), also known as cylindroma, a rare adenocarcinoma arising within secretory glands, occurs mainly in the minor salivary glands of the palate, and in the major glands [1-5]. Besides the oral cavity, other locations may be affected in accordance to the anatomical distribution of the minor salivary glands, as for example nasal cavity, paranasal sinus, pharynx, esophagus, larynx, tracheobronchial tree, eye and external auditory canal [1,3]. ACC of the head and neck is responsible for 0.5% - 1% of malignancies in this area and for 7.5% - 10% of salivary gland tumors [1-3,6]. In fact, the largest epidemiological study that included 2611 cases from European countries, found an ACC (ICD-0-2 Code 8200) incidence of 0.5% [2].

The biological behavior of ACC of head and neck is clinically represented by a slow and indolent growth generally in sub mucosal localization, making these tumors hard to diagnose [1,4,6]. It is frequently associated with a late recurrence rate and distant metastasis, especially to the lungs, and they are associated with poor prognosis [1, 3,6].

Histologically, three subtypes of ACC (cribriform, tubular and solid) have been described, with tubular subtypes having a better prognosis in contrast to solid pattern histology [1,3].

Standard treatment for patients diagnosed with ACC is surgical, in some cases associated with radiotherapy, al-

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though the benefit of this last option has not been unequivocally proven [1,3]. Radiotherapy has been considered for patients with criteria of poor prognosis, as perineural invasion, positive margins and advanced stages [7,8].

Albeit ACC has been the subject of many epidemiological studies on several populations, predictive and prognostic factors in this type of cancer are scarce. The objective of this retrospective study was to characterize epidemiologically your population of patients in a tertiary cancer-institution, and analyze factors involved in local control, treatment failure, distant metastasis and other prognostic variables associated with overall survival.

2. Material and Methods

2.1. Patients

A retrospective analysis including all patients with ACC diagnosed and treated at the Oporto Oncologic Institute between 1974 and 2011 was conducted. This study was approved by the Institution's Ethics Committee. Of the 152 ACC patients initially identified, 38 were excluded due to insufficient clinical data (**Figure 1**). Demographic and clinical in formation (age, gender, initial symptoms and its duration, histologic subtype, location of primary, perineural invasion, distant metastasis, staging and treatment options) was obtained from the remaining 114 patients.

Anatomical distribution of these tumors was grouped as tumors with origin in minor or major glands, though different locations were registered. Staging was performed in accordance with the 2010 American Joint Committee on Cancer (AJCC) staging system. In some cases, there were more than one histologic subtype in the tumor, but the characterization has been made according to the most predominant subtype. Margin statuses after surgery were not analyzed in all patients due to in sufficient information in clinical charts. Only 101 patients submitted to surgery followed or not by radiotherapy were subject to further analysis. Primary and secondary end-points analyzed were overall survival (OS), defined as the time from diagnosis until death or last clinical visit, and disease free survival, defined as the time-to-locoregional recurrence (TTR), or time-to-distant metastasis (TTM) determined as the time interval, in months, between diagnosis and local recurrence or distant metastasis.

2.2. Statistical Analysis

Global analysis included only 101 patients, those that were submitted to surgery followed or not by radiotherapy. Tertiles of age at diagnosis were used for analyses. For time-to-event analyses, univariate Kaplan-Meier with log-rank tests and multivariate Cox proportional hazards model were used, to identify predictors of overall survival, local recurrence and distant metastasis. Hazard ratios (HR) and 95% confidence intervals (CIs) were used for estimating the association between clinical and pathological characteristics with each of the outcomes of interest. Selection of variables to include in the multivariate model was submitted to empirical evaluation through univariate analysis. Variables with *p*-values lower than 0.10 on univariate analysis were included in the multivariate model. SPSS version 17 was used for statistical analysis.

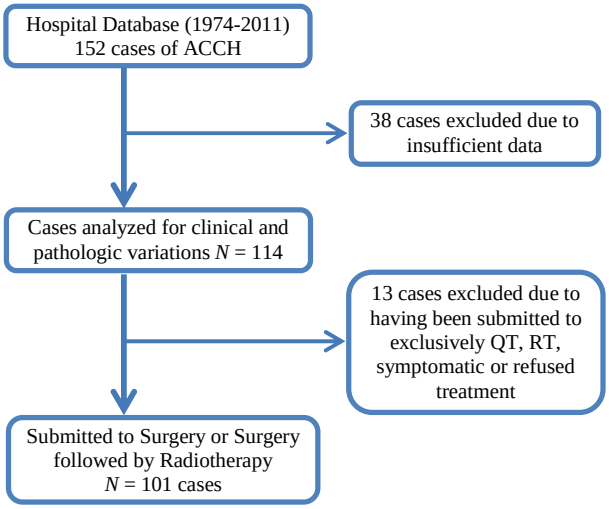

Figure 1. Diagram depicting the analysis criteria of the population.

3. Results

3.1. Clinical Features

Table 1 outlines the clinical characteristics of the 114 patients. Mean age at diagnosis was 55.8 years (range 19 to 83 years). The incidence in the female gender was higher than in men, 63.2% and 36.8% respectively.

The main symptom at the time of diagnosis was a nodular mass (52.6%), followed by pain associated to a nodule (18.4%), nasal symptoms (14%) (nasal obstruction, hemorrhagic rhinorrhea). Other symptoms less frequent were dyspnea, odynophagia, otalgia, facial paralysis and hearing impairment.

Median time elapsed between onset of symptoms and diagnosis was 10 months, with a minimum of 0 months and a maximum of 144 months. Eighty one percent of the patients were diagnosed in the first 24 months after-symptom initiation. ACC was diagnosed less frequently in major salivary glands (39.5%) than in anatomic locations where minor salivary glands are represented (60.5%). The most common location was the oral cavity with 44 cases (38.6%), 28 cases of which in the hard palate. The

second most frequent location was the submandibular gland with 28 cases (24.6%), followed by the parotid gland (17 cases, 14.9%), the paranasal sinus (12 cases, 10.5%) and the larynx (7 cases, 6.1%). Other locations seldom involved include the parapharyngeal space, the scalp, the external auditory meatus and the nasopharynx (**Table 1**).

3.2. Pathologic Characteristics

The pathologic characteristics of the ACC resected are outlined in **Table 2**. Histologic sub classification was only determined in 68 patients, 29.4% were predominantly tubular, 44.1% primarily cribriform and 26.5% mainly solid.

Sixty one patients (53.5%) had perineural invasion of which 32 cases had exclusive perineural invasion and in the remaining, vascular (18 cases), lymphatic (18 cases) and bone invasion (11 cases) were also present. Perineural invasion was present more frequently in tumors of major salivary glands (30/43) than in minor glands (28/58) a finding with statistical significance ($p = 0.031$).

Table 1. Population characteristics.

	Cases	Percent
Age		
<52 years	40	35.1
52 until 64 years	32	28.1
>64 years	42	36.8
Gender		
Female	72	63.2
Male	42	36.8
Initial symptom		
Nodular mass	60	52.6
Nodular mass and pain	21	18.4
Nasal symptoms	16	14.0
Dyspnea and dysphonia	6	5.3
Odynophagia	4	3.5
Cervical adenopathy	2	1.8
Otalgia	2	1.8
Facial Paralysis and nodular mass	2	1.8
Hipoacusis	1	0.9
Location		
Hard Palate	28	24.6
Submandibular	28	24.6
Parotid	17	14.9
Sublingual glands and minor glands of the oral cavity	16	14.0
Paranasal sinus	12	10.5
Larynx	7	6.1
Others (scalp 2, parapharyngeal space 2, external acoustic meatus 1, nasopharynx 1)	6	5.3

Table 2. Pathologic characteristics.

	Cases	Percent
Histology		
Tubular	20	29.4
Cribriform	30	44.1
Solid	18	26.5
Total	68	100.0
Invasion		
Perineural invasion	61	53.5
No invasion	48	42.1
No Perineural invasion but with other type of invasion (lymphatic, vascular, bone)	5	4.4
Total	114	100

3.3. Staging

TNM classification and stages can be observed in **Table 3**. Of all tumors, 10.5% had regional metastasis and only 6.1% had distant metastases at the time of diagnosis (lungs in 5 cases and bone in 1 case). Approximately half of the patients were diagnosed at an initial stage (I and II).

3.4. Treatment

The distribution of patients according to treatment options is shown in **Table 4**. Of the 114 patients, 4 refused treatment and 9 were considered inoperable and were selected for supportive care or palliative treatment with radiotherapy or chemotherapy. These 13 patients were excluded from further analysis. Of the 101 patients submitted to surgery, 58 cases were proposed for subsequent radiotherapy (RT). Many factors interfered with the decision of post-operative RT such as the surgeon's option, location, presence of positive margins and perineural invasion. The average time from diagnosis until surgery was 2.3 months.

3.5. Univariate and Multivariate Survival Analysis for Overall Survival

Univariate analysis of the clinical, epidemiologic and pathologic variables analyzed for overall survival (**Table 5**) revealed that older patient's had a worse outcome.

Table 3. TMN stage according to AJCC.

	Cases	Percent
Size of tumor (T)		
T1	34	29.8
T2	35	30.7
T3	20	17.5
T4a	20	17.5
T4b	5	4.5
Regional metastasis (N)		
N0	102	89.5
N+	12	10.5
Distant metastasis		
M0	108	93.9
M1	6	6.1
Stage		
I	29	25.4
II	31	27.2
III	24	21.1
IVa	18	15.8
IVb	5	4.4
IVc	7	6.1
Total	114	

Table 4. Distribution of treatment options.

Treatment	Cases	Percent
Surgery and radiotherapy	58	50.9
Surgery	43	37.7
Exclusive chemotherapy, radiotherapy or no treatment	13	11.4
Total	114	100.0

Though not significant ($p = 0.064$), females seem to survive for ~~a~~ longer periods than males, with a median difference of 4 years. There was no statistical significance on overall survival between tumors appearing from minor or major salivary glands (**Figure 2**). Comparing specific locations (**Table 6**) lower survival was observed in tumors localized in the nasal cavity and larynx, but the differences were not statistically significant ($p > 0.082$). Analyses of overall survival showed that there was no difference between treatment options. A trend was observed towards surgery alone although we could presume that the worst cases were the ones that were indicated for RT and there forth may have a poorer prognosis (**Figure 3**). In univariate analysis, advanced disease, solid histologic subtype and perineural invasion were statistically

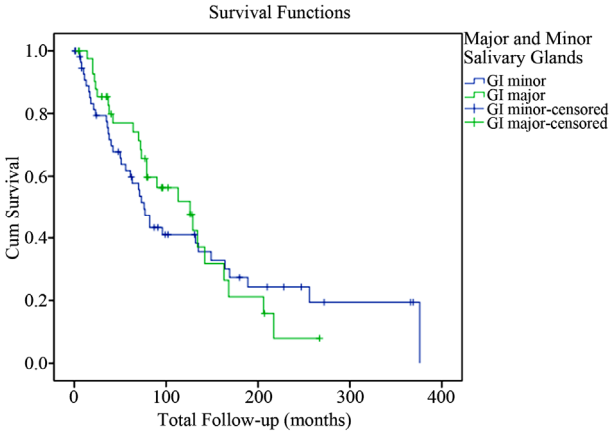

Figure 2. Survival of patients according to location.

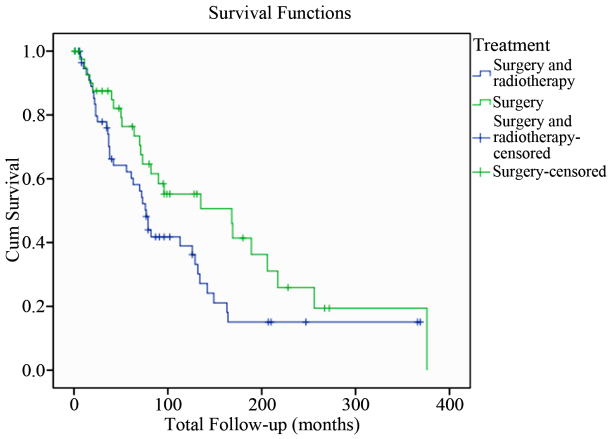

Figure 3. Overall survival for patients according to omission or inclusion of postoperative radiation therapy.

significant ($p = 0.001$, $p = 0.042$, $p = 0.036$ respectively). Increased T and solid histologic subtype were also associated with decreased survival, as presented respectively in **Figures 4** and **5** respectively.

When patients only submitted to surgery or surgery followed by RT were analyzes separately, it was observed that RT was relevant to the prognosisin some histologic subtypes. We observed a similar survival in all histologic subtypes that were submitted to radiotherapy ($p = 0.410$), but patients that had only surgery had significant ($p = 0.04$) differences of survival according to histologic subtypes, with the prognosis of the solid subtype being considerably lower. As may be seen on **Table 7**, mean survival of patients with solid pattern that were treated only with surgery have a lower survival in about 100 months in comparison with the other. The same is not verified in patients treated with surgery and radiotherapy. In this group, probably with worse prognosis to begin with, the solid subtype had a higher overall survival than patients treated with surgery alone and similar to the other subtypes. This data suggests the eventual recommendation for radiotherapy in the solid histologic

Table 5. Time-to-event univariate analysis for clinicopathological variables according to mortality, local recurrence and distant metastasis.

	Overall survival				Local recurrence				Distant metastasis			
	Events	Median	95% CI	*p*	Events	Median	95% CI	*p*	Events	Median	95% CI	*p*
Age, yrs*												
<52	14	168	77.8 - 258.3		22	102	59.0 - 145.0		10	264	48.5 - 49.5	
52 - 64	25	64	44 - 84		20	79	57.3 - 100.7		9	144	53.9 - 234.2	
>65	23	73	66.6 - 79.4	**0.002**	20	82	74.4 - 89.6	**0.347**	6	-	-	**0.800**
Gender												
Female	33	126	74.6 - 177.4		39	91	67.8 - 114.2		13	264	-	
Male	30	76	58.8 - 93.2	**0.064**	23	79	73.3 - 84.7	**0.305**	12	119	-	**0.172**
Tumor location												
Minor glands	38	76	62.6 - 89.4		24	87	69.0 - 105.0		10	-	-	
Major glands	25	126	76.5 - 175.5	**0.715**	28	79	69.8 - 88.2	**0.247**	15	108	72.0 - 144.0	**0.056**
Clinical stage												
Initial	29	142	105.7 - 178.3		39	91	69.9 - 112.4		11	-	-	
Advanced	34	63	40.3 - 85.7	**0.001**	24	76	45.9 - 106.1	**0.103**	14	99	56.1 - 141.9	**0.04**
Treatment												
Surgery plus RT	39	77	66.9 - 87.1		40	77	68.9 - 85.1		18	108	83.4 - 132.6	
Surgery	24	168	72.4 - 263.6	**0.056**	22	99	20.0 - 177.9	**0.336**	7	-	-	**0.290**
Histology												
Tubular	11	79	18.1 - 139.9		10	91	71.2 - 110.8		5	99	-	
Cribriform	15	113	73.7 - 152.3		17	80	37.3 - 122.7		9	119	70.9 - 167.2	
Solid	14	51	33.1 - 68.9	**0.042**	8	38	27.3 - 48.7	**0.397**	4	-	-	**0.899**
Perineural invasion												
No	23	126	31.5 - 220.5		24	102	32.4 - 171.6		5	-	-	
Yes	37	73	51.2 - 94.8	**0.036**	34	76	30.7 - 121.3	**0.006**	18	102	65.9 - 138.1	**0.001**

RT—radiotherapy; HR—hazard ratio; Ref—Reference. Events calculated as deaths at the time of last follow-up. Median referred in months. Cut off used for multivariate analysis was 0.10. Covariates included in multivariate model: age, gender, stage, treatment and perineural invasion.

Table 6. Survival according to location.

Variable	No.	Survival, %		*p*-Value
Location		5 years	10 years	
Hard Palate	24	70.5	54.6	0.082
Submandibular	26	86.2	64.2	
Parotid	17	85.6	52.5	
Minor glands of the oral cavity (except hard palate)	14	78.6	53	
Nasal cavity	12	56.8	45.5	
Larynx	5	40		
Others	3	66.7	66.7	
Treatment				
Surgery and radiotherapy	58	62.2	39.9	0.056
Surgery	43	76.4	55.2	

Table 7. Overall survival in different histologic subtypes for different treatments.

	Surgery and Radiotherapy			Surgery		
	Mean	95% CI	*p* value	Mean	95% CI	*p* value
Tubular	99.6	63.6 - 135.6	0.41	166	66.8 - 265.2	0.004
Cribriforme	70.5	43.5 - 97.4		179.4	72.1 - 286.6	
Solid	72.1	35.6 - 108.5		50.7	26.5 - 74.8	

subtype. All other variables subject to analysis between these two groups did not show a statistical difference.

Multivariate analysis (**Table 8**) confirmed significance of univariate analysis in the cases of age ($p = 0.001$) and tumor stage ($p = 0.020$) as independent predicators. The hazard ratio for people older than 52 and 64 years old is 3.6 and 3.5 respectively. The hazard ratio for advanced

Table 8. Multivariate analysis with predictive variables for mortality, local recurrence and distant metastasis.

	Overall survival			Local recurrence			Distant metastasis		
	HR	95% CI	*p*	HR	95%CI	*p*	HR	95% CI	*p*
Age, yrs *									
<52	Referent			Referent			Referent		
52 - 64	3.6	1.7 - 7.6	0.001	1.4	0.7 - 2.8	0.318	-	-	-
>65	3.5	-	0.002	1.7	0.8 - 3.4	0.138	-	-	-
Gender									
Female	Referent			Referent			Referent	-	-
Male	1.2	0.7 - 2.1	0.450	1.1	0.6 - 1.9	0.864			
Tumor location									
Minor glands	Referent			1.3	1.7 - 2.4		1.6	0.7 - 3.9	0.293
Major glands	1.0	0.6 - 1.8	0.987	Referent		0.493	Referent		
Clinical stage									
Initial	Referent			1.2			1.8		
Advanced	2.0	1.1 - 3.6	0.020	Referent	0.7 - 2.4	0.493	Referent	0.8 - 4.3	0.185
Treatment									
Surgery plus RT	Referent			1.0					
Surgery	1.0	0.5 - 1.7	0.864	Referent	0.6 - 1.9	0.949	Referent	-	-
Histology									
Tubular									
Cribriform	-			-			-		
Solid		-	-		-	-		-	-
Perineural invasion									
No	Referent			2.1	1.1 - 3.9	0.028	Referent		
Yes	1.6	0.9 - 2.8	0.107	Referent			3.5	1.2 - 10.3	0.025

Cut off used for multivariate analysis was 0.10. Covariates included in multivariate model: Age, gender, stage, treatment, perineural invasion. Histology subtypes not included due to low number.

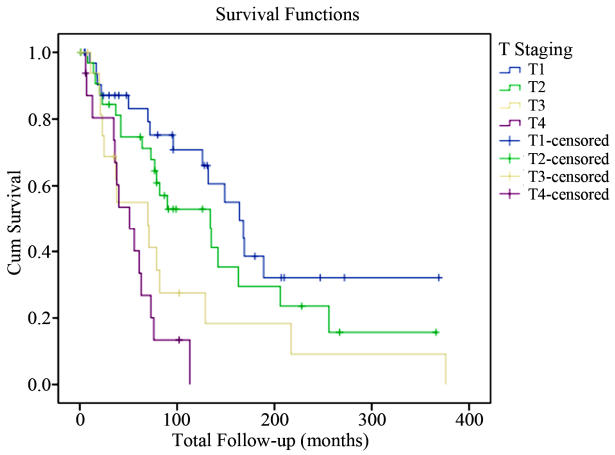

Figure 4. Overall survival according to *T*.

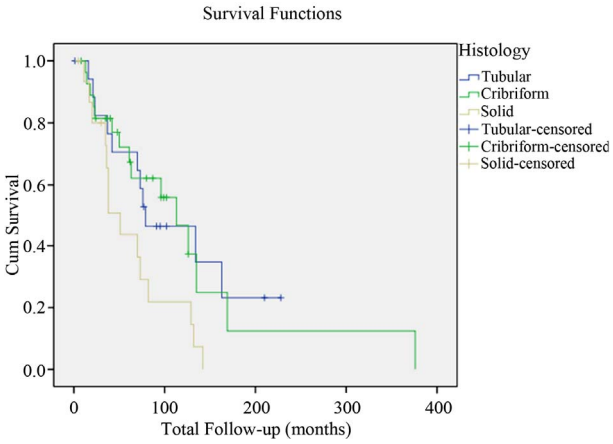

Figure 5. Survival rates according to histologic type (grading).

stage is 2.0 with a 95% confidence interval of 1.1 to 3.6.

3.6. Follow-Up and Global Survival Rates

No definite policy on follow-up was observed, but the median follow-up period was 90 months (95% CI 42.7 - 137.3). The overall survival rates were 68.2%, 45.7% and 19.4% for 5 years, 10 years and 20 years respectively. The disease free survival rates for 5 years and 10 years was 52.9% and 34.4%.Survival at 5 and 10 years depending on variables (gender, perineural invasion, stage and treatment) and the results can be observed in **Table 9**.

3.7. Univariate and Multivariate Survival Analysis of Local Recurrence and Distant Metastasis

Following the initial treatment, four patients had persistent disease and have been submitted to chemotherapy or supportive treatment. Thirty-five patients (34.7%) had local recurrence after a mean time of 42.2 months. Patients were selected for palliative treatment (5 cases), chemotherapy (5 cases) and surgery with or without radiotherapy (25 cases) and, survival following treatment was 51.6 months, 40.4 months and 63.4 months, respectively. These results suggest that chemotherapy has no indication in the recurrence of ACC and the treatment should be secondary surgery followed or not by radiotherapy when possible.

Twenty five patients (24.8%) had distant metastasis after a mean time of 67.6 months (median of 48 months). Twenty one of these patients had lung metastasis) and in 5 of these, there were also metastasis to other locations namely, liver (2 cases), bone, kidney and brain with one each. In the remaining 4 patients, 1 had bone metastasis, 1 had liver metastasis and 2 had both these locations. Even though distant metastasis was observed, patients had prolonged survival after their identification, with a mean time survival of 40 months (range 3 - 133 months). Survival times were similar in spite of different metastasis location. The 5 patients that had metastasis in more than 1 location had a mean survival time of 61 months. When comparing treatment of distant metastasis, secondary surgery followed or not by radiotherapy prolonged lifetime for an average of 70 months, while only chemotherapy prolonged life for 36 months and patients only treated symptomatically survived on an average of 20 months. This finding supports the need for treatment of distant metastasis with surgery followed or not by radiotherapy.

Univariate and multivariate analyses for local recurrence and distant metastasis revealed that perineural invasion was significantly associated with local recurrence rate and distant metastasis (**Tables 5** and **7**). In univariate analysis, advanced disease was statistically ($p = 0.04$) associated to a poorer prognosis with earlier distant metastasis. Distant metastasis developed in all histologic subtypes with no statistical difference between them, but is important to note that the solid histologic subtype recurs much earlier than the other 2 subtypes of ACC (median 38 months).

Table 9. Survival at 5 and 10 years (gender, perineural invasion, clinical stage, treatment).

Variable	Survival, %	
	5 years	10 years
Gender		
Female	72.1	52.4
Male	62.7	35.9
Perineural invasion		
Yes	58.2	40.5
No	77.9	52.4
Clinical stage		
I and II	79.3	63.3
III and IV (a e b)	53.1	23.3
Treatment		
Surgery + RT	62.2	39.0
Surgery	76.4	55.2

The main reason for death in these patients was local-recurrence and distant dissemination, but location of the primary was not relevant neither for local recurrence nor for distant metastasis. Local recurrence occurred in 7 patients after 5 years and in 2 patients after 10 years. Considering distant metastasis 12 cases occurred after 5 years and 2 after 10 years.

4. Discussion

There are doubts that the prevalence of ACC is gender related, none the less some studies claim a higher frequency and better prognosis in the female population, has was found in our series [1,2,4,9,10]. According to the literature available, there is a great variability on the age of onset, from 10 to 99 years, with more frequency above the age of 64 years, which is coherent with our findings. [2,4,6,11]. Symptoms in [12] most cases are unspecific and vary in accordance to the location of the tumor [6]. Manifestations in cases of oral and major salivary glands tumors are nodular mass, often associated with pain, which is usually related to perineural invasion [1]. The most frequent location is the hard palate (34%) due to the greater number of minor salivary glands, followed by the submandibular and the parotid glands, concordant to our series [4,8,10].

The median time from the first complain until diagno-

sis was 10 months, nonetheless, as shown in our findings, some cases may take several years to be diagnosed due to slow and indolent growth pattern of these tumors. In spite of delayed diagnosis, in our series, patients rarely had regional or distant metastasis at the time of diagnosis, as reported by other investigators [13].

It was verified that tubular and cribriform subtypes had a greater time interval between first symptom and diagnosis than the solid subtype, probably due to a faster growth pattern or a greater invasive capacity. Tubular subtype is expected to have a better prognosis, although our data demonstrated a greater median survival time for the cribriform subtype [1,3,4,14]. This aspect may be attributed to different percentages of the histologic subtypes in the tumors, emphasizing the importance of a correct histologic classification. Different prognosis and behavior patterns have been referred between histologies, however subtypes are often not registered by pathologists. Cribriform subtype was the most common in our series (44.1%), coherent with the literature, that states that this subtypeis responsible for 50% of the cases and the tubular and the solid patterns for 25% each [1,3,13]. Our data suggests that all cases of solid histologic subtype should be submitted to radiotherapy, due to the finding of similar life expectancy in patients of different histologic subtypes, treated with surgery followed by radiotherapy as opposed to patients treated exclusively with surgery, which had differences of 100 months.

The most important prognostic factors of poor overall survival referred in literature are advanced initial stage, advanced age, histologic subtype (solid), location and incomplete surgical resection [1-3,12,14]. We found in our series that the first two were statistically significant (p = 0.001 and p = 0.002 respectively). Concerning the location, a large overall survival difference was observed between sites, namely for the larynx and paranasal sinus with a poorer survival, which results are coherent with the study of Ciccolallo, although in our series the results did not achieve statistical significance due to the scarce number of cases (**Table 6**). Accepted factors predicting recurrence are tumor stage at the time of diagnosis, positive surgical margins and perineural invasion [2,3,8,12]. Perineural invasion was observed in 53.5% of our patients, confirming the reported neurotropism of this tumor [1,3]. Our study emphasizes the importance of perineural invasion, which was considered an independent prognostic factor for all outcomes. In our series other referred prognostic factors did not achieve significance value due maybe to small amount of patients analyzed.

Our exclusion of some cases (152-to-101) was made in an attempt to eliminate in sufficient data and selection bias for treatment modalities, since patients with advanced or unresectable disease tend to be treated with palliative measures. Our findings suggest that there is no benefit in submitting patients to post-operative radiotherapy (p = 0.056) which is coherent with the studies published by Silverman *et al.* (2004) e Chen A.M. *et al.* (2006), with the exception of patients with solid histologic subtype [5,7,8,15]. The best treatment option is surgery with wide safe margins, with special attention to sub mucosal expansion, perineural and lympho-vascular invasion [3,6,8,12-14,16]. Chemotherapy in ACC has not been proved as beneficial [12].

Recurrence disease in our population (34.7%) was not as rare as described in the literature (10% - 20%) [3,11]. Concerning distant metastasis these may occur in 16% - 35% of the cases, which is similar to our results (27.7%) [3,13]. Distant metastasis are located predominantly in the lungs (78.6% in our series), in few patients in the liver and bones (21% each in our series) and rarely in the kidneys and brain (3.5% each) [1,3,4,6,12,14]. Tumor associated survival was poor, with a 15 - 20 year prognosis inferior to 20% [1,7,17]. Due to the tumoral behavior and the possibility of late recurrences and of distant metastasis after many years, it is important to have a longer follow-up period [13,14,18].

5. Conclusion

In summary, increased age and advanced clinical stage were independent significant prognostic factors for overall survival in our series. Perineural invasion was an independent significant prognostic factor for local recurrence and distant metastasis. Our study advises clinicians to request different subtype characterization from the pathologist, due to different growth patterns and survivals. We recommend radiotherapy only in patients with solid histologic subtypes. Our findings indicate that patients with local recurrence and/or distant metastasis survive longer if submitted to secondary surgery followed or not by radiotherapy, so we recommend salvage surgery for all possible cases. Multi-center studies are necessary in order to determine with certainty which are the best treatment options.

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