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Parotid adenoid cystic carcinoma: Retrospective single institute analysis

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ABSTRACT

Purpose: Adenoid cystic carcinoma (ACC) is a uncommon salivary malignant tumor. Our aim was to review our experience with parotid ACC, to identify clinical-pathological parameters predictive for outcome.
Materials and methods: We retrospectively reviewed 228 patients affected by parotid gland carcinomas surgically treated at our Institution. Forty-four ACC were included in this study. Multivariate analysis risk models were built to predict recurrence free probability (RFP), distant recurrence free probability (DRFP), overall survival (OS) and disease free survival (DFS).
Results: Twenty-one patients (47.7%) died from ACC and 2.3% for other causes. The 41% presented local-regional recurrence, with a regional-RFP rate of 93%, and the 34% reported distant metastases (DM). The five and ten-year OS rates were 74% and 50%, respectively.
Conclusions: Recurrences were mainly influenced by the presence of perineural invasion and nerve paralysis, whilst female gender and age < 50 were predictors for good prognosis.

1. Introduction

Adenoid cystic carcinoma (ACC) is a malignant tumor of the head and neck district, it represents approximately the 1% of all epithelial salivary carcinomas and most frequently it involves major and minor salivary glands of the oral cavity [1]. It presents three different morphologic patterns of growth, including tubular, cribriform and solid configuration, but all of them are characterized by a locally aggressive clinical course, with infrequent regional metastases, slowly progressive and relatively indolent distant metastasis onset, with a usually fatal outcome [2]. The estimated 5-year survival rate is approximately 36%, with a local recurrence rate that ranges from 16% to 85% in accordance with literature [3]. Recurrence is usually a sign of incurability, and unpredictable factors such as tumor extension along perineurial sheaths and distant metastasis appearance, notably to the lungs, together with the ACC rare incidence, make this tumor treatment challenging for every physicians.

Surgery remains the mainstay of treatment for this pathology, since its response to radiotherapy and chemotherapy has always resulted unforeseeable. Complete local resection is recommended and ipsilateral cervical lymph node dissection is warranted in case of suspicious cervical lumps on clinical examination or in case of advanced local disease [4].

Recent reports have tried to identify clinical and pathological prognostic factors of these patients, but outcomes have generally consisted on small single-institution retrospective series or cohort of patients affected by ACC involving different anatomical head and neck sites, without focusing on a single specific region [5–8]. Factors that usually emerge to influence prognosis of parotid malignancies count clinical stage, bone involvement and resection margins status, but these general variables need to be replaced by more accurate and specific characteristics that should help in assessing single patient outcome. For instance, the American Joint Committee on Cancer (AJCC) TNM staging system [9], according to the T-status, the N-status, and the M-status, does not add anything to single cancer patient biology, because it does not enclose more specific variables such perineurial invasion or histologic grading, tumor site, and other patients characteristics i.e.: age, gender, smoking status and/or alcohol consumption, type of surgery performed with/without adjuvant radiotherapy or chemotherapy, late distant metastasis onset [10,11]. Only one multi center international study [12] has recently published the first nomogram analysis with the aim to predict single ACC patient prognosis using different clinical and pathological parameters never established before.

On the wake of this new enthusiasm, we have retrospectively analyzed our institutional case series of 44 patients affected by ACC with the main aim to describe their epidemiological, clinical and pathological characteristics, and to correlate all of these variables to each patient

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outcome in terms of RFP, DRFP, OS and DFS. Secondly, a comparison between ACC and other 184 parotid carcinomas not classified as ACC has been performed to refine and distinguish specific ACC prognostic characteristics among multiple other same-site malignancies.

2. Materials and methods

2.1. Study population

Between January 1980 and December 2005, a total of 228 patients affected by parotid gland carcinomas were treated at the Otorhinolaryngology University Clinic of Florence and 44 cases out of them received the diagnosis of ACC. All the participants signed an informed consent agreement before undergoing surgery. The indications for treatment included the presence of a parotid mass with a pre-operative fine-needle aspiration cytology (FNAC) report indicative for salivary malignancy. The study was approved by the local institutional review board (IRB) committee. All patients were reviewed and retrospectively restaged in accordance with the 7th edition of American Joint Committee on Cancer AJCC [9] and with the WHO classification [2].

Patient, tumor, and treatment characteristics were extracted from each patient notes. Clinical characteristics included patient gender, age (divided into three different categories: <50 y, 50–70 y, >70 y), cT and cN status, clinical stage, the presence or absence of clinical facial nerve paralysis and skin invasion. Tumor characteristics included the presence of perineurial invasion (PNI), type of pattern of growth (tubular, cribriform, solid) [13], pathological T-status (pT), pathological N-status (pT) and surgical resection margins status. Clear margins were defined as tumor-free margins ≥5 mm, and positive margins if ≤1 mm^3. All of tissue samples were revised by a single pathologist (AF). Treatment characteristics included type of primary tumor resection (superficial parotidectomy, total parotidectomy with facial nerve preservation and radical parotidectomy), neck dissection and use of postoperative radiation and/or chemotherapy.

Local, regional and distant recurrences onset were analyzed over a 10-year follow-up period that was done by frequent protocolled outpatient controls i.e.: every 2–3 months during the first two-year post-treatment period, every 4 months during the third year of clinical control and six monthly in the fourth and fifth year after treatment. After 5 years clinical control continued yearly for life. Diagnostic imaging, despite not routinely performed, counted CAT scans of head, neck and chest.

2.2. Statistical analysis

Categorical variables were calculated in terms of frequencies and percentages for all of the 228 parotid malignancies. First, an internal analysis of 44 ACC clinical and treatment parameters was performed. Standard descriptive statistics were used to summarize data, with respect to demographic and clinical characteristics. Chi-squared test, or Fisher exact test when appropriate, were used to compare the ACC groups against the other 184 patients.

Outcome was analyzed by univariate and multivariate survival analyses, by using STATA version 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp. LP). Logistic regression was used to investigate which factors were associated with each response variables. Afterwards, multiple logistic regression analyses were performed to account for several confounding variables simultaneously. Multiple logistic regression included all variables of interest, taking into account multicollinearity and sample size.

The Kaplan–Meier method was used to estimate overall survival (OS) defined as the period from date of diagnosis to date of death or last follow-up visit, with patients censored at their last follow-up visit by patients groups and the Log-Rank test was used to compare survival curves. The same procedure was used to analyze disease-free survival (DFS), distant recurrence-free probability (DRFP), disease-specific survival (DSS), defined as the period from date of diagnosis to date of local and regional relapse, distant metastasis onset, and death from disease, respectively, were similarly censored at the last follow-up visit for all of the clinical and pathological characteristics collected. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to analyze the equality of survivor functions by subgroup for the same variables. A p value <0.05 was considered statistically significant. A two tailed p-value <0.05 was considered significant.

3. Results

3.1. Continuous data description

Table 1 summarizes patient and disease characteristics for the ACC groups ($n = 44$) and the other histologic types of parotid malignancies rather than ACC ($n = 184$).

Mean age in the cohort of ACC patients was 54.18 years ± 17.36 SD (95% CI 48.90–59.46; range 11–83 years), with a slightly female preponderance (52% females vs. 48% males).

More than 70% of patients presented with an intermediate-advanced T-stage status (cT2 34% and cT3 39%) and the vast majority of the 44 ACC was cervical lymph node negative (82%). A final clinical stage status IV was recorded in the 25% of patients. Clinical characteristics of local tumor aggressiveness were documented in the 25% and 9% of cases, respectively for facial nerve paralysis and skin tumor invasion. Most patients received conservative surgical treatment (75%) instead of radical local tumor resection (25% out of 44) but despite the moderate presence of microscopic positive resection margins (20%), PNI was documented in half of the case series (50%). The final pathological report was almost completely in accordance with the clinical tumor staging, and the distribution of the three patterns of growth saw the cribriform as the most frequent one (41%), followed by the tubular (32%) and solid (27%) patterns. Radiotherapy (59% of cases) with concomitant chemotherapy (14% of cases) were performed for ACC patients when advanced tumor stage, with/without pathological neck nodes, or presence of PNI or positive resection margins were documented.

Local relapse appeared in 16 out of 44 patients (36%), whilst regional recurrence was less represented (7%); distant metastases occurred mainly in lungs (30%), and other two cases reported brain and bones recurrences, respectively, with a global rate of 34% of distant metastases.

ACC in comparison to the other 184 parotid malignancies showed a higher cT stage ($p = 0.001$) and lower presence of neck metastases ($p = 0.039$) at the primary diagnosis, together with a higher rate of PNI ($p < 0.001$) and positive microscopic resection margins ($p = 0.017$) at the final pathologic report. Finally, local recurrence and distant metastasis disease incidence showed a prevalence in the ACC group ($p = 0.017$ and $p = 0.016$, respectively).

3.2. Univariate and survival analyses

Table 2 represents survival outcomes stratified by disease and treatment variables at the univariate analysis for the 44 ACC patients; it shows that ACC local recurrence is mainly influenced by advanced primary cT stage (cT3, $p = 0.050$), suspected neck metastasis at the clinical stage (cN1, $p = 0.041$) which did not found any statistical significance at the pathologic N-status; clinical advanced stage presented a progressive worsening of local-DFS with a p value of 0.007 for TNM IV. And, indirect signs of local aggressiveness such facial nerve paralysis ($p = 0.007$), presence of PNI ($p = 0.001$), corresponded to a worse local prognosis and together with indications for adjuvant radiotherapy ($p = 0.004$). Concerning pathologic patterns of growth the solid feature was the most represented among a higher incidence of local relapse ($p = 0.005$).

By comparing the ACC to the other malignancies in terms of local-DFS (Fig. 1a), it emerged that for the ACC group local relapse incidence continued to appear over a longer follow-up time ($p = 0.1975$); whilst,

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Table 1
Clinical characteristics of 44 ACC.

Variables	Level	ACC N (%)	Others N (%)	*p*-Value
Gender	Female	23 (52)	71 (39)	0.098
	Male	21 (48)	113 (61)	
Age	<50	165 (34)	50 (27)	0.416
	50–70	22 (50)	89 (48)	
	>70	7 (16)	45 (25)	
cT	T1	8 (18)	30 (16)	**0.001**
	T2	15 (34)	79 (43)	
	T3	17 (39)	26 (14)	
	T4a	4 (9)	49 (27)	
cN	N0	36 (82)	151 (82)	**0.039**
	N1	7 (16)	11 (6)	
	N2a	0 (0)	6 (3)	
	N2b	0 (0)	14 (7)	
	N2c	1 (2)	1 (1)	
	N3	0 (0)	1 (1)	
Clinical stage	1	7 (16)	28 (15)	0.325
	2	14 (32)	68 (37)	
	3	12 (27)	29 (16)	
	4	11 (25)	59 (32)	
Facial nerve paralysis	No	33 (75)	151 (82)	0.286
	Yes	11 (25)	33 (18)	
Skin invasion	No	40 (91)	179 (97)	0.051
	Yes	4 (9)	5 (3)	
Type of surgery	Radical parotidectomy	11 (25)	60 (32)	0.723
	Total parotidectomy + facial nerve preservation	32 (73)	118 (64)	
	Superficial parotidectomy	1 (2)	6 (3)	
Perineurial invasion	No	22 (50)	160 (87)	<**0.001**
	Yes	22 (50)	24 (13)	
Cribriform pattern	No	26 (59)		
	Yes	18 (41)		
Tubular pattern	No	30 (68)		
	Yes	14 (32)		
Solid pattern	No	32 (73)		
	Yes	12 (27)		
pT	T1	8 (18)	32 (17)	**0.016**
	T2	16 (36)	73 (40)	
	T3	14 (32)	25 (14)	
	T4a	6 (14)	54 (29)	
pN	N0	36 (82)	136 (84)	0.578
	N1	6 (14)	19 (10)	
	N2a	1 (2)	7 (4)	
	N2b	1 (2)	18 (10)	
	N2c	0 (0)	2 (1)	
	N3	0 (0)	2 (1)	
Resection margins status	No	35 (80)	169 (92)	**0.017**
	Yes	9 (20)	15 (8)	
Radiotherapy	No	18 (41)	75 (41)	0.986
	Yes	26 (59)	109 (59)	
Chemotherapy	No	38 (86)	172 (93)	0.116
	Yes	6 (14)	12 (7)	
Local recurrence	No	28 (64)	148 (80)	**0.017**
	Yes	16 (36)	36 (20)	
Regional recurrence	No	41 (93)	162 (88)	0.327
	Yes	3 (7)	22 (12)	
Distant metastasis	No	29 (66)	156 (85)	**0.016**
	Polmone	13 (30)	23 (12)	
	Ossa	1 (2)	4 (2)	
	Cerebrale	1 (2)	1 (1)	
Death	No	22 (50)	113 (61)	0.164
	Yes	21 (48)	70 (38)	
	Yes, other	1 (2)	1 (1)	

ACC regional recurrence was influenced by the pathological N-status, only ($p = 0.032$). On the contrary, other type of parotid malignancies showed a higher incidence of regional-recurrence in comparison to ACC patients during the clinical follow-up ($p = 0.2007$) (Fig. 1b), which was mainly influenced by the presence of neck metastasis at the final pathological report ($p < 0.001$), PNI ($p = 0.003$) and positive microscopic resection margins ($p = 0.005$).

Distant metastasis (DM) onset in ACC patients was statistically due to the presence of a solid pattern of growth ($p = 0.044$). The other 184 malignancies presented an incidence of DM of 15% (28 out of 184), whose appearance resulted to be linked to an advanced clinical TNM stage ($p = 0.042$ for stage IV), facial nerve paralysis ($p = 0.017$), PNI ($p = 0.003$) and adjuvant radiotherapy ($p = 0.002$). Their Kaplan-Meyer curves (Fig. 1c) evidenced a higher incidence of DM in the ACC group (34% vs 15%), with their progressive appearance over the whole long follow-up period of 120 months ($p = 0.1402$).

Throughout a median follow-up time of 95 months (mean 92.48 ± 50.89 SD; 95% CI 77.01–107.95; range 7–180 months), the 48% of ACC patients died for disease and one (2%) for other causes. Again, advanced clinical stage ($p = 0.016$), facial nerve paralysis at the primary clinical exam ($p = 0.024$), PNI ($p = 0.001$), solid pattern of growth ($p = 0.001$) and post-operative radiation treatment ($p = 0.004$) showed the most statistically significant correlations with mortality rate. The other type of malignancies presented a global mortality rate of 38.5%, where 64 patients died for disease (35%) and 5 for other causes (3%). The OS curves of both groups are represented in Fig. 1d ($p = 0.601$).

3.3. Multivariate analysis

Despite the absence of significant *p* values, among the variables sorted from the univariate analysis, the PNI conserved the highest OR (14.1) for incidence of local recurrence and facial nerve paralysis was associated with a higher mortality rate (OR 5.9) (Table 3). Their graphic representations are shown in Fig. 2a and b.

On the other hand, regional-recurrence and distant metastases multivariate analyses were not statistically significant enough to organize their graphics.

4. Discussion

ACC is an uncommon tumor and concerning anatomical site incidence the parotid reports a value between 6–10% of interest [14]. ACC has classically been described as having an indolent but persistent and recurrent growth and, in contrast to other epithelial malignancies with poor prognosis, ACC has a good 5-year survival rate. ACC is a disease with long evolution, featuring recurrence, not so much locally as by remote metastasis. The literature reports 55–90% 5-year and 30–70% 10-year overall survival [15], and accordingly, our results showed how overall survival continues to drop after the 5-year follow up period, producing considerably lower 10-year survival rate (Fig. 1d) in accordance with literature results [16,17].

In our single center cohort of study we retrospectively reviewed several clinical-pathological parameters found to affect ACC patients prognosis; in specific, accordingly to literature, the advanced cT and clinical tumor stage, positive pathological N-stage, the presence of PNI or of a solid pattern of growth, and a positive microscopic resection margins status have been considered suggestive for severe outcome. On the other hand, low malignancies (tubular and cribriform) and tumor-free surgical margins have been correlated to a better local control rate, lower incidence of early metastasis and better mortality rate [18–21].

In specific we found that ACC in comparison to the other 184 parotid malignancies showed a higher cT stage ($p = 0.001$) and lower presence of neck metastases ($p = 0.039$) at the primary diagnosis, together with a higher rate of PNI ($p < 0.001$) and positive microscopic resection margins ($p = 0.017$) at the final pathologic report, and these resulted to be main factors influencing prognosis in terms of local-relapse incidence, DM appearance and cancer specific mortality.

Local relapse, DM and mortality reported a progressive decrease over 10 years of clinical follow-up (Fig. 1a, c, d), where the above mentioned variables were the main prognostic factors involved except for

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Table 2
Univariate analysis of 44 ACC for local and regional recurrence, distant metastasis onset and mortality rate.

Variables	Level	Local relapse. OR (CI) *p*	Regional relapse OR (CI) *p*	DM OR (CI) *p*	Mortality OR (CI) *p*
Gender	Female	Ref.	Ref.	Ref.	Ref.
	Male	0.52 (0.15, 1.82) 0.307	2.32 (0.19, 27.6) 0.507	0.94 (0.27, 3.27) 0.919	0.99 (0.30, 3.24) 0.989
Age	<50	Ref.	Ref.	Ref.	Ref.
	50–70	0.65 (0.17, 2.48) 0.532	0.67 (0.04, 11.6) 0.781	1.14 (0.29, 4.55) 0.850	1.37 (0.37, 5.12) 0.638
	>70	0.19 (0.02, 1.99) 0.166	2.33 (0.12, 43.8) 0.571	0.8 (0.11, 5.68) 0.823	0.86 (0.14, 5.23) 0.867
cT	T1	Ref.	Ref.	Ref.	Ref.
	T2	1.1 (0.08, 14.1) 0.955	n.c.	4.7 (0.45, 48.3) 0.196	1.5 (0.22, 10.3) 0.680
	T3	10 (0.99, 100) **0.050**	n.c.	4.9 (0.49, 49.2) 0.177	5.5 (0.84, 36.2) 0.076
	T4a	21 (0.96, 459) 0.053	n.c.	2.3 (0.11, 51.0) 0.590	n.c.
cN	N0	Ref.	Ref.	Ref.	Ref.
	N1	6.5 (1.08, 39) **0.041**	2.8 (0.22, 36) 0.424	1.5 (0.29, 7.81) 0.630	3.1 (0.53, 18.3) 0.206
	N2c	n.c.	n.c.	n.c.	n.c.
Clinical stage	1	Ref.	Ref.	Ref.	Ref.
	2	0.46 (0.02, 8.7) 0.606	n.c.	3.3 (0.31, 36.1) 0.322	0.7 (0.09, 5.4) 0.718
	3	3.0 (0.26, 34.2) 0.376	n.c.	4.3 (0.39, 47.6) 0.236	3.5 (0.47, 25.9) 0.220
	4	60 (3.1, 1147) **0.007**	n.c.	3.4 (0.30, 39.6) 0.324	25 (1.8, 347) **0.016**
Facial nerve paralysis	No	Ref.	Ref.	Ref.	Ref.
	Yes	8.3 (1.77, 39.1) **0.007**	7.1 (0.58, 87) 0.126	1.14 (0.27, 4.8) 0.854	6.9 (1.28, 37.3) **0.024**
Skin invasion	No	Ref.	Ref.	Ref.	Ref.
	Yes	6.23 (0.59, 65.9) 0.128	n.c.	0.62 (0.06, 6.5) 0.690	3.3 (0.32, 34.7) 0.317
Type of surgery	Radical parotidectomy	Ref.	Ref.	Ref.	Ref.
	Total parotidectomy + facial nerve preservation	0.33 (0.08, 1.4) 0.136	n.c.	0.67 (0.16, 2.7) 0.575	0.50 (0.12, 2.1) 0.337
	Superficial parotidectomy	0.28 (0.02, 3.6) 0.326	n.c.	n.c.	0.19 (0.01, 2.5) 0.207
Perineurial invasion	No	Ref.	Ref.	Ref.	Ref.
	Yes	17.5 (3.2, 95) **0.001**	n.c.	2.8 (0.77, 10.4) 0.117	11.6 (2.8, 47.3) **0.001**
Cribriform pattern	No	Ref.	Ref.	Ref.	Ref.
	Yes	0.52 (0.14, 1.91) 0.328	n.c.	0.62 (0.17, 2.26) 0.464	0.47 (0.14, 1.59) 0.223
Tubular pattern	No	Ref.	Ref.	Ref.	Ref.
	Yes	0.19 (0.04, 1.00) **0.050**	1.07 (0.09, 13) 0.953	0.41 (0.09, 1.8) 0.234	0.27 (0.07, 1.05) 0.059
Solid pattern	No	Ref.	Ref.	Ref.	Ref.
	Yes	10.7 (2.27, 50.6) **0.003**	6.2 (0.51, 75.8) 0.153	4.2 (1.04, 17) **0.044**	21 (2.4, 184) **0.006**
pT	T1	Ref.	Ref.	Ref.	Ref.
	T2	1.6 (0.14, 18.6) 0.700	n.c.	4.2 (0.41, 43) 0.227	1.8 (0.27, 12.0) 0.543
	T3	9.3 (0.89, 97.7) 0.062	n.c.	3.9 (0.37, 41) 0.260	4.0 (0.59, 27.2) 0.157
	T4a	14 (0.94, 207) 0.055	n.c.	7 (0.50, 98) 0.148	n.c.
pN	N0	Ref.	Ref.	Ref.	Ref.
	N1	2.3 (0.4, 13.1) 0.358	17.5 (1.28, 238) **0.032**	2.27 (0.39, 13.1) 0.358	7 (0.74, 66) 0.090
	N2a	n.c.	n.c.	n.c.	n.c.
	N2b	n.c.	n.c.	n.c.	n.c.
Resection margin status	Negative	Ref.	Ref.	Ref.	Ref.
	Positive	n.c.	2.1 (0.17, 25.7) 0.574	0.96 (0.1, 4.5) 0.957	n.c.
Radiotherapy	No	Ref.	Ref.	Ref.	Ref.
	Yes	23.2 (2.67, 201) **0.004**	n.c.	1.63 (0.44, 6.0) 0.464	7.9 (1.9, 31.6) **0.004**
Chemotherapy	No	Ref.	Ref.	Ref.	Ref.
	Yes	n.c.	3.6 (0.27, 47.3) 0.330	0.96 (0.16, 6.0) 0.966	n.c.

the DM incidence which was affected mainly by solid pathologic pattern of growth.

By analyzing each single significant factor, perineurial invasion has already shown its association with a high local failure in head and neck cancers [22], and the reason lays in the correlated high probability of residual microscopic disease in adjacent tissues. In contrast with this, positive microscopic resection margins status resulted in our case series to be a strong predictor in all survival analyses for all parotid malignancies rather than the ACC, suggesting a more important prognostic role acted by other pathologic variables such PNI and solid pattern of growth. The vast majority (63%) of ACC neoplasm excisions with clear margins were early T-stage (*c*T1 and *c*T2) tumors, the reaming cases included 10 *c*T3 and 3 *c*T4; whilst, among positive resection margins (9 out of 44 cases), seven were represented by advanced stage cancers (78%). These results are in agree with the general concept that wide resection of ACC is mandatory. The percentage of positive margins often does not reflect the wide surgical intent performed by surgeons and this might find its reason in the intrinsic nature of ACC neoplasms; it arises from a not capsulated organ such parotid gland, thus its infiltrative growth is not hindered letting ACC invades adjacent tissue without well-defined borders and it impacts mainly on local control rate [23,24].

Despite the relatively indolent progress of ACC in about the 50% of patients, once the metastatic disease is present, it has been documented that survival rate is about 3 years where most patients die from recurrence disease [25]. In literature, the incidence of distant metastasis is estimated to be around 25–55% and usually only 20% of patients with distant metastasis survive 5-years [19,21]. Here, DM presented a percentage of incidence of 34, and the 40% of patients was dead within the first 60 months of follow-up and it seemed to be mainly influenced by the solid pattern.

Adjuvant radiotherapy resulted to negatively affect prognosis of ACC in terms of local relapse incidence, DM appearance and cancer specific mortality. Its role has been debated, so far [26–28]; in our study, patients who received it accordingly to standard treatment concept of radical resection followed by high radiotherapy dose [29], showed a worse prognosis, in contrast with other reports where different radiotherapy protocols showed a significant improvement in local control rate, progression-free disease survival and over-all survival [30]. These controversies might find a reason in the need to find a balance between aggressive surgical procedures to obtain clear margins and the intent to not make post-operative morbidity rate higher than necessary, such as performing facial nerve sacrifice even when there is no macroscopic

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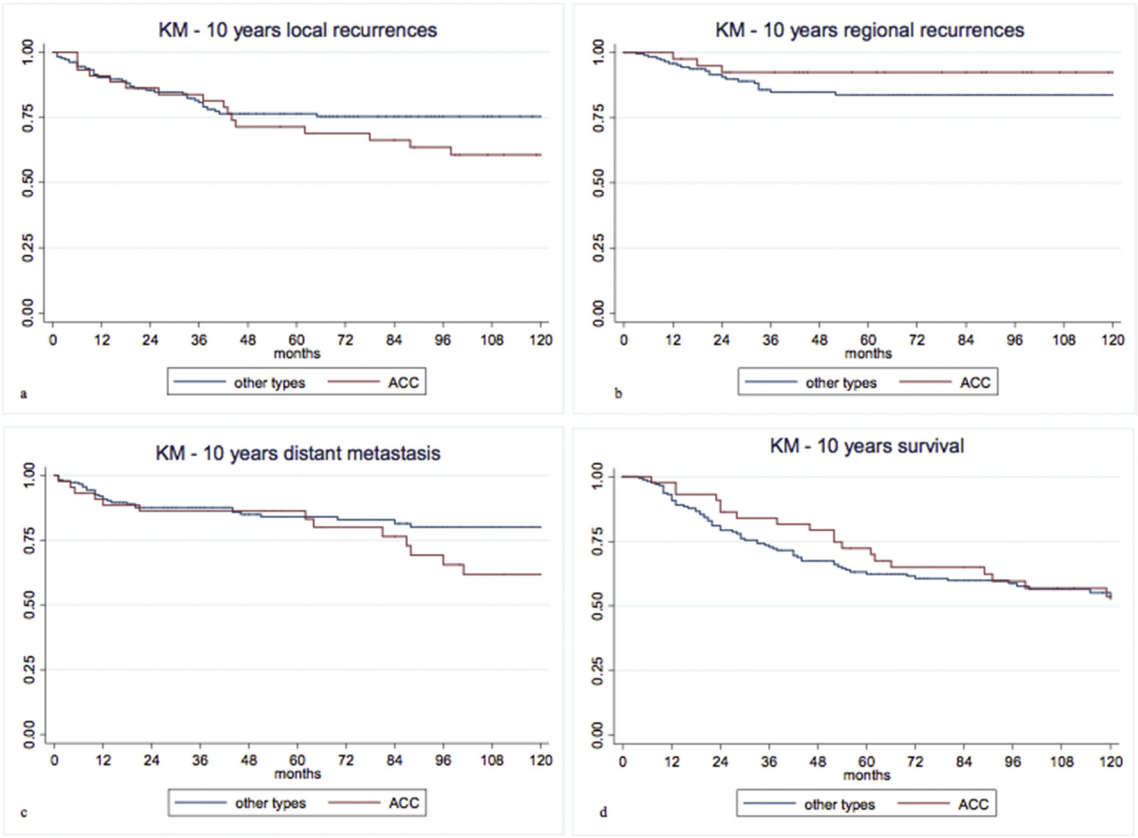

Fig. 1. a) Local DFS curves comparing ACC and other-types groups; b) Regional DFS curves comparing ACC and other-types groups; c) DM DFS curves comparing ACC and other-types groups; d) OS curves comparing ACC and other-types groups.

evidence of disease. The counterpart of a less aggressive surgical tumor resection, is applying radiotherapy on microscopic close or positive margins without gaining any additional chances to prevent relapses.

Unfortunately, classical chemotherapies have not proved effective in ACC so far; and since chemotherapy appears to be ineffective against most salivary gland ACCs, testing a patient's tumor for sensitivity to a chemotherapy agent before giving it is recommended thus there are no convincing data supporting its routine use, except for metastatic disease [31,32].

Although the indolent course of ACC correlates with relatively acceptable survival rates, this is a small number of patients, with poor survival rates and uncontrollable disease progress for which improved and more effective adjuvant therapy may be warranted. Our results support other studies already published in literature [12], based mainly on single-Institution case series with different anatomical sites analyzed [5–8]. Even multi centric studies reporting wider case-series did not focus on single anatomical site, for instance the REFCOR [4] network provided a large prospective cohort, considering the rarity of ACC, but follow-up was insufficient to assess long-term prognostic factors for overall survival.

Here, we reported an accurate analysis of one single site ACC disease, the parotid gland, with the highest number of patients so far. Of course, a number of inherent limitations of the present study need to be addressed. First, this series was a retrospective study and the patients were heterogeneous regarding the extent of surgery and radiotherapy. For the same reason, the correlation between therapy and prognosis cannot be compared with other reports. At the same time we analyzed survivals along a long-term follow-up period, even longer than 10 years in the vast majority of cases. Second, more accurate predictive nomograms should count on larger case series and should study the anatomical site as independent prognostic factor, as well, in addition to all of the clinical and pathological characteristics known, to better characterize the disease and to define optimal treatments.

In summary, despite several limitations, this study comprehensively analyzed the clinicopathologic features of a large single-Institution and one-anatomical site case series of ACC to date. In more than half of our patients, distant metastases was detected later than a 5-year follow-up period, confirming the delayed appearance reported in the literature. Development of distant metastasis occurred irrespectively of and despite complete control of the tumor in the primary site. Margin status (positive versus clear) was significantly associated with local recurrence but not with distant metastasis. No other histological or clinical parameter proved to be a reliable prognostic factor for the development of distant metastases, other than perineural invasion.

Whereas its rarely and the shortage of large case series, some reports have looked for molecular markers to improve prognosis prediction because of the lack of strong significant correlation between commons clinical and pathological features with outcomes [13,33]. In this view, nomograms based on strong prognostic parameters, grounded on

Table 3
Multivariate analysis for local-recurrence incidence and mortality rate in ACC patients.

	Variables	OR	95% CI	*p*-Value
Local-recurrence	Radiotherapy	4.7	(0.34, 64.3)	0.247
	Solid pattern	1.1	(0.09, 13.8)	0.917
	Tubular pattern	0.32	(0.02, 4.6)	0.400
	PNI	14.1	(0.90, 220)	0.059
	Facial nerve paralysis	3.6	(0.38, 33.2)	0.266
	cN positive status	4.9	(0.31, 76.7)	0.259
Mortality rate	Solid pattern	4.3	(0.26, 70.6)	0.312
	Tubular pattern	0.41	(0.06, 2.6)	0.342
	PNI	4.1	(0.65, 25.6)	0.132
	Facial nerve paralysis	5.9	(0.81, 43.0)	0.079
	pN positive status	4.2	(0.21, 82.9)	0.348

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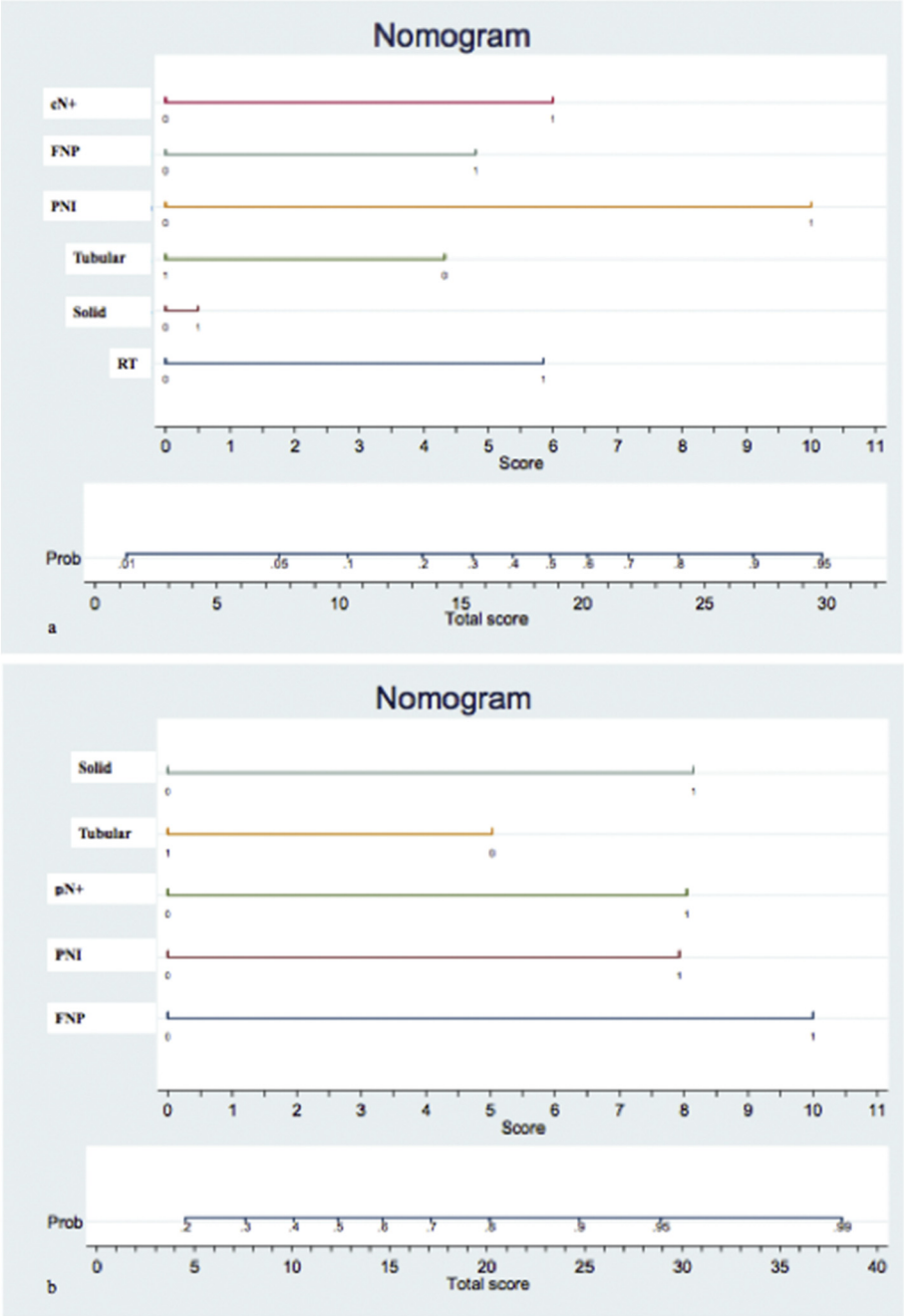

Fig. 2. a) Nomogram for 10 years local recurrence probability for parotid ACC; b) Nomograms for 10 year disease specific death probability for parotid ACC. (cN+ = cN positive status; pN+ = pN positive status; FNP = facial nerve paralysis; PNI = perineural invasion; Tubular = tubular pattern of growth; Solid = solid pattern of growth; RT = adjuvant radiotherapy).

large case series with a long-time of follow-up up to 20 years since the primary diagnosis, could help clinicians in identifying high risk patients who might benefit from a more aggressive combined treatment and more restricted follow-up.

5. Conclusion

Adenoid cystic carcinoma, even though is a relatively uncommon neoplasia, proves to be a problematic pathology due to many controversies existing regarding knowledge about its clinical and biological behavior and its treatment's response.

Predictive nomograms, in accordance with Gangly and colleagues [12], could be useful tolls for patient counseling and treatment decision making, which might guide towards more tailored patient care protocol together with the addition of future possible target therapies.

To reach this purpose further clinical trials are needed.

Authorship

All authors ensure that they all gave substantial contributions: 1) to conception and design, acquisition of data, or analysis and interpretation of data; 2) in drafting the article or revising it critically for important intellectual content; 3) for the final approval of the version to be published, and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

[1] Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2807 patients. Head Neck Surg 1986;8:177–84.
[2] Barnes L, Eveson JW, Reichart P, et al. WHO Classification Head and Neck Tumors. IARC Press yon; 2005.
[3] Garden AS, Weber RS, Morrison WH, et al. The influence of positive margins and nerve invasion in adenoid cystic carcinoma of the head and neck treated with surgery an radiation. Int J Radiat Oncol Biol Phys 1995;32:619–26.
[4] Meyers M, Granger B, Herman P, et al. Head and neck adenoid cystic carcinoma: a retrospective multi centre REFCOR study of 95 cases. Our Ann Otorhinolaryngol Head Neck Dis 2016;133:13–7.
[5] Kokemueller H, Eckardt A, Brachvogel P, et al. Adenoid cystic carcinoma of the head and neck-a 20 years experience. Int J Oral Maxillofac Surg 2004;33:25–31.
[6] Avery CME, Moody AB, Mckenna FE, et al. Combined treatment of adenoid cystic carcinoma of the salivary grands. Int J Oral Maxillofac Surg 2000;29:277–9.
[7] van Weert S, Bloemena E, van der Wall I, et al. Adenoid cystic carcinoma of the head and neck: a single-centre analysis of 105 consecutive cases over 30-year period. Oral Oncol 2013;49:824–9.
[8] Hirvonen K, Back L, Saarilahti K, et al. Pattern of recurrent disease in major salivary gland adenocystic carcinoma. Virchws Arch 2015;467:19–25.
[9] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471.
[10] Ko JJ, Siever JE, Hao D, et al. Adenoid cystic carcinoma of head and neck: clinical predictors of outcome from a Canadian centre. Curr Oncol 2016;23:26–33.
[11] Sur RK, Donde B, Levin V, et al. Adenoid cystic carcinoma of the salivary glands: a review of 10 years. Laryngoscope 1997;107:1276–80.
[12] Gangly I, Amit M, Palmer FL, et al. Nomograms for predicting survival and recurrence in patients with adenoid cystic carcinoma. An international collaborative study. Eur J Cancer 2015;51:2768–76.
[13] Perzin KH, Gullane P, Clairmont AC. Adenoid cystic carcinomas arising in salivary glands; a correlation of histologic features and clinical course. Cancer 1978;42:265–82.
[14] Zhang CY, Xia RH, Han J, et al. Adenoid cystic carcinoma of the head and neck: clinicopathologic analysis of 218 cases in a Chinese population. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:368–75.
[15] DeAngelis AF, Tsui A, Wiesenfeld D, et al. Outcomes of patients with adenoid cystic carcinoma of the minor salivary glands. Int J Oral Maxillofac Surg 2011;40:710–4.
[16] Spiro RH, Huvos AG, Strong EW. Adenoid cystic carcinoma of salivary origin: a clinicopathologic study of 242 cases. Am J Surg 1974;128:512–20.
[17] Huang M, Ma D, Sun K, et al. Factors influencing survival rate in adenoid cystic carcinoma of the salivary glands. Int J Oral Maxillofac Surg 1997;26:435–9.
[18] Batsakis JG, Luna MA. Histopathologic grading of salivary gland neoplasms: III. Adenoid cystic carcinomas. Ann Otol Rhinol Laryngol 1990;99:1007–9.
[19] Fordice J, Kershaw C, El-Naggar A, et al. Adenoid cystic carcinoma of the head and neck: predictors of morbidity and mortality. Arch Otolaryngol Head Neck Surg 1999;125:149–52.
[20] Silverman DA, Carlson TP, Khunntia D, et al. Role for postoperative radiation therapy in adenoid cystic carcinoma of the head and neck. Laryngoscope 2004;114:1194–9.
[21] Gondivkar SM, Gadbail A, Chole R, et al. Adenoid cystic carcinoma: a rare clinical entity and literature review. Oral Oncol 2011;47:231–6.
[22] Soo K, Carter RL, Barr LB, et al. Prognostic implications of perineural spread in squamous carcinomas of the head and neck. Laryngoscope 1986;96:1145–8.
[23] Horiuchi J, Shibuya H, Suzuki S, et al. The role of radiotherapy in the management of adenoid cystic carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1987;13:1135–41.
[24] Fu KK, Leibel SA, Levine ML, et al. Carcinoma of the major and minor salivary glands. Cancer 1977;40:2882–90.
[25] van der Wal JE, Becking AG, Snow GB, et al. Distant metastases of adenoid cystic carcinoma of the salivary glands and the value of diagnostic examinations during follow-up. Head Neck 2002;24:779–83.
[26] McNaney D, McNeese MD, Guillamondegui OM, et al. Postoperative irradiation in malignant epithelial tumors of the parotid. Int J Radiat Oncol Biol Phys 1983;9:1289–95.
[27] Miglianico L, Eschwege F, Marandas P, et al. Cervico-facial adenoid cystic carcinoma: study of 102 cases:influence of radiation therapy. Int J Radiat Oncol Biol Phys 1987;13:673–8.
[28] Simpson J, Thawley S, Matsuba H. Adenoid cystic salivary gland carcinoma: treatment with irradiation and surgery. Radiology 1984;151:509–12.
[29] Terhaard CHJ, Lubsen H, Rasch CR, et al. Dutch Head and Neck Oncology Cooperative Group. The role of radiotherapy in the treatment of malignant salivary gland tumors. Int J Radiat Oncol Biol Phys 2005;61:103–11.
[30] Jensen AD, Nikoghosyan AV, Poulakis M, et al. Combined intensity-modulated radiotherapy plus raster-scanned carbon ion boost for advanced adenoid cystic carcinoma of the head and neck results in superior locoregional control and overall survival. Cancer 2015;121:3001–9.
[31] Dodd RL, Slevin NJ. Salivary gland adenoid cystic carcinoma: a review of chemotherapy and molecular therapies. Oral Oncol 2006;42:759–69.
[32] Laurie SA, Ho AL, Fury MG, et al. Systemic therapy in the management of metastatic or locally recurrent adenoid cystic carcinoma of the salivary glands: a systematic review. Lancet Oncol 2011;12:815–24.
[33] Khan AJ, Di Giovanna MP, Ros DA, et al. Adenoid cystic carcinoma: a retrospective clinical review. Int J Cancer (Radiat Oncol Invest) 2001;96:149–58.

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