Original Research
Oral Pathology

Laura Borges KIRSCHNICK[a]
Felipe Martins SILVEIRA[b]
Lauren Frenzel SCHUCH[a]
Ana Carolina Uchoa VASCONCELOS[c]
Ana Paula GOMES[c]
Jean Nunes dos SANTOS[d]
Dandara Andrade SANTANA[d]
Felipe Paiva FONSECA[e]
Ricardo Alves MESQUITA[e]
Elismauro Francisco de MENDONÇA[f]
Sebastião Silvério SOUSA-NETO[f]
Hélder Antônio Rebelo PONTES[g]
Liam ROBINSON[h]
Willie van HEERDEN[h]
Román CARLOS-BREGNI[i]
Elena María José Román TAGER[i]
Luan César da SILVA[a]
Virgílio Gonzales ZANELLA[ii]
Luis Fernando RIVERO[k]
Raquel BITTENCOURT[k]
Marco Antonio Trevizani MARTINS[l]
Márcio Ajudarte LOPES[a]
Vivian Petersen WAGNER[m]
Pablo Agustin VARGAS[a]
Manoela Domingues MARTINS[n]

[a]Universidade Estadual de Campinas – UNICAMP, Piracicaba Dental School, Department of Oral Diagnosis, Piracicaba, SP, Brazil.
[b]Universidad de la República – UDELAR, School of Dentistry, Division of Molecular Pathology, Montevideo, Uruguay.
[c]Universidade Federal de Pelotas – UFPel, School of Dentistry, Diagnostic Center for Oral Diseases, Pelotas, RS, Brazil.
[d]Universidade Federal da Bahia – UFBA, School of Dentistry, Department of Pathology, Graduate Program in Dentistry and Health, Salvador, BA, Brazil.
[e]Universidade Federal de Minas Gerais – UFMG, School of Dentistry, Department of Oral Surgery and Pathology, Belo Horizonte, MG, Brazil.
[f]Universidade Federal de Goias – UFG, School of Dentistry, Department of Stomatology, Goiânia, GO, Brazil.
[g]Universidade Federal do Pará – UFPA, João de Barros Barreto University Hospital, Department of Oral Pathology, Belém, PA, Brazil.
[h]University of Pretoria – UP, School of Dentistry, Department of Oral Pathology and Oral Biology, Pretoria, South Africa.
[i]Clinical Center of Head and Neck/Hospital Herrera Llerandi, Division of Pathology, Guatemala City, Guatemala.
[ii]Santa Casa de Misericórdia de Porto Alegre, Santa Rita Hospital, Department of Head and Neck Surgery, Porto Alegre, RS, Brazil.
[k]Universidade Federal do Rio Grande do Sul – UFRGS, Faculty of Medicine, Department of Pathology, Porto Alegre, RS, Brazil.
[l]Universidade Federal do Rio Grande do Sul – UFRGS, Hospital de Clínicas de Porto Alegre, Department of Oral Medicine, Porto Alegre, RS, Brazil.
[m]University of Sheffield, Academic Unit of Oral and Maxillofacial Medicine and Pathology, Department of Clinical Dentistry, Sheffield, UK.
[n]Universidade Federal do Rio Grande do Sul – UFRGS, School of Dentistry, Department of Oral Pathology, Porto Alegre, RS, Brazil.

Declaration of Interests: The authors certify that they have no commercial or associative interest that represents a conflict of interest in connection with the manuscript.

Corresponding Author:
Manoela Domingues Martins
E-mail: manomartins@gmail.com

https://doi.org/10.1590/1807-3107bor-2023.vol37.0050

Submitted: June 7, 2022
Accepted for publication: December 12, 2022
Last revision: February 6, 2023

Acinic cell carcinoma of the oral and maxillofacial region: an international multicenter study

Abstract: The aim of this study was to describe the prevalence, clinicopathological, and prognostic features of acinic cell carcinoma (AciCC) of the oral and maxillofacial region. AciCC cases were retrospectively retrieved from 11 pathology centers of three different countries. Medical records were examined to extract demographic, clinical, pathologic, and follow-up information. A total of 75 cases were included. Females (65.33%) with a mean age of 45.51 years were mostly affected. The lesions usually presented as an asymptomatic (64.28%) nodule (95.66%) in the parotid gland (70.68%). The association of two histopathological patterns was the most common finding (48.93%) and the tumors presented mainly conventional histopathological grades (86.11%). Surgical treatment was performed in the majority of the cases (59.19%). Local recurrence was observed in 20% of the informed cases, regional metastasis in 30.43%, and distant metastasis in 12.50%. The statistical analysis showed that the cases with a solid histopathological pattern (p=0.01), high-grade transformation (p=0.008), recurrence (p=0.007), and regional metastasis (p=0.03) were associated with poor survival. In conclusion, high histopathological transformation, presence of nodal metastasis, and recurrence were prognostic factors for AciCC of the oral and maxillofacial region.

Keywords: Carcinoma, Acinar Cell; Salivary Gland Neoplasms; Retrospective Studies.

Introduction

Acinic cell carcinoma (AciCC) was first described by Nasse in 1892 as a benign tumor. In 1953, it was recognized by Buxton et al. as a malignancy because of its metastatic potential and tendency for recurrence.[1,2] Currently, AciCC is a rare malignant tumor of salivary glands, representing 6–8% of all salivary gland neoplasms. Its overall incidence rate is 1.20–1.63 cases per 1,000,000 patients/year.[3,4]

A recent systematic review performed by our group demonstrated that AciCC showed a predilection for the parotid gland in females in the fifth decade of life. Most cases presented as an indolent mass.[5] Histologically, AciCC shows four main patterns: solid, papillary cystic, microcystic, and follicular. These patterns may occur individually or in combination, without a prognostic significance.[5,6] Although AciCC

does not have a definitive histological grading system defined by the World Health Organization (WHO), cases with high-grade transformation – mitotic activity (> 2 mitoses/10 high-power field), presence of necrosis and pleomorphic cells, extracapsular tumor extension, and positive resection margins – have been linked to a poorer prognosis.[5,7,8] Furthermore, in 2010, Skálová et al.[9] described a neoplasm previously mistaken for AciCC by means of histopathological features, but with a translocation resulting in an ETV6-NTRK3 fusion gene. This neoplasm was originally named mammary analogue secretory carcinoma (MASC), but was subsequently renamed secretory carcinoma (SC), and has led pathologists to review and reclassify AciCCs as SCs.[9,10,11]

AciCC is considered a low-grade neoplasm with a good prognosis; however, its metastatic ability and recurrence rate, given the high-grade transformation seen in some cases, lead to an uncertain biological course. In addition, an association of histological patterns and grading with overall prognosis in patients diagnosed with AciCC is still lacking in the literature. Accordingly, this multicenter study aims to integrate data in terms of prevalence and clinicopathological features from a sample of AciCC cases diagnosed at different oral and maxillofacial pathology laboratories from around the world.

Methodology

Ethical approval and multicenter collaboration

This international multicenter retrospective study was approved by the local Research Ethics Committee of the University of Campinas (process no. 43463521.1.0000.5418). All procedures followed the ethical standards of the 1975 Declaration of Helsinki revised in 2008.

Cases were retrospectively reviewed in the period 1954 to 2021 from the archives of multiple oral and maxillofacial pathology laboratories from three countries: Brazil (nine centers), Guatemala (one center), and South Africa (one center). The following centers collaborated on this study: University of Campinas, Federal University of Pelotas, Federal University of Bahia, Federal University of Minas Gerais, Western Paraná State University, Federal University of Goiás, Federal University of Pará, Clinical Hospital of Porto Alegre, and Santa Rita Hospital, all from Brazil. Additionally, Centro Clínico de Cabeza y Cuello, Guatemala, and University of Pretoria, South Africa, also contributed to this study.

Samples

All cases with a confirmed histopathological diagnosis of AciCC involving the oral and maxillofacial region, in accordance with the 2017-WHO classification,[7] were included. The following data were retrieved for each case: a) sex; b) age; c) skin color; d) anatomical location; e) clinical presentation; f) symptoms; g) clinical duration; h) clinical diagnostic hypothesis; i) imaging characteristics;j) histological pattern and presence of high-grade transformation characteristics – mitotic activity (> 2 mitoses/10 high-power field), presence of necrosis and pleomorphic cells, extracapsular tumor extension, and positive resection margins;[8] k) immunohistochemical markers; l) treatment; m) follow-up; n) recurrence or metastasis; and o) survival status. Any missing data were reported as not informed (N.I.).

Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) software, version 20.0 (IBM Corporation, Armonk, USA). Initially, a descriptive analysis was performed, and categorical variables were presented as absolute value and percentage, and continuous variables as mean, standard deviation (SD), and range. The association between age and sex was compared using the Mann-Whitney test. Association of independent variables with regional metastasis (absent vs. present) and outcome status (alive vs. dead) were evaluated by Fisher's exact test and chi-square test. Kaplan-Meier survival curves were constructed and compared using the log-rank test. For all tests, a p-value of < 0.05 was interpreted as statistically significant.

Results

A total of 75 cases of AciCC were included in this study following their review (62 cases from Brazilian centers, eight from Guatemala, and five from South Africa). Table 1 summarizes the demographic and clinicopathological findings. Females (n = 49/65.33%) were more frequently affected than males (n = 26/34.67%), with a male to female ratio of 1:1.8. The mean age of all patients was 46.35 ± 18.23 years, which was similar among males (47.88 ± 16.08 years) and females (45.51 ± 19.43 years) (p = 0.73, Mann-Whitney test). The age was not reported for two patients. Two cases involved pediatric patients (9- and 11-years old) and five adolescents/young adults less than 21 years of age. White individuals (n = 26/66.66%) were most frequently affected.

The parotid gland (n = 53/70.68%) was the main anatomical location affected, followed by palate (n = 6/8%), buccal mucosa (n=5/6.67%), submandibular gland (n = 3/4%), and lips (n = 2/2.67%). A single case (1.33%) was diagnosed on each of the following subsites: tongue, nasal septum, ethmoidal sinus, parapharyngeal space, and auditory canal. Most cases (95.66%) presented with a nodule, which was asymptomatic in 18 cases (64.28%) (Figures 1A and B). The clinical duration was reported in 23 cases, with a mean of 21.00±20.58 months (range: 1 to 72 months). The clinical diagnostic hypothesis was diverse, with formulation of more than one clinical hypothesis for an individual case. The main clinical hypothesis included nonspecific salivary gland neoplasms (n = 16), benign salivary gland tumors (n = 11), malignant salivary gland tumors (n = 6), and squamous cell carcinoma, lymphoma, and sarcoma (n = 1). Advanced imaging (n = 12) was mainly performed on parotid gland lesions (n = 8), followed by buccal mucosa (n = 1) and ethmoidal sinus (n = 1). Computed tomography (CT) imaging was performed in five cases (41.67%) (Figure 1C), ultrasonography (US) in four cases (33.33%), and magnetic resonance imaging (MRI) in one case (8.33%). The main aspects described by all imaging studies included a delineated cystic or expansile mass. Moreover, radiological exams were

Table 1. Summarized data on the cases of AciCC included in the present multicenter study.

Variable	n (%)
Sex (n = 75)	
Female	49 (65.33)
Male	26 (34.67)
Male-to-female ratio	1:1.8
Age (n = 73)	
Mean (SD)	46.35 ± 18.23 years
Range	9–87 years
Anatomical location (n = 75)	
Parotid gland	53 (70.68)
Palate	6 (8.00)
Buccal mucosa	5 (6.67)
Submandibular gland	3 (4.00)
Symptoms (n = 28)	
No	18 (64.28)
Yes	10 (35.72)
Clinical presentation of the lesion (n = 46)	
Nodular mass	44 (95.66)
Ulcer	1 (2.17)
Papillomatous lesion	1 (2.17)
Clinical duration (n = 23)	
Mean (SD)	21.00 ± 20.58 months
Range	1–72 months
Histopathological pattern (n = 47)	
Mixed patterns	23 (48.93)
Solid	15 (31.92)
Microcystic	7 (14.89)
Histopathological grade (n = 36)	
Conventional	31 (86.11)
High-grade transformation	5 (13.89)
Treatment (n = 49)	
Surgery	29 (59.19)
Surgery and radiation therapy	11 (22.45)
Surgery, radiation therapy, and chemotherapy	7 (14.28)
Follow-up period (n = 22)	
Mean (SD)	62.22±49.79 months
Range	4 –192 months
Status (n = 24)	
Alive	21 (87.50)
Dead from the disease	3 (12.50)

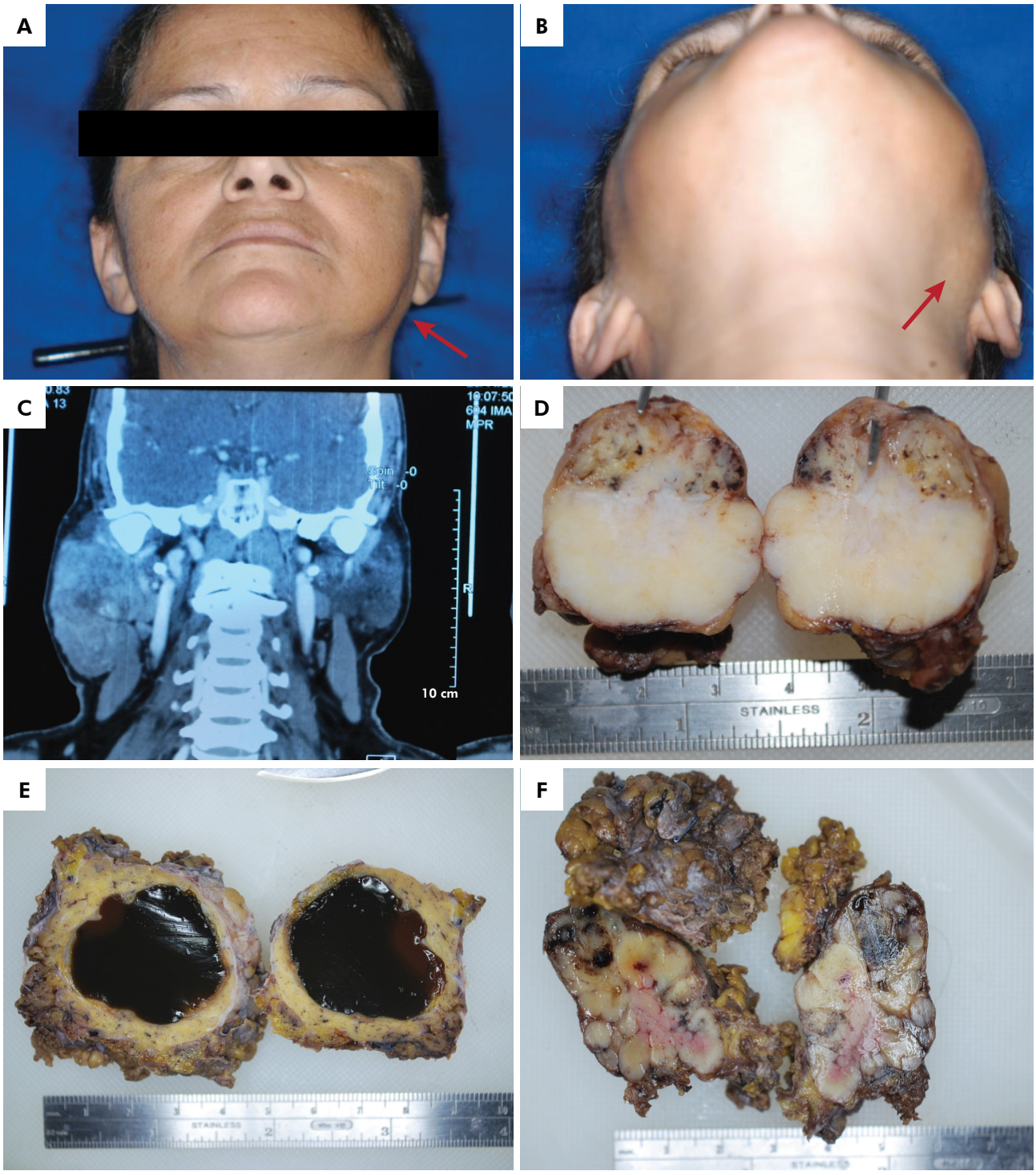

Figure 1. Clinical, radiological, and macroscopic characteristics of AciCC cases included in this study. A and B, clinical appearance of AciCC nodular lesion in left parotid gland causing face deformation (arrows) in a 47-year-old woman who reported pain for 2 years. C, coronal CT section showing a heterogeneous hyperdense image in the parotid-masseteric region on the right side of a 40-year-old man diagnosed with AciCC. D, surgical specimen showing a well-circumscribed ovoid tumor with pale appearance. E, AciCC removed from the right parotid gland of a 58- year-old man, showing macroscopic aspect of a cavity (cystic appearance) filled with bloody mucous material. F, macroscopic aspect of AciCC with poorly defined borders with infiltration in the left parotid of a 46-year-old woman.

performed in two cases (16.67%) – buccal mucosa and parotid gland tumors – with no evidence of bone involvement.

Regarding the histopathological features, a combination of two patterns was seen in 23 cases (48.93%), followed by the solid pattern (n = 15/31.92%), microcystic pattern (n = 7/14.89%), papillary cystic pattern (n = 1/2.13%), and follicular pattern (n = 1/2.13%). Most cases presented with a conventional histological grade (n = 31/86.11%) (Figure 2). Immunohistochemical reactions were performed in 18 cases, including cytokeratin 7 (positive in 7 of 7 cases), S100 (negative in 7 of 7 cases), cytokeratin 8 (positive in 6 of 7 cases), AE1/AE3 (positive in 5 of 5 cases), Ki67 (proliferative index ranging between 5 and 10%), p63 (negative in 3 of 4 cases), cytokeratin 18 (positive in 3 of 3 cases), DOG1 (positive in 3 of 3 cases), and vimentin (negative in 2 of 3 cases).

Treatment information was only available for 49 cases, with surgical excision performed in most cases (29/59.19%). Six cases (20.00%) presented with local recurrence (n = 30). Regional metastases were reported in 14 patients (30.43%) out of 46 cases for which this information was recorded. Information on distant metastases was available for 32 cases, with distant metastases to the bones, lungs, thyroid, and brain in four patients (12.50%). No association was found between the presence of regional metastasis and anatomical location (p = 0.70, Fisher's exact test), presence of symptoms (p = 0.61, Fisher's exact test), histological pattern (p=0.45, chi-square test), histological grade (p = 1.00, chi-square test), and treatment (p=0.75, chi-square test) (Table 2). A statistically significant association was noted between regional metastasis and recurrence (p = 0.01, Fisher's exact test), in which most patients (n=5) with recurrences also had regional metastases (Table 2).

Survival analysis

Of the 75 cases reported in the current study, follow-up data were available for 24 cases. Twenty-one patients (87.50%) were alive and three (12.50%) were dead from the disease by the time of the last follow-up appointment. No association was found between patient status (alive or dead) and anatomic location (p = 0.52, Fisher's exact test), presence of symptoms (p = 1.00, Fisher's exact test), histological grade (p = 0.35, chi-square test), and distant metastasis (p = 0.15, Fisher's exact test) (Table 3). Although there was no significant association between patient status and histological pattern (p = 0.06, chi-square test), it was observed that cases with a solid histological pattern (66.70%) were more common among patients who eventually succumbed to the disease. A statistically significant association was observed between treatment and status at follow-up (p = 0.01, chi-square test). All three patients who eventually succumbed to the disease received surgery with adjuvant therapy (Table 3). A statistically significant relationship between recurrence and/or regional metastasis with patients who succumbed to the disease was found (Table 3, p = 0.006 and p = 0.04, respectively – Fisher's exact test).

Survival analysis was performed for 13 cases, which presented with information on both follow-up status and time. Among these patients, two succumbed within 12 months after the diagnosis. The mean follow-up time for the remaining 11 patients was 92.45 months. The 2-year survival rate was 84% (Figure 3A). Survival curves were constructed and compared for histological grade, histological pattern, recurrence, regional metastases, and distant metastases (Figures 3B, 3C, 3D, 3E, and 3F). No association was found between survival time and treatment (p = 0.30, log-rank test); however, high-grade transformation (p = 0.008, log-rank test), solid histological pattern (p = 0.01, log-rank test), recurrence (p = 0.007, log-rank test), and regional metastases (p = 0.03, log-rank test) were significantly associated with poor overall survival. A lower overall survival time was also observed for patients with distant metastases, but no statistical significance was obtained (p = 0.06, log-rank test).

Discussion

Malignant salivary gland tumors are rare, representing 6–8% of all head and neck tumors, while AciCC comprises 17% of all salivary gland malignancies.[3,4] AciCC used to be considered a

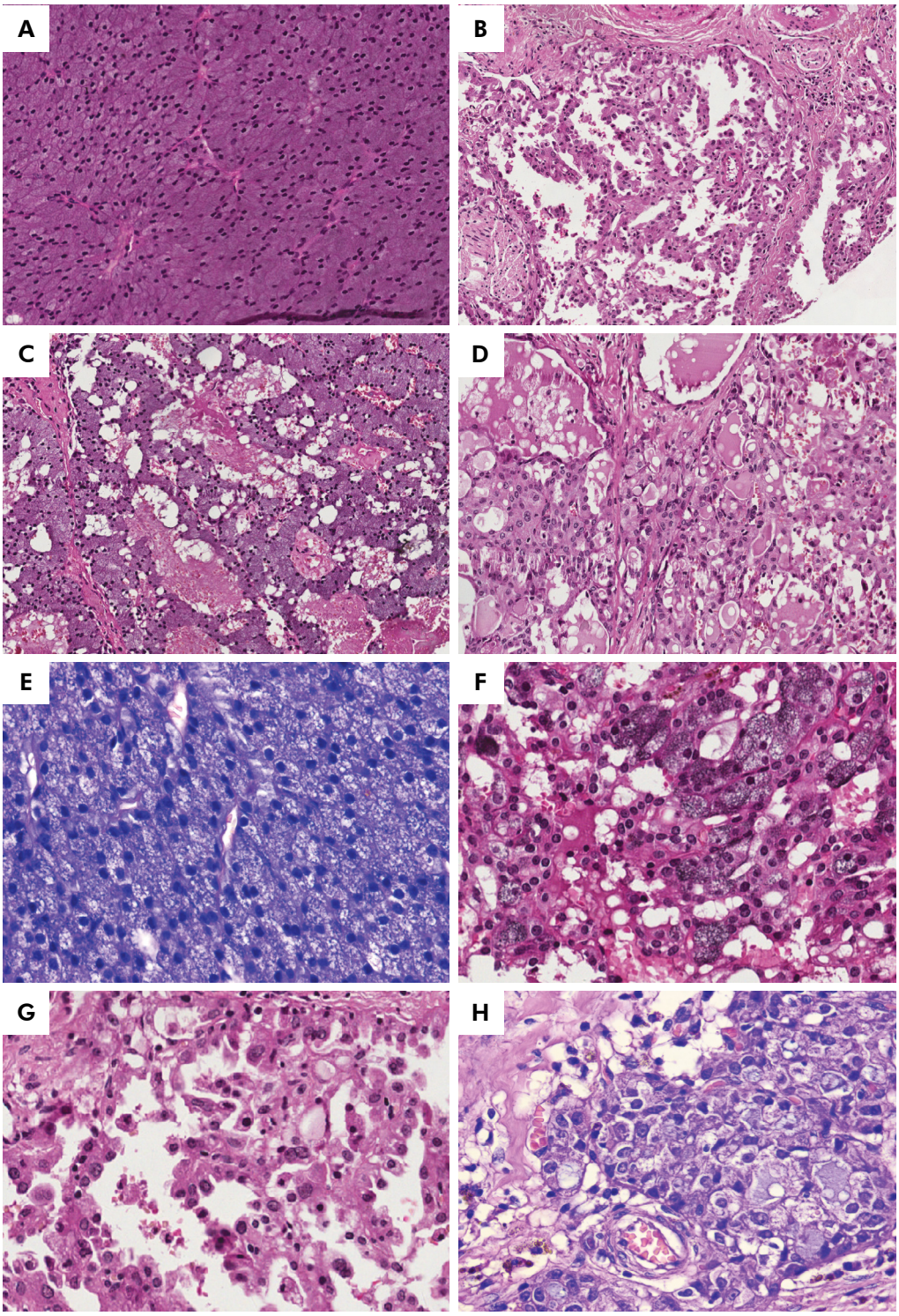

Figure 2. Histopathologic aspects of AciCC cases included in this study. A–D, several histomorphologic growth patterns could be observed such as solid (A), papillary (B), and microcystic (C and D) (H&E, x200). E, AciCC characterized by serous acinar cell differentiation. The parenchyma of the tumor was composed of large cells with cytoplasmic zymogen – such as secretory granules and uniform, round, and eccentric nuclei. F, different cell types could be observed. Acinic cells with basophilic cytoplasm were the least frequent. They are surrounded by abundant nonspecific glandular cells, intercalated with duct-like cells and few cells with vacuolated cytoplasm. G, cells with aspects of intercalation with duct-like cells showing cuboidal and eosinophilic to amphophilic cytoplasm and central basophilic to vesicular nuclei. H, AciCC with high-grade transformation composed of nonspecific glandular cells and few acinic cells (E- H, H&E, x400).

Table 2. Association between independent variables and regional metastasis.

Variable	Regional metastasis		p-value
	Present - n(%)	Absent - n(%)	
Anatomical location			
Major salivary glands	12 (85.7)	25 (78.1)	0.70
Minor salivary glands	2 (14.3)	7 (21.8)	
Histopathological pattern			
Solid	3 (33.3)	5 (31.3)	
Microcystic	2 (22.3)	1 (6.3)	0.45
Mixed	4 (44.4)	10 (62.5)	
Histopathological grade			
Conventional	6 (85.7)	12 (80)	1.00
High-grade transformation	1 (14.3)	3 (20)	
Symptoms			
Present	1 (20)	5 (38.5)	0.61
Absent	4 (80)	8 (61.5)	
Treatment			
Surgery	6 (54.5)	13 (56.5)	
Surgery + RT	2 (18.2)	6 (26.1)	0.75
Surgery + RT + CT	3 (27.3)	4 (17.4)	
Recurrence			
Yes	5 (55.6)	1 (5.9)	0.01
No	4 (44.4)	16 (94.1)	

RT: radiation therapy; CT: chemotherapy; Fisher's exact test and the chi-square test were performed for the statistical analyses. p-values in bold indicate statistical significance.

Table 3. Association between independent variables and follow-up status.

Variable	Follow-up status		p-value
	Alive - n(%)	Dead - n(%)	
Anatomical location			
Major salivary gland	17 (81)	2 (66.7)	0.52
Minor salivary gland	4 (19)	1 (33.3)	
Histopathological pattern			
Solid	2 (13.3)	2 (66.7)	
Papillary cystic	0 (0)	0 (0)	0.06
Microcystic	3 (20)	1 (33.3)	
Mixed	10 (66.7)	0 (0)	
Histopathological grade			
Conventional	12 (85.7)	1 (50)	0.35
High-grade transformation	2 (14.3)	1 (50)	
Symptoms			
Present	2 (20%	0 (0)	1.00
Absent	8 (80)	2 (100)	
Treatment			
Surgery	9 (52.9)	0 (0)	
Surgery + RT	7 (41.2)	1 (33.3)	0.01
Surgery + RT + CT	1 (5.9)	2 (66.6)	
Recurrence			
Yes	2 (10.5)	3 (100)	0.006
No	17 (89.5)	0 (0)	
Nodal metastasis			
Present	4 (26.7)	3 (100)	0.04
Absent	11 (73.3)	0 (0)	
Distant metastasis			
Present	1 (12.5)	2 (66.7)	0.15
Absent	7 (87.5)	1 (33.3)	

RT: radiation therapy; CT: chemotherapy; Fisher's exact test and the chi-square test were performed for the statistical analyses. p-values in bold indicate statistical significance.

low-grade tumor with a good prognosis; however, recently, high-grade transformation described in some instances has a lower overall survival rate. Further studies on AciCC are needed to better understand its biological behavior.[12] The current retrospective multicenter study included 75 new cases of AciCC from all regions of Brazil, Guatemala, and South Africa.

The first case series of AciCC was published in 1954 by Godwin et al. Their study found that AciCC was more prevalent in women, presenting at a mean age of 41.26 years.[13] More recent studies have shown a slightly higher mean age at presentation (50 years), with a range between 47 and 54 years.[5,7,14] Moreover, AciCC often presents at a lower mean age than do other salivary gland tumors, except for mucoepidermoid carcinoma.[7] In the current study, a female predominance was noted, with a mean age at diagnosis of 46.35 years, which is in line with the current literature.

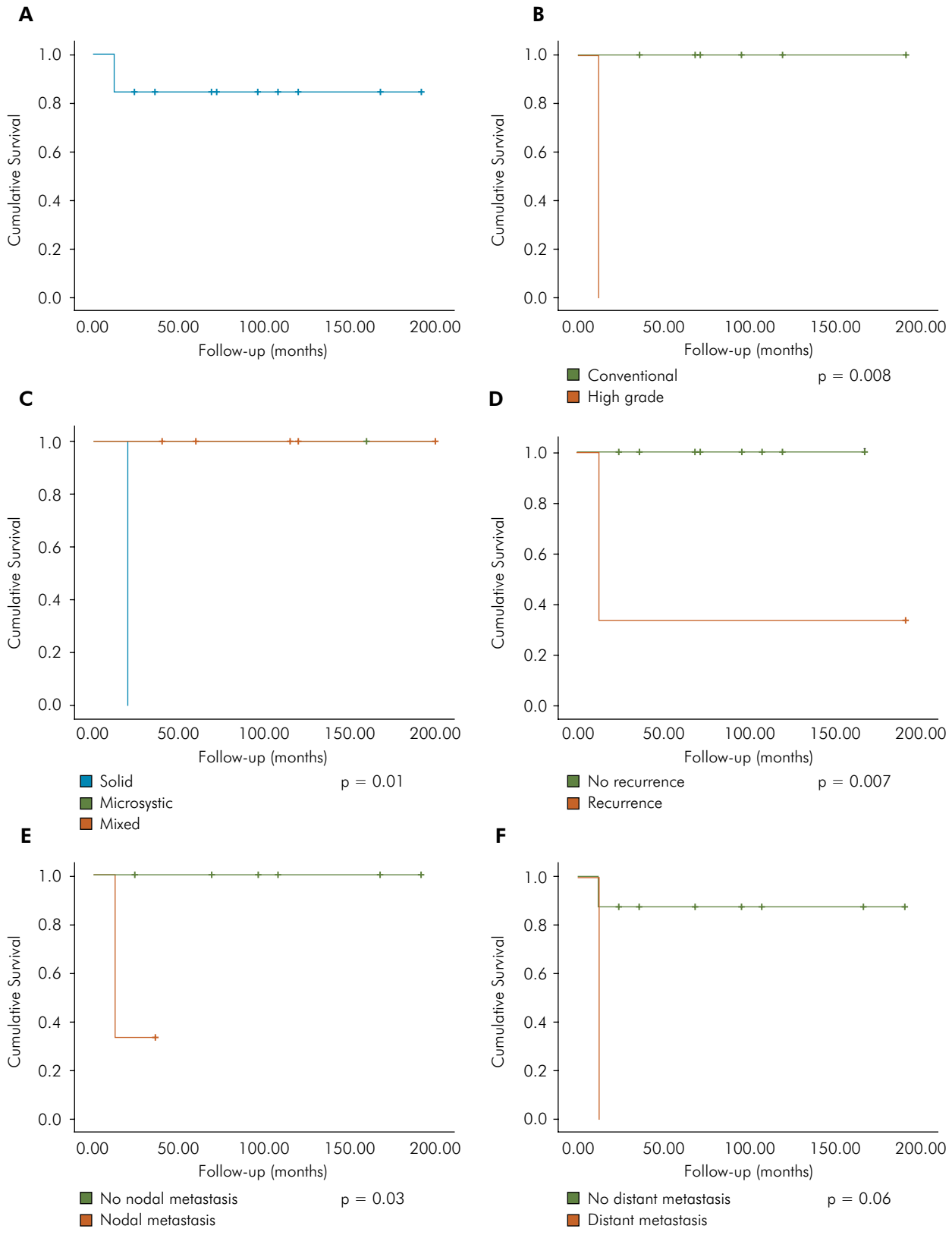

Figure 3. A, 2-year survival curve. B, survival curve for histological grade. C, survival curve for histological pattern. D, survival curve for recurrence. E, survival curve for regional metastasis. F, survival curve for distant metastasis.

The parotid gland is the most frequently involved salivary gland,[15] as pointed out in the current study, in which 70.68% of all cases involved this major salivary gland. The minor salivary glands of the buccal mucosa and palate, followed by the submandibular gland, were affected at lower frequencies. A systematic review of the literature showed a similar distribution, with involvement of the minor glands of the buccal mucosa and palate in nearly 5% of the cases.[5] AciCC commonly presents as a slow-growing asymptomatic nodule.[5,6] This finding is consistent with the one found in the current study, in which 95.66% of cases presented as a nodule, without symptoms in 64.28% of the cases.

Imaging exams serve as an auxiliary method for the diagnosis of AciCC. Although imaging features are nonspecific, they assist in the evaluation of circumscription, extension, and relationship of lesions with the neighboring structures.[3,6,16] In the current study, imaging exams such as CT, US, and MRI were performed in 12 cases, mainly in those affecting the parotid gland. Most cases presented as a nodular mass without bone involvement in imaging studies.

AciCC is defined by serous acinar differentiation with four main histological growth patterns – solid, microcystic, papillary cystic, and follicular. AciCC may present with a combination of two growth patterns in more than 20% of the cases.[3,5,7] In the current study, two patterns were seen in 48.93% of the cases, followed by the solid pattern in 31.92% of the cases. Histological grade is considered the most important prognostic factor for AciCC.[6] Any grading system for characterizing the high-grade transformation of AciCC is recognized by WHO, but some authors have suggested a classification based on the proliferation characteristics of the lesions as follows: high mitotic activity (> 2 mitoses/10 high-power field), presence of necrosis and pleomorphic cells, extracapsular tumor extension, and positive resection margins.[7,8] High-grade transformation usually affects older patients and it is associated with low overall survival because of their aggressive behavior, higher recurrence rates, and regional or distant metastases.[5,12]

Immunohistochemical (IHC) staining is useful to rule out other differential diagnoses with a similar morphology, such as secretory carcinoma.[9] IHC is particularly useful in tumors containing microcystic and solid areas with abundant PAS-positive secretory material similar to vacuolated colloid.[9] Some markers, such as S100, which is positive in SC and negative in AciCC, and DOG1, which is negative in SC and positive in AciCC, were used in this retrospective study to confirm the diagnosis of AciCC. Only 24% of the cases in the current study had available IHC data for analysis; the other cases had enough morphological evidence to confirm the AciCC diagnosis. Recently, a novel marker – nuclear receptor subfamily 4 group A member 3 (NR4A3), has been described as highly specific and sensitive to AciCC.[17] Unfortunately, this maker was not available for use in any of the cases in the current study. Furthermore, cytokeratin 7 expression varies according to the histopathological pattern of AciCC, with positive results usually seen in microcystic, papillary cystic, and follicular patterns. Cytokeratin 7 was performed on seven cases in the current study, with positivity in all cases, including two papillary cystic lesions and three cases with mixed patterns.[18]

Surgical excision alone was performed in 59.19% of the cases, with 22.45% receiving a combination of surgery and radiation therapy. Complete surgical excision is the mainstay of treatment for AciCC and it is associated with the best prognostic outcome.[15] The use of radiation therapy is still controversial and it is often used in tumors with high-grade transformation, recurrent tumors, positive surgical margins, or cases with metastasis.[3,16,19] AciCC is considered a chemoresistant lesion, but chemotherapy may be useful in the treatment of pain.[3] Seven cases in the current study were treated with a combination of surgery, radiation therapy, and chemotherapy. Patients (n = 3) who succumbed to the disease had received adjuvant therapy, in addition to surgical excision.

AciCC is known to have a good prognosis when compared to other salivary gland malignancies. However, high-grade tumors are associated with recurrence, metastases, and a lower overall survival.[5,12,14] In the current study, tumor recurrence (20%), regional metastases (30.43%), and distant metastases (12.50%) were all described. Distant

metastases in this study mostly occurred via hematological spread, predominantly involving the bones and lungs.[16] Recurrence ($p = 0.006$) and regional metastases ($p = 0.04$) were significantly associated with patients who succumbed to the disease, confirming previous reports.[5,14]

Given the retrospective nature of this study, some data were not available for all cases. Additional limitations include lack of treatment and follow-up information, possibly due to outside referral for treatment in some dental schools. The low percentage of cases with information on follow-up status and time hinders the survival statistical analysis, which was restricted only to Kaplan Meier/log-rank analysis. Regression analyses were not performed because of very high confidence intervals, as a result of the low number of cases with available information.

Conclusion

In summary, this international multicenter study highlights the rarity of AciCC. AciCC usually presents during the fifth decade of life, with a female predominance and a predilection for the parotid gland. AciCC has a good overall prognosis, with low recurrence and death rates. Despite the lack of information in some cases, it can be concluded that cases with high-grade transformation, regional metastases, and tumor recurrence are important prognostic factors for AciCC. Histological grading should be performed on all cases to better define the treatment approach to each case and improve the overall prognosis.

Acknowledgements

Pablo A. Vargas, Marcio A. Lopes, Jean N. Santos, Ricardo A. Mesquita, Elismauro F. Mendonça, and Manoela D. Martins are research fellows funded by the Brazilian National Council for Scientific and Technological Development (CNPq). The authors thank the Coordination for the Improvement of Higher Education Personnel (CAPES, Finance Code 001), Brazil. Laura B Kirschnick and Lauren F Schuch are fellowship recipients. Felipe P Fonseca was supported by research grants from the CNPq (#406452/2018-0) and FAPEMIG (#APQ-00623-18).

References

1. Nasse D. Die Geschwülste Der Speicheldrüsen Und VerwandteTumoren Des Kopfes. Arch Klin Chir. 1892;44:233-302.
2. Buxton RW, Maxwell JH, French AJ. Surgical treatment of epithelial tumors of the parotid gland. Surg Gynecol Obstet. 1953 Oct;97(4):401-16.
3. Al-Zaher N, Obeid A, Al-Salam S, Al-Kayyali BS. Acinic cell carcinoma of the salivary glands: a literature review. Hematol Oncol Stem Cell Ther. 2009;2(1):259-64. https://doi.org/10.1016/S1658-3876(09)50035-0
4. Gupta A, Koochakzadeh S, Neskey DM, Nguyen SA, Lentsch EJ. Incidence and survival trends of parotid malignancies over 42 years. Head Neck. 2020 Sep;42(9):2308-15. https://doi.org/10.1002/hed.26172
5. Kirschnick LB, Silveira FM, Schuch LF, Fonseca FP, Martins MA, Lopes MA, et al. Clinicopathological analysis of oral and maxillofacial acinic cell carcinoma: A systematic review. J Oral Pathol Med. 2021 Sep;50(8):741-9. https://doi.org/10.1111/jop.13159
6. Vander Poorten V, Triantafyllou A, Thompson LD, Bishop J, Hauben E, Hunt J, et al. Salivary acinic cell carcinoma: reappraisal and update. Eur Arch Otorhinolaryngol. 2016 Nov;273(11):3511-31. https://doi.org/10.1007/s00405-015-3855-7
7. El-Naggar AK, Chan JK, Grandis JR, Takata T, Slootweg PJ. WHO Classification of head and neck tumours. 4th ed. France: IARC; 2017. v. 9.
8. Gomez DR, Katabi N, Zhung J, Wolden SL, Zelefsky MJ, Kraus DH, et al. Clinical and pathologic prognostic features in acinic cell carcinoma of the parotid gland. Cancer. 2009 May;115(10):2128-37. https://doi.org/10.1002/cncr.24259
9. Skálová A, Vanecek T, Sima R, Laco J, Weinreb I, Perez-Ordonez B, et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. Am J Surg Pathol. 2010 May;34(5):599-608. https://doi.org/10.1097/PAS.0b013e3181d9efcc
10. Chiosea SI, Griffith C, Assaad A, Seethala RR. The profile of acinic cell carcinoma after recognition of mammary analog secretory carcinoma. Am J Surg Pathol. 2012 Mar;36(3):343-50. https://doi.org/10.1097/PAS.0b013e318242a5b0

11. Seethala RR, Stenman G. Update from the 4th Edition of the World Health Organization Classification od Head and Neck Tumors: tumors of the salivary gland. Head Neck Pathol. 2017;11(1):55-67. https://doi.org/10.1007/s12105-017-0795-0
12. Skálová A, Leivo I, Hellquist H, Agaimy A, Simpson RH, Stenman G, et al. High-grade transformation/dedifferentiation in salivary gland carcinomas: occurrence across subtypes and clinical significance. Adv Anat Pathol. 2021 May;28(3):107-18. https://doi.org/10.1097/PAP.0000000000000298
13. Godwin JT, Foote FW Jr, Frazell EL. Acinic cell adenocarcinoma of the parotid gland; report of twenty-seven cases. Am J Pathol. 1954;30(3):465-77.
14. Scherl C, Kato MG, Erkul E, Graboyes EM, Nguyen SA, Chi AC, et al. Outcomes and prognostic factors for parotid acinic cell carcinoma: a national cancer database study of 2362 cases. Oral Oncol. 2018 Jul;82:53-60. https://doi.org/10.1016/j.oraloncology.2018.05.002
15. Yibulayin F, Feng L, Wang M, Lu MM, Luo Y, Liu H, et al. Head & neck acinar cell carcinoma: a population-based study using the seer registry. BMC Cancer. 2020 Jul;20(1):631. https://doi.org/10.1186/s12885-020-07066-y
16. Cavaliere M, De Luca P, Scarpa A, Savignano L, Cassandro C, Cassandro E, et al. Acinic cell carcinoma of the parotid gland: from pathogenesis to management: a literature review. Eur Arch Otorhinolaryngol. 2020 Oct;277(10):2673-9. https://doi.org/10.1007/s00405-020-05998-6
17. Haller F, Skálová A, Ihrler S, Märkl B, Bieg M, Moskalev EA, et al. Nuclear NR4A3 immunostaining is a specific and sensitive novel marker for acinic cell carcinoma of the salivary glands. Am J Surg Pathol. 2019 Sep;43(9):1264-72. https://doi.org/10.1097/PAS.0000000000001279
18. Li X, Shi Z, Wang Y, Liu Y, Liu T. Immunohistochemical expression of cytokeratins in human salivary gland acinic cell carcinomas. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015 Aug;120(2):248-57. https://doi.org/10.1016/j.oooo.2015.04.014
19. Andreoli MT, Andreoli SM, Shrime MG, Devaiah AK. Radiotherapy in parotid acinic cell carcinoma: does it have an impact on survival? Arch Otolaryngol Head Neck Surg. 2012 May;138(5):463-6. https://doi.org/10.1001/archoto.2012.226