Adenoid Cystic Carcinoma of Salivary Gland: A Ten-Year Single Institute Experience

IULIA CRISTIANA BELULESCU1, CLAUDIU MARGARITESC2, CRISTIANA IULIA DUMITRESCU2, LUMINITA DĂGUCI3, CRISTINA MUNTEANU4, OTILIA CLARA MARGARITESC5

1Department of Pathology, University of Medicine and Pharmacy of Craiova, Romania
2Department of Clinical Pharmacology, University of Medicine and Pharmacy of Craiova, Romania
3Department of Prosthodontics, Faculty of Dentistry, University of Medicine and Pharmacy of Craiova, Romania
4Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University of Medicine and Pharmacy of Craiova, Romania
5Department of Neurosurgery, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania

ABSTRACT: Adenoid cystic carcinoma is a rare tumor, accounting for about 7.5% of all salivary gland neoplasms. More frequent developing in minor salivary gland, this is a slow-growing tumor with a long-lasting natural evolution, quite aggressive locally, but which has a tendency toward local recurrence and even for distant metastasis. We conducted a retrospective study limited to a period of 10 years in a single medical institution to investigate the morphoclinical profile of this tumor. Thus, we have established that about 60% of the tumors developed in men, with near 40% of the cases in patients in the sixth decade and, most common, the pathology affected the parotid and minor salivary glands from the hard palate mucosa. Histopathologically, prevailed the solid variant, with 72% cases presenting perineural invasion, and 41% cases showing positive surgical resection margins. Most cases had a long-standing asymptomatic evolution, so that at the time of diagnosis, more than two thirds of the patients were at least in stage II-pTNM, and in one-fifth of the cases histopathology showed lymph nodes disseminations.

KEYWORDS: Adenoid cystic carcinoma, salivary gland, epidemiology, histopathology.

Introduction

Even though it is a rare tumor with an annual incidence of maximum 4.5 cases per million, adenoid cystic carcinoma (ACC) represent near 10% of salivary gland neoplasms [1], and is the most common malignancy of the minor salivary glands [2].

Men, mostly middle-aged are more common involved, with an incidence rate of 0.71 cases per 100,000 individuals [2].

Clinically, the patient with salivary gland ACC has an indolent course, growing slowly but relentlessly, with a tendency for delayed recurrence and metastasis [3].

This evolution is due primarily to its neurotropism, which can justify the regional aggression; the tumors can extend along the large nerve trunks to the vital craniofacial structures [4].

The literature has reported a high rate of distant metastases (about 40%), with lung, as the most commonly affected site [5].

However, high rate of survival rates were reported, respectively about 77.3% at five years and 44.9% at fifteen-years after surgery [6].

On the other hand, due to its longstanding evolution, it can undergo high-grade transformation, and then became more clinical aggressive, shortening the survival period of the patient [7].

At the same time, we must bear in mind that such tumours do not respond to chemotherapy or radiation therapy and that is why unresectable tumors are often fatal [8].

This study aimed to investigate the epidemiological and morphological profile of ACC diagnosed in the last decade at the Emergency Clinical County Hospital from Craiova.

Materials and Methods

In this retrospective study we included 32 patients diagnosed with salivary gland ACC, between 2010 and 2019 in the Emergency Clinical County Hospital from Craiova.

The patients records have been reviewed and the corresponding histopathological slides were reevaluated according to the diagnostic criteria established by WHO classification (2005) [9].

As clinical and morphological variables of interest were included: age, gender, tumor...
topography, the predominant histologic subtype (tubular, cribriform and solid), presence of perineural invasion, lymph nodes metastases, pTNM status, and the margins status.

In order to establish the predominant type of tumor growth pattern and thus the ACC histological variant at least 80% of the sample was examined.

Tumors originating from major salivary gland were staged in accordance with the American Joint Committee on Cancer (AJCC) Classification Staging Manual, 8th Edition [10].

For those ACC arising from minor salivary glands we used the AJCC classification staging of the oral squamous cell carcinoma in similar sites.

The study protocols were approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova.

We used the SPSS version 12 software for descriptive statistics.

A Students’t test was utilized to assess the differences between two groups of continuous variables, and an Analysis of Variance (ANOVA) test was utilized in order to compare the means of more than two groups of data.

The Chi-squared test was used to evaluate the dependencies between categorical variables.

Throughout the analysis, p<0.05 was considered statistically significant. Data were plotted as average±standard deviation of the mean (SD).

Results

During the period between 2010 to 2019 a total of 32 cases of salivary gland ACC were diagnosed.

At the time of diagnosis, the patient’s average age was 58.31 years, with a median of 57.5 years, and with limits ranging from 31 to 91 years.

Male were more commonly affected then female, namely 19 cases (59.37%) versus 13 cases (40.63%).

The male to female ratio was of 1.46:1.

In our casuistry were included only the ACC cases developed from major salivary glands and minor salivary gland from the oral mucosa.

Our investigated cases were evenly distributed between the major salivary glands and the minor oral salivary glands, with 16 cases in each category.

Parotid salivary gland was the most common site of ACC origin, 9 cases, respectively 28.12% of these tumors being developed at this level.

The hard palate was the second most common site of origin, 6 cases (18.75%) arising at this level.

Also, this site was the most frequent ACC origin for the minor oral salivary glands (37.5%).

Of the other major salivary glands, the sublingual gland was more frequently affected than the submaxillary gland, with 4 cases (12.5%) and respectively 3 cases (9.37%) originating in these sites.

The second most common site for ACC tumors developed from the minor oral salivary glands was the oropharynx with 5 cases (15.62%), followed by jugal mucosa with 3 cases (9.37%) and the lips with 2 cases (6.25%).

Histopathological investigation highlighted the prevalence of the solid histological variant observed in 15 patients (46.88%).

The second most common histological variant in our casuistry was the tubular one, noticed in11 patients (34.37%).

The least frequent observed variant was the cribriform type, noticed in 6 cases (18.75%).

Tumor proliferations were mainly composed of small neoplastic cells with hyperchromatic, angular nuclei and scant clear cytoplasm, and with poorly defined cell borders (Figure 1A).

We identified 3 major tumor growth patterns: solid, tubular and cribriform.

All these patterns were present in various proportions in the composition of all investigated cases, but one of them prevailed. Solid ACC were mainly composed of sheets of basaloid cells without formation lumina (Figure 1B).

In the tubular ACC cases, there were observed numerous ducts and tubules, lined by luminal cells that were coated by non-luminal myoepithelial cells (Figure 1C).

In the cribriform ACC cases, prevailed variable size of oval to rounded masses of basaloid cells with scattered microcystic spaces, that usually were filled with pink or bluish material on HE staining (Figure 1D).
Figure 1. Salivary gland adenoid cystic carcinoma (ACC). A. Predominance of small neoplastic cells with hyperchromatic, angular nuclei and scant clear cytoplasm, and with poorly defined cell borders. HE staining, x600; B. Solid variant of ACC consisting of sheets of basaloid cells without lumina formation. HE staining, x25; C. Tubular variant of ACC made of ducts and tubules, lined by luminal cells that were coated by non-luminal myoepithelial cells. HE staining, x50; D. Cribriform variant of ACC composed by oval to rounded masses of basaloid cells with scattered microcystic spaces, that usually are filled with pink or bluish material. HE staining, x25.

Commonly, the tumor stroma was scant, and made up of hyalinized fibrous tissue (Figures 2A, E) and rarely had mucinous or myxoid features. Perineural invasion was observed in 23 cases (71.87%), five of them showing intraneural invasion (Figure 2B).

Lymph nodes metastases (Figure 2C) have been diagnosed in 6 cases (18.75%) and in two cases was observed lymphovascular invasion (Figure 2D).
Most of our patients presented at the stage II-pTNM, respectively 23 cases (71.87%), followed far away by patients with III-pTNM stage (6 cases, 18.75%), patients with IV-pTNM stage (2 cases, 6.25%) and one patient with I-pTNM stage (3.12%).

Positive margins have been identified in 13 cases (40.62%).

Statistical analysis did not find significant difference between the most of the investigated parameters.

However, there was a significant difference between the average age of patients with involvement of major salivary glands (54.31±13.85 years old), compared to those with tumors of the minor salivary glands (62.31±9.97 years old), t(30)=−1.87, p=0.035 (Figure 3).

Thus, we noticed a tendency for the minor salivary gland ACC to develop in older patients, at least 10 years older than those who develop tumors in the major salivary glands.

Figure 2. Salivary gland adenoid cystic carcinoma (ACC). A. Stroma between neoplastic proliferations was made of hyalinized fibrous tissue. Masson's trichrome staining, x100; B. Peri-and intraneural neoplastic cell invasion. HE staining, x100; C. Lymph nodes metastases from a solid variant of parotid ACC. HE staining, x25; D. Vein invaded by hard palate ACC. HE staining, x50.
Also we have found that there was a significant difference between the average age of patients with perineural invasion (54.00±13.80 years old), compared to those without perineural invasion (60.72±11.46 years old), $t(30)=-1.65$, $p=0.048$ (Figure 4). Thus, we suggest that patients with perineural invasion developed tumors at a slightly younger age (at least 6 years younger) compared to those who had no perineural invasion.

Figure 3. Statistical analysis proving significant difference between the average age of patients with involvement of major salivary glands (54.31±13.85 years old), compared to those with tumors of the minor salivary glands (62.31±9.97 years old), $t(30)=-1.87$, $p=0.035$.

Figure 4. Statistical analysis proving significant difference between the average age of patients with perineural invasion (54.00±13.80 years old), compared to those without perineural invasion (60.72±11.46 years old), $t(30)=-1.65$, $p=0.048$. 
Discussions

This tumor entity was first described in 1853 by Robin C et al., one in the parotid and two in the nose, having in common a cribriform growth pattern, invasion of the surrounding tissues and spreading along nerves [11].

Three years later, Billroth named this tumor as “cilindroma” [12], and only in 1930 the current name of adenoid cystic carcinoma was used [1].

Its malignant behavior was finally established in 1943 by the Dockerty MB and Mayo CW [13].

It is a rare tumor with an annual incidence of 3-4.5 cases per million people [1] that accounts for 10% to 12% of salivary gland tumours [14], and about 22% of all salivary gland cancers [15].

Between 1993 and 2007 there was a decrease in its incidence, especially for the early stages [14,16].

Although ACC represents only 3-5% of head and neck carcinomas [14], it was reported to be the most common malignancy of the submaxillary and minor salivary glands [14,17].

Our investigation on the salivary gland malignancies casuistry recorded in the Emergency Clinical County Hospital from Craiova between 2010 and 2019 revealed a total of 32 cases of ACC.

These cases prevailed in men (59.37%) in the sixth decade of life (37.5%) and the most common location was the parotid gland (28.12%), followed by the hard palate (18.75%) and oropharynx (15.62%) sites.

The literature records specify that this kind of salivary gland tumor is more common in the 5th and 6th decades, but it can develop in all age groups [18,19].

Most authors indicate 52 age as the average age of ACC patients [18,20,21].

There have been no reports on the association of age with survival [20,21], but some authors argue that there would be a correlation between age and local relapse rate [Chang CF et al. 2018].

These authors reported an ACC incidence of 0.71 per 100,000 peoples in men, and respectively of 0.39 per 100,000 women, with a Male: Female ratio of 1.8:1 [2].

However, literature data regarding ACC gender predilection are controversial. So if most authors indicate slight tumor prevalence among women, some have observed the prevalence in men or even no gender predilection [3,19,22].

Gamboa-Hoiil SI et al. (2020) reported a female prevalence for those ACC developed from nasal cavity and paranasal sinuses [20].

The most frequent ACC location appears to be in the minor salivary glands within the palate, followed by paranasal sinuses as the most often affected sites [1,17,23].

On one of the largest series of salivary gland tumors, Spiro RH (1986), highlighted the ACC prevalence at the site of minor salivary gland (65%), followed by the parotid (19%), and submandibular salivary gland (16%) [15].

However, it seems that there are geographical variations, thus Danish report stated a 40% ACC frequency in minor salivary gland, 32% in parotid gland, 23% in the submandibular gland and 4% in the sublingual gland [24].

It seems that ACC that originate from minor salivary glands are associated with a higher risk of recurrence and a poorer prognosis [25].

It is worth noting that this type of tumor can develop anywhere in the body where there are mucus glands.

Thus, there have been reported ACC cases developed in the mammary gland [26], vulva [27], esophagus [28], cervix [29], bronchi [30], and skin [31].

Histopathologically, our study revealed the prevalence of solid variant (46.88%), followed by the tubular (34.37%) and the last the cribriform histological type (18.75%).

Perineural invasion was noticed in 71.87% cases and lymph nodes metastases were observed in 18.75% of ACC cases.

The majority of patients presented in stage II-pTNM (71.87%) and positive margins were identified in 40.62%.

Statistically, we noticed that minor salivary gland seems to develop ACC in people at least 10 years older than the major salivary glands and perineural invasion seems to develop in younger people compared to the cases that did not present this feature.

Classically, this type of tumor is considered to develop from the intercalated salivary duct, being made up of duct-like cells and modified myoepithelial-like cells [32].

Commonly, ACC contain a combination of two or three possible growth patterns (cribriform, tubular and solid), but with the predominance of one of them [1].

The literature records highlight cribriform type as the most frequent histological variant.
followed by the solid type (20.6-29.3%) [18,20,21].

It seems that this histological classification has prognostic value, since most authors found a high frequency of distant metastases, advanced stage and worse prognosis associated with solid pattern [1,17,19].

Instead, the tubular and cribriform histological subtypes are linked to a better prognosis [33].

For these reasons it was proposed a histologic grading algorithm for ACCs, based on the degree of solid pattern presence [34].

Thus, were recognized three grades: A) Grade I: tubular and cribriform pattern, without solid component; B) Grade II: pure cribriform pattern, or mixed with >30% of solid component; and C) Grade III: predominantly solid pattern. Recently a new grading system was proposed, based on the presence or absence of solid pattern, with grade II as the worse prognostic ACC cases, those cases being composed mainly of solid growth pattern [35].

Perineural invasion seems to be a common finding, even among early-stage tumors [9,17].

Together with distant metastases, perineural invasion was regarded as an unfavorable prognostic factor [36,37].

More recently, it was noticed that while perineural invasion does not have survival impact, intraneural invasion could be an independent predictor marker for a poor outcome [38].

Moreover, the same authors suggested that neural invasion could not predict hematogenous spread, distant metastases correlated only with age, primary site and nodal status.

On the contrary, working on a small group of ACC cases, Teymoortash A et al. (2014) proposed a new classification system for this tumor, namely as: A) p1, for cases with true perineural or endoneural invasion and B) p2, for those cases with nerves adjacent to tumor masses, but without them being invaded [39].

According to these authors, patients with p1 ACC had a higher recurrence rate than p2 patients.

Most of the authors reported high frequency for T2 tumors (60% to 74% of diagnosed ACC cases) with an average size of 3.1-4.3cm (range between 1cm to 7cm) [1,18,40,41].

Regarding lymph nodes metastasis, the literature recorded a rate of 17-19% in ACC cases developed from major salivary glands [42,43].

More recently, Qian ZJ et al. (2019) reported a rate of 5% to 15% for occult nodal metastasis in patients with ACC, values that have been shown to increase with the number of investigated lymph nodes [44].

While some authors have shown that the number of sampled lymph nodes in ACC patients were not associated with survival regardless of T classification [44], others reported that in patients with advanced T (T3 and T4) the risk of nodal metastasis was increased 4 to 9 times more compared to T1 and T2 tumors [42].

Regarding the status of resection margins, literature data mentions the existence of a residual tumor in about 32.6% to 65.2% of ACC cases [18,20].

The high percentage of positive margins seems to be related to tumor site which can put technical problems in achieving adequate margins [17,45].

Some authors reported the prognostic value of positive margins for overall survival rate of patients with ACC [46], while others have shown that negative margins are not a guarantee of better survival, but rather of a better local control [47].

Local recurrences were reported to vary from 10.3% to 74% [2,21,33,40,48].

Recently, Gamboa-Hoil SI et al. (2020) reported 53% local recurrences and 40% distant recurrences, with a 65% recurrence rate at 5 years [20].

The same authors noticed a median time of 23 months for the local and distant recurrences. The rate of local recurrence may be increased by: positive surgical margins, invasion of major nerve, and origin in the minor salivary gland [49].

Thus, in a study regarding ACC developed from minor salivary glands it was reported a rate of local recurrence of around 40% [50].

Also, Ouyang DQ et al. (2017) showed that positive lymph nodes, lymphovascular invasion and T3-T4 status, are risk factors for local recurrence [21].

In the literature, for the ACC metastasis rate were reported values ranging between 17.2% to 68.5% [2,21,33,40,48].

Recently, it was observed a trend for distant metastases to become more common than regional recurrences [19].

Evan for early ACC stages (T1-2/N0) it was reported a rate of 20% for distant metastases [51].
Lungs seem to be the most common location for distant metastases [1,19,23,33,52].

Another frequent localization of ACC metastasis is the bones, and in these cases the evolution is rapid [49].

Although lung metastases occur much earlier than other possible metastatic locations, patients with lung metastases survive at least one year longer than patients with metastases in other sites [52].

For lung metastases is quoted a median time of development of about 28.5 months [20].

The five-year overall survival in patients with ACC without recurrences varies from 62.9% [45] to 100% [20], and for those cases with recurrences these values dropped to 56.2% [45] and 66% [20].

As the most important independent prognostic factors for the overall survival and disease specific survival rates are quoted: age, site, N classification and the presence of distant metastases [33].

Other authors found perineural invasion to be a prognostic factor for the overall survival rate of ACC patients [50], or solid histologic type and positive surgical margins, especially for those tumors that developed in the minor salivary glands [4,50,53].

Conclusions

Our ten years single institute experience proved that parotid and minor salivary glands, especially the hard palate, are the most affected sites.

The epidemiological profile showed salivary gland ACC prevalence in men, in the sixth decade of life, and the histopathological investigation revealed the high incidence of solid variant, with about two-thirds of the cases presenting perineural invasion, and approximately one third with positive surgical margins.

Lymph nodes metastases were documented in about one fifth of the cases and near two-thirds of cases presented in stage II-pTNM.

Conflict of interests

None to declare.

References

1. Coca-Pelaz A, Rodrigo JP, Bradley PJ, Vander Poorten V, Triantafyllou A, Hunt JL, Strojan P, Rinaldo A, Haigentz M Jr, Takes RP, Mondin V, Teymoortash A, Thompson LD, Fertilto A. Adenoid cystic carcinoma of the head and neck - An update. Oral Oncol, 2015, 51(7):652-681.

2. Chang CF, Hsieh MY, Chen MK, Chou MC. Adenoid cystic carcinoma of head and neck: A retrospective clinical analysis of a single institution. Auris Nasus Larynx, 2018, 45(4):831-837.

3. Gondivkar SM, Gadable AR, Chole R, Parikh RV. Adenoid cystic carcinoma: a rare clinical entity and literature review. Oral Oncol, 2011, 47(4):221-236.

4. Barrett AW, Speight PM. Perineural invasion in adenoid cystic carcinoma of the salivary glands: anatomical influences on oncological management. Curr Cancer Ther Rev, 2011, 7:78-82.

5. Spiro RH. Distant metastasis in adenoid cystic carcinoma of salivary origin. Am J Surg, 1997, 174(5):495-498.

6. Lloyd S, Yu JB, Wilson LD, Decker RH. Determinants and patterns of survival in adenoid cystic carcinoma of the head and neck, including an analysis of adjuvant radiation therapy. Am J Clin Oncol, 2011, 34(1):76-81.

7. Hellquist H, Skalová A, Barnes L, Cardesa A, Thompson LD, Triantafyllou A, Williams MD, Devaney KO, Gnepp DR, Bishop JA, Wenig BM, Suárez C, Rodrigo JP, Coca-Pelaz A, Strojan P, Shah JP, Hamoir M, Bradley PJ, Silver CE, Slootweg PJ, Vander Poorten V, Teymoortash A, Medina JE, Robbins KT, Pitman KT, Kowalski LP, de Cree R, Mendenhall WM, Eloy JA, Takes RP, Rinaldo A, Fertilto A. Cervical Lymph Node Metastasis in High-Grade Transformation of Head and Neck Adenoid Cystic Carcinoma: A Collective International Review. Adv Ther, 2016, 33(3):357-368.

8. Cai WY, Zhuang Y, Yan F, Li T, Song WT, Sun JH. Effect of survivin downregulation by simvastatin on the growth and invasion of salivary adenoid cystic carcinoma. Mol Med Rep, 2018, 18(2):1939-1946.

9. EL-Naggar AK, Huvos AG. Adenoid cystic carcinoma. In: Barnes L, Eveson JW, Reichart P, Sidransky D (Eds.): World Health Organization classification of tumours: pathology and genetics of head and neck tumours, 4th ed. Lyon, 2005, 221-223.

10. Amin MB. American Joint Committee on Cancer. American Cancer Society. In: Edge SB, Greer WR, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (Eds.): AJCC staging manual. 8th ed. Amin Chicago IL: American Joint Committee on Cancer, Springer, 2017, New York, 1024.

11. Eto PM. Adenoid cystic carcinoma. Clin Otolaryngol Allied Sci, 1986, 11(4):267-291.

12. Kokemueller H, Eckardt A, Brachvogel P, Haasenme J. Adenoid cystic carcinoma of the head and neck—a 20 years experience. Int J Oral Maxillofac Surg, 2004, 33(1):25-31.

13. Dockerty MB, Mayo CW. Primary tumors of submaxillary gland with special reference to mixed tumors. Surg Gynecol Obstet, 1942, 74:1033-45.
14. Bjørndal K, Krogdahl A, Therkildsen MH, Overgaard J, Johansen J, Kristensen CA, Homée P, Sørensen CH, Andersen E, Bundgaard T, Primdahl H, Lambertsen K, Andersen LJ, Godballe C. Salivary gland carcinoma in Denmark 1990-2005: a national study of incidence, site and histology. Results of the Danish Head and Neck Cancer Group (DAHANCA). Oral Oncol, 2011, 47(7):677-682.

15. Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. Head Neck Surg, 1986, 8(3):177-184.

16. Carlson J, Licitra L, Locati L, Raben D, Persson F, Stenman G. Salivary gland cancer: an update on present and emerging therapies, Am Soc Clin Oncol Educ Book, 2013, Alexandria, 257-263.

17. Bradley PJ. Adenoid cystic carcinoma of the head and neck: a review. Curr Opin Otolaryngol Head Neck Surg, 2004, 12(2):127-132.

18. Luna-Ortiz K, Villavicencio-Valencia V, Rodríguez-Falconi A, Peteuil N, Mosqueda-Taylor A. Adenoid Cystic Carcinoma in a Mexican Population. J Maxillofac Oral Surg, 2016, 15(2):236-242.

19. Shum JW, Chatzistefanou I, Qaisi M, Lubeck JE, Ord RA. Adenoid cystic carcinoma of the minor salivary glands: a retrospective series of 29 cases and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol, 2016, 121(3):210-214.

20. Gamboa-Hoil SL, Silva-Godínez JC, Abrego-Vásquez JA. Adenoid cystic carcinoma of head and neck. A 5-year retrospective study: Experience in a single third-level reference center. Cir Cir, 2020, 88(1):34-40.

21. Ouyang DQ, Liang LZ, Zheng GS, Ke ZF, Weng DS, Yang WF, Su YX, Liao GQ. Risk factors and prognosis for salivary gland adenoid cystic carcinoma in southern China: A 25-year retrospective study. Medicine (Baltimore), 2017, 96(5):e5964.

22. Dantas AN, Morais EF, Macedo RA, Tinóco JM, Morais Mde L. Clinicopathological characteristics and perineural invasion in adenoid cystic carcinoma: a systematic review. Braz J Otorhinolaryngol, 2015, 81(3):329-335.

23. Balamucci CJ, Amdur RJ, Werning JW, Vaysberg AM, Beckerman MW, Morris CG, Kirwan JM, Mendenhall WM. Adenoid cystic carcinoma of the head and neck. Am J Otolaryngol, 2012, 33(5):510-518.

24. Bjørndal K, Krogdahl A, Therkildsen MH, Charabi B, Kristensen CA, Andersen E, Schytte S, Primdahl H, Johansen J, Pedersen HB, Andersen LJ, Godballe C. Salivary adenoid cystic carcinoma in Denmark 1990-2005: Outcome and independent prognostic factors including the benefit of radiotherapy. Results of the Danish Head and Neck Cancer Group (DAHANCA). Oral Oncol, 2015, 51(12):1138-1142.

25. Ko YH, Lee MA, Hong YS, Lee KS, Jung CK, Kim YS, Sun DI, Kim BS, Kim MS, Kang JH. Prognostic factors affecting the clinical outcome of adenoid cystic carcinoma of the head and neck. Jpn J Clin Oncol, 2007, 37(11):805-811.

26. Treitl D, Rachkani F, Bizer M, El Hussein S, Paramo JC, Mesko TW. Adenoid cystic carcinoma of the breast, 20 years of experience in a single center with review of literature. Breast Cancer, 2018, 25(1):28-33.

27. Johnson LR, Nair RP, Sambasivan S, Mony RP, Gangadharan J, Kumar A, Ahamed IM. Adenoid Cystic Carcinoma of Vulva-11 Years’ Single-Institution Experience. J Obstet Gynaecol India, 2017, 67(3):196-201.

28. Shou CH, Li ZJ, Yang WL, Tjiho WEH, Zhao ZC, Yu JR. Adenoid cystic carcinoma of the gastroesophageal junction: A case report. Medicine (Baltimore), 2019, 98(35):e16999.

29. Benhayoune K, El Fatemi H, Bannani A, Melhout A, Harmouch T. Adenoid cystic carcinoma of cervix: two cases report and review of the literature. Pan Afr Med J, 2015, 20:77.

30. Zhao Y, Zhao H, Fan L, Shi J. Adenoid cystic carcinoma in the bronchus behaves more aggressively than its tracheal counterpart. Ann Thorac Surg, 2013, 96(6):1998-2004.

31. Alkan BI, Bozdogan O, Karadeniz M, Bozdogan N. Two Different Cell Populations Is an Important Clue for Diagnosis of Primary Cutaneous Adenoid Cystic Carcinoma: Immunohistochemical Study. Case Rep Pathol, 2017, 2017:7949361.

32. Chen JC, Gnepp DR, Bedrossian CW. Adenoid cystic carcinoma of the salivary glands: an immunohistochemical analysis. Oral Surg Oral Med Oral Pathol, 1988, 65(3):316-326.

33. Amrit M, Binenbaum Y, Sharma K, Rramer N, Ramer I, Agbetoba A, Miles B, Yang X, Lei D, Bjørndal K, Godballe C, Mücke T, Wolff KD, Fiss D, Eckardt AM, Copelli C, Sesenna E, Palmer F, Patel S, Gil Z. Analysis of failure in patients with adenoid cystic carcinoma of the head and neck. An international collaborative study. Head Neck, 2014, 36(7):998-1004.

34. Szanto PA, Luna MA, Tortoledo ME, White RA. Histologic grading of adenoid cystic carcinoma of the salivary glands. Cancer, 1984, 54(6):1062-1069.

35. van Weert S, van der Waal I, Witte BL, Leemans CR, Bloemena E. Histopathological grading of adenoid cystic carcinoma of the head and neck: analysis of currently used grading systems and proposal for a simplified grading scheme. Oral Oncol, 2015, 51(1):71-76.

36. Huang M, Ma D, Sun K, Yu G, Guo C, Gao F. Factors influencing survival rate in adenoid cystic carcinoma of the salivary glands. Int J Oral Maxillofac Surg, 1997, 26(6):435-439.

37. Sequeiros Santiago G, Rodrigo Tapia JP, Llorente P, Pérez Esteban P, Pérez-Eléritche A, Paredes de León EM, Pérez Patiño A, Pérez-Clavijo FJ. Prognostic factors in adenoid cystic carcinoma of the salivary glands [in Spanish]. Acta Otorrinolaringol Esp, 2005, 56(6):361-367.

38. Amit M, Binenbaum Y, Trejo-Leider L, Sharma K, Ramer N, Ramer I, Agbetoba A, Miles B, Yang X, Lei D, Bjørndal K, Godballe C, Mücke T, Wolff KD, Eckardt AM, Copelli C, Sesenna E, Palmer F, Ganly I, Patel S, Gil Z. International collaborative validation of intraneural invasion as a prognostic marker in adenoid cystic carcinoma of the head and neck. Head Neck, 2015, 37(7):1038-1045.

39. Teymoortash A, Zieger L, Sprenger P, Hohenberger W. Distinct microscopic features of perineural invasion in adenoid cystic carcinoma of the head and neck. Histopathology, 2014, 64(7):1037-1039.
40. da Cruz Perez DE, de Abreu Alves F, Nobuko Nishimoto I, de Almeida OP, Kowalski LP. Prognostic factors in head and neck adenoid cystic carcinoma. Oral Oncol, 2006, 42(2):139-146.

41. Guntinas-Lichius O, Kreppel MP, Stuezter H, Semrau R, Eckel HE, Mueller RP. Single modality and multimodality treatment of nasal and paranasal sinuses cancer: a single institution experience of 229 patients. Eur J Surg Oncol, 2007, 33(2):222-228.

42. Megwalu UC, Sirjani D. Risk of Nodal Metastasis in Major Salivary Gland Adenoid Cystic Carcinoma. Otolaryngol Head Neck Surg, 2017, 156(4):660-664.

43. Pitman KT. Rationale for elective neck dissection. Am J Otolaryngol, 2000, 21(1):31-7.

44. Qian ZJ, Chen MM, Divi V, Megwalu UC. Impact of lymph node sampling on survival in cN0 major salivary gland adenoid cystic carcinoma. Head Neck, 2019, 41(6):1903-1907.

45. Lupinetti AD, Roberts DB, Williams MD, Kupferman ME, Rosenthal DI, Demonte F, El-Naggar A, Weber RS, Hanna EY. Sinonasal adenoid cystic carcinoma: the M.D. Anderson Cancer Center experience. Cancer, 2007, 110(12):2726-2731.

46. Amit M, Na’ara S, Trejo-Leider L, Ramer N, Burstein D, Yue M, Miles B, Yang X, Lei D, Bijjendral K, Godballe C, Mücke T, Wolff KD, Eckardt AM, Copelli C, Sesenna E, Patel S, Ganly I, Gil Z. Defining the surgical margins of adenoid cystic carcinoma and their impact on outcome: An international collaborative study. Head Neck, 2017, 39(5):1008-1014.

47. Pinakapani R, Chaitanya NC, Lavanya R, Yarram S, Boringi M, Shefali W. Adenoid cystic carcinoma of the head and neck: epidemiology and predictors of prognosis. Qual Prim Care, 2015, 23:309-314.

48. Monteiro D, Lino J, Bernardo T, Fernandes J, Monteiro E. Adenoid cystic carcinoma of head and neck: epidemiology and predictors of prognosis. Int. J Otolaryngol Head Surg, 2013, 2:165-173.

49. Dodd RL, Slevin NJ. Salivary gland adenoid cystic carcinoma: a review of chemotherapies and molecular therapies. Oral Oncol, 2006, 42(8):759-769.

50. He S, Li P, Zhong Q, Hou L, Yu Z, Huang Z, Chen X, Fang J, Chen X. Clinicopathologic and prognostic factors in adenoid cystic carcinoma of head and neck minor salivary glands: A clinical analysis of 130 cases. Am J Otolaryngol, 2017, 38(2):157-162.

51. Bhayani MK, Yener M, El-Naggar A, Garden A, Hanna EY, Weber RS, Kupferman ME. Prognosis and risk factors for early-stage adenoid cystic carcinoma of the major salivary glands. Cancer, 2012, 118(11):2872-8.

52. van der Wal JE, Becking AG, Snow GB, van der Vaal I. Distant metastases of adenoid cystic carcinoma of the salivary glands and the value of diagnostic examinations during follow-up. Head Neck, 2002, 24(8):779-783.

53. Marcinow A, Ozer E, Teknos T, Wei L, Hurtuk A, Old M, Agrawal A, Carrau R, Iwenofu OH. Clinico-pathologic predictors of recurrence and overall survival in adenoid cystic carcinoma of the head and neck: a single institutional experience at a tertiary care center. Head Neck, 2014, 36(12):1705-1711.