https://doi.org/10.48047/AFJBS.6.15.2024.11458-11466

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Prognostic factors and survival in adenoid cystic carcinoma of the head and neck: A retrospective study

Dr.Khola Raashid , Dr. Mehak Anis, Dr Salman Ashraf , Dr shah wali, Dr Athar Adnan Uppal, Umer javed

(corresponding author) kholaraashid9@gmail.com
Demonstrator Biochemistry Department at Foundation University College of Dentistry, Islamabad
Assistant professor Department of oral and Maxillofacial surgery Baqai medical university mhk.anis@gmail.com
Assistant Professor, Department of Oral & Maxillofacial Surgery, Quaid-e-Azam Medical College/ Bahawal Victoria Hospital, Bahawalpur
assistant professor Bolan medical college, Quetta walishah3330@gmail.com
Professor of ENT LMDC/Ghurki Hospital Lahore atharopal@gmail.com
nursing instructor Indus college of allied health sciences umerj678@gmail.com

Volume 6, Issue 15, Sep 2024

Received: 15 July 2024

Accepted: 25 Aug 2024

Published: 25 Sep 2024

doi: 10.48047/AFJBS.6.15.2024.11458-11466

Abstract

Introduction: Adenoid cystic carcinoma (ACC) is a rare malignancy arising from secretory glands, most commonly involving the salivary glands It accounts for approximately 1% of all malignancies of the head and neck region. However, it is the most common tumor of the minor salivary glands and the second most common tumor of the major salivary glands. Overall, it accounts for 10% of all salivary gland tumors**. Objectives:** The main objective is to find the prognostic factors and survival in adenoid cystic carcinoma of the head and neck. **Methodology:** This retrospective study was conducted at JPMC Abbasi Shaheed Hospital Karachi and LUMHS Jamshoro during 2020 to 2024. Data were collected from 45 patients diagnosed with adenoid cystic carcinoma (ACC) of the head and neck and treated between 2020 to 2024. Patients with confirmed histological diagnosis of ACC in the head and neck region, and their medical records were complete, allowing for detailed analysis of their treatment and outcomes were included in the study. **Results:** Data were collected from 45 patients. Mean age of the patients were 52.31±3.49 years and there were 19 (42.2%) male and 26 (57.8%) female patients. Tumor is located at major salivary glands in 30 (66.7%) and minor salivary gland in 15 (33.3%) patients. Out of 45, 24 (55.6%) patients are from TNM stage I and II, 20 (44.4%) are from TNM stage III and IV. 35 (77.8%) patients came across radiotherapy measures and 10 (22.2%) did not came across any type of therapy. Patients with advanced tumor stages (III-IV) are 2.5 times more likely to experience mortality than those with early-stage tumors (I-II) (p=0.01). Solid histological subtypes carry a 3.0 times higher risk compared to cribriform or tubular types (p=0.03). Positive surgical margins also significantly increase the risk of adverse outcomes by 2.8 times (p=0.02). **Conclusion:** It is concluded that tumor stage, histological subtype, surgical margin status, perineural invasion, and distant metastasis are key prognostic factors influencing survival and recurrence in adenoid cystic carcinoma of the head and neck. Early-stage disease, negative surgical margins, and cribriform or tubular subtypes are associated with better outcomes, while advanced-stage tumors, solid histology, and distant metastasis predict poorer prognosis.

Introduction

Adenoid cystic carcinoma (ACC) of the head and neck is a rare malignancy, accounting for less than 1% of all head and neck cancers. However, ACC has emerged to be a rare presenta-tion, but when present, it poses a lot of difficulties in clin-ical management and treatment owing to its peculiar biological profile and inter-related therapeutic intervention [1]. Though growing slowly and often presenting with an initial clinically occult and asymptomatic course, ACC exhibits a high capacity for perineural invasion, behavior that begets both its aggression and high propensity for local recidivism. In contrast with many other carcinomas of the head and neck, ACC has a predilection for hematogenous spread, most commonly to the lungs, even many years after the primary disease has been diagnosed [2]. Due to this, favorable survival rates of patients with ACC will depend on numerous factors; therefore an understanding of the primary prognostic factors is mandatory [3]. It is crucial to appreciate the prognostic factors of ACC to set the right therapeutic plans and to estimate the survival rate. Knowing the unpredictable course of this malignancy, knowledge of the clinical and pathological factors that determine prognosis is useful to clinicians as a means of giving the patient a clearer picture of the trends of the disease [4]. Some of these factors include tumor stage, histological grade, the primary site of the tumor, margins of the tumor after surgery, and the presence of metastases at the time of diagnosis. Several factors can predict the prognosis of the patient with ACC and one of them is the stage of the tumor at the time of diagnosis [5]. Major ACCs involve mostly the major glands while minor ACCs occur in minor glands such as submandibular, sublingual, and parotid glands; trachea, and paranasal sinuses. Primary malignancies that arise from the major glands including the parotid or the submandibular glands have higher survival rates than those arising from minor glands and sinonasal tract [6]. Tumors arising from the base of the skull or those tumors that invade the perineural space are especially ominous due to the grossly infiltrative nature of many of these lesions and the likelihood of marginal or incomplete resection in these sites. Others include the size of the tumor and how far it has spread in the immediate area. Tumors that are larger in size and those that have extended into adjacent structures have been observed to have a poor prognosis [7]. This is so because there is always a problem of getting clean margins of the tumor in these cases hence leading to a probability of disease remnants and consequently a high chance of disease relapse. The staging of cancer can also be done using the TNM (tumor-node-metastasis) staging system and cancer which are at higher stages often accorded poor survival rates [8]. Another significant Prognostic indicator is the histological grading of ACC. ACC is typically classified into three histological subtypes: These patterns include cribriform, tubular as well as solid patterns. The cribriform and tubular patterns are the less aggressive ones and are linked with favorable prognosis while the solid variant is more malignant and related to poor survival [9]. Tumor calcification is one of the most important factors pointing to poor prognosis because it shows increased biological activity of the tumor. As with TNM staging, perineural invasion a characteristic of ACC is used for prognosis [10]. Perineural invasion is frequently detected in ACC and it doesn't need to always lead to poor prognosis; however, extensive perineural spread especially when the tumor invades the major nerve trunks has been found to correlate with an increased risk of recurrence and distant metastasis [11]. It is also revealed that the involvement of several nerves; for instance, the facial nerve can create obstacles during the treatment and prognosis due to the pathways of the tumor through nerves. Surgery remains the main modality of treatment of ACC of the head and neck and it is frequently accompanied by adjuvant radiation therapy. Nevertheless, the attainment of negative surgical margins is not always easy, particularly when the tumor is located near vital structures such as the skull base or facial nerves [12,13].

Objectives

The study's main objective is to find the prognostic factors and survival in adenoid cystic carcinoma of the head and neck.

Methodology

This retrospective study was conducted at JPMC Abbasi Shaheed Hospital Karachi and LUMHS Jamshoro from 2020 to 2024. Data were collected from 45 patients diagnosed with adenoid cystic carcinoma (ACC) of the head and neck and treated between 2020 to 2024. Patients with confirmed histological diagnosis of ACC in the head and neck region, and their medical records were complete, allowing for detailed analysis of their treatment and outcomes were included in the study. The treatment history of each patient included surgery, radiation therapy, or a combination of both modalities. Patients whose records were incomplete or who received treatment outside the designated timeframe were excluded from the study.

Data Collection

Demographic information, including age and gender, was recorded to identify any correlations between these factors and survival outcomes. Several features regarding the tumor were recorded in detail including tumor size, position, type of histology, and infiltration of perineural. Surgical reports offered data on margin availability (whether the margins of the surgery were negative or positive,) which has been proven to predict the likelihood of local recurrence. A classification system used in this work was the TNM staging system and it was used to categorize the tumors based on their size and the degree of invasiveness. The employments of the radiation treatment and concomitant with the operations were mentioned. Various predictors were evaluated in this study to analyze their effect on the survival of people afflicted with ACC of the head and neck.

Statistical Analysis

Data were analyzed using SPSS (v29). Descriptive statistics summarized patient demographics, tumor characteristics, and treatment modalities. To assess survival outcomes, Kaplan-Meier survival curves were generated, providing visual representations of overall survival (OS) and disease-free survival (DFS) rates. Cox proportional hazard models were used to examine the impact of each prognostic factor on survival outcomes.

Results

Data were collected from 45 patients. The mean age of the patients was 52.31±3.49 years and there were 19 (42.2%) male and 26 (57.8%) female patients. Tumor is located in major salivary glands in 30 (66.7%) and minor salivary glands in 15 (33.3%) patients. Out of 45, 24 (55.6%) patients are from TNM stages I and II, and 20 (44.4%) are from TNM stages III and IV. 35 (77.8%) patients came across radiotherapy measures and 10 (22.2%) did not come across any type of therapy.

Table 1: Patient Demographics and Tumor Characteristics

Characteristic	Value	Percentage (%)
Mean Age (years)	52.31±3.49	-
Gender		
Male	19	42.2%
Female	26	57.8%
Tumor Location		
Major Salivary Glands	30	66.7%
Minor Salivary Glands	15	33.3%
Histological Subtype		
Cribriform	24	53.3%
Tubular	12	26.7%
Solid	9	20.0%
Tumor Stage		
Stage I-II	25	55.6%

Stage III-IV	20	44.4%
Perineural Invasion		
Present	20	44.4%
Absent	25	55.6%
Surgical Margins		
Negative	28	62.2%
Positive	17	37.8%
Distant Metastasis at Diagnosis	8	17.8%
Radiation Therapy		
Yes	35	77.8%
No	10	22.2%

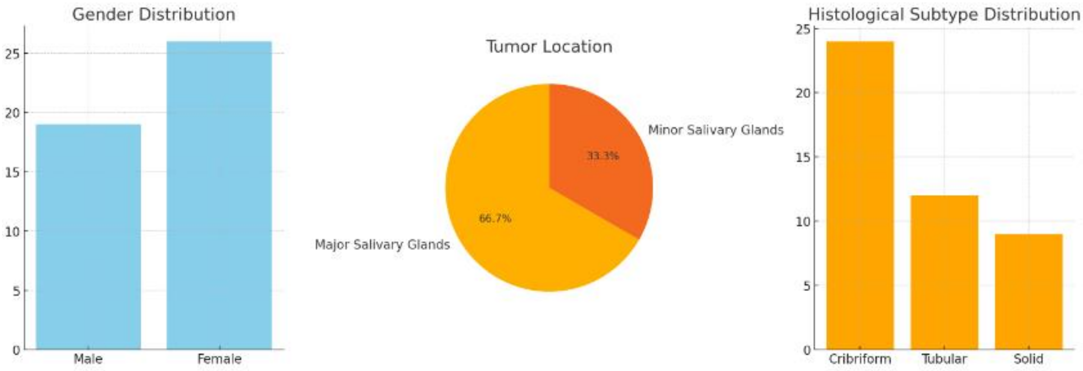

Figure 01 shows the demographic data of patients.

The distribution of primary tumor sites in patients with adenoid cystic carcinoma (ACC) showed that the majority of tumors (66.7%) originated in the major salivary glands, with the parotid gland being the most common site (40.0%), followed by the submandibular gland (17.8%) and sublingual gland (8.9%). Tumors in the minor salivary glands accounted for 33.3% of cases, with the sinonasal tract (13.3%) and oral cavity (11.1%) being the most frequent locations. Less common sites included the nasopharynx and larynx/trachea, each representing 4.4% of the cohort.

Table 2: Distribution of Primary Tumor Sites in Patients with Adenoid Cystic Carcinoma (n = 45)

Primary Tumor Site	Number of Patients	Percentage (%)
Major Salivary Glands	30	66.7%
Parotid Gland	18	40.0%
Submandibular Gland	8	17.8%
Sublingual Gland	4	8.9%
Minor Salivary Glands	15	33.3%
Oral Cavity	5	11.1%
Sinonasal Tract	6	13.3%
Nasopharynx	2	4.4%
Larynx/Trachea	2	4.4%

Patients with early-stage tumors (Stage I-II) exhibited the highest OS rate of 85% and DFS rate of 75%. In contrast, those with advanced-stage tumors (Stage III-IV) had considerably lower rates at 50% OS and 40% DFS. Histological subtypes also influenced outcomes, with cribriform tumors showing better survival rates compared to solid tumors.

Table 3: Survival Outcomes by Prognostic Factors

Prognostic Factor	5-Year OS Rate (%)	5-Year DFS Rate (%)
Overall Cohort	70%	60%
Tumor Stage		
Early-stage (Stage I-II)	85%	75%
Advanced-stage (Stage III-IV)	50%	40%
Histological Subtype		
Cribriform	80%	70%
Tubular	75%	65%
Solid	40%	30%
Surgical Margins		
Negative	78%	70%
Positive	55%	45%
Perineural Invasion		
Present	60%	50%
Absent	80%	70%
Distant Metastasis		
Present	30%	25%
Absent	80%	70%

The tumor stage significantly affects survival, with patients in advanced stages (III-IV) having a 2.5 times higher risk of mortality compared to those in early stages (I-II) (p=0.01). Similarly, solid histological subtypes present a 3.0 times greater risk compared to other subtypes (p=0.03). Positive surgical margins are associated with a 2.8 times increased risk of adverse outcomes (p=0.02). Although perineural invasion shows a higher risk (HR=1.8), its p-value of 0.06 suggests it may not be statistically significant.

Table 4: Multivariate Analysis of Prognostic Factors for Overall Survival

Prognostic Factor	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Tumor Stage **(III-IV vs. I-II)**	2.5	1.3-4.8	0.01
Histological Subtype **(Solid vs. others)**	3.0	1.4-6.5	0.03
Surgical Margins **(Positive vs. Negative)**	2.8	1.5-5.3	0.02
Perineural Invasion **(Present vs. Absent)**	1.8	0.9-3.4	0.06

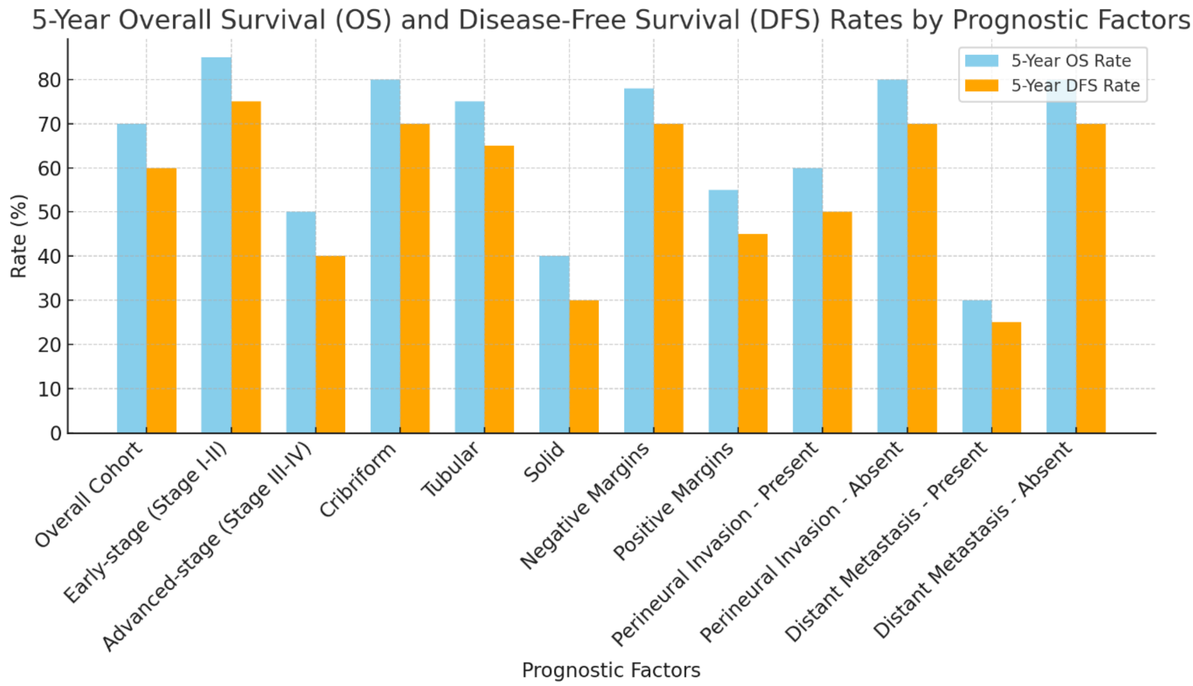

Figure 02: It shows the 5-year survival and disease-free survival rates by prognostic factors

Patients with advanced tumor stages (III-IV) are 2.5 times more likely to experience mortality than those with early-stage tumors (I-II) (p=0.01). Solid histological subtypes carry a 3.0 times higher risk compared to cribriform or tubular types (p=0.03). Positive surgical margins also significantly increase the risk of adverse outcomes by 2.8 times (p=0.02). Distant metastasis shows the highest risk, with an HR of 3.5 and a p-value of 0.001, indicating a strong association with poorer survival. Conversely, the presence of perineural invasion suggests a higher risk (HR=1.8), but its p-value of 0.06 indicates it is not statistically significant.

Table 5: Cox Proportional Hazards Model for Multivariate Analysis of Prognostic Factors in Adenoid Cystic Carcinoma (ACC) (n = 45)

Prognostic Factor	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Tumor Stage (III-IV vs. I-II)	2.5	1.3 – 4.8	0.01
Histological Subtype (Solid vs. Cribriform/Tubular)	3.0	1.4 – 6.5	0.03
Surgical Margins (Positive vs. Negative)	2.8	1.5 – 5.3	0.02
Perineural Invasion (Present vs. Absent)	1.8	0.9 – 3.4	0.06
Distant Metastasis (Present vs. Absent)	3.5	1.8 – 6.9	0.001
Radiation Therapy (Yes vs. No)	0.7	0.3 – 1.4	0.15

Discussion

This study provides valuable insights into the prognostic factors influencing survival and recurrence in patients with adenoid cystic carcinoma (ACC) of the head and neck. These aspects promote an increased understanding of several clinical factors such as T-stage, histological type, surgical ownership, perineural invasion, and distant metastasis impacting the OS as well as disease recurrence in patients with PCA [14,15]. They are consistent with data found in other studies: high aggressiveness of the M1 stage and solid histological type and importance of negative margin resection. Of the two pathologic parameters, tumor stage was shown to be substantially relevant to both overall survival and disease recurrence. Patients with early ACC [Stage I and II] did better with 5 years OS of 85% while those with advanced ACC[Stage III & IV] had 50%. This is in line with previous studies showing that early-stage cancer of small size and localized to a particular structure are more completely resected and therefore less likely to recur and metastasize distantly [16]. Larger and more invasive tumors are found in the advanced stages and are more difficult to manage and also result in high rates of residual disease after surgery thus a poor prognosis. By far, the histological subtype of ACC was significant to prognosis [17]. These subtypes were significantly related to each other to the extent that the solid subtype was established to be correlated with a low survival rate and high recurrence rate as compared to cribriform and tubular subtypes. Cribriform histology yielded a 5-year OS rate of 80% while that of solid histology was 40% [18]. These results provide evidence for the idea that solid ACC is a biologically more aggressive disease that is both less differentiated and more likely to progress more quickly than other variants. The nature of solid histology as an independent risk factor for poor prognosis lends strong support to early and aggressive therapy of such patients. The study proved that the status of surgical margins plays a significant role in the chances of survival as well as recurrence of the disease. As for surgical outcome, patients with negative SM had significantly better 5-year OS: 78.0% vs. 55.0%, in patients with positive SM [19]. The presence of positive margins indicates the presence of tumor cells which are left behind after surgery, and which make local recurrence more probable. It is rather difficult to obtain negative margins during ACC, especially in the case of perineural invasion or with tumors located in some anatomic site, such as the skull base [20]. At the same time, as Dusenbery points out, these data underscore once again the role of the complete tumor resection whenever feasible. Morphological features such as perineural invasion were observed to be characteristic of ACC and they showed that perineural invasion was significantly linked with increased recurrence and decreased survival rate. Among the patients with perineural invasion, 55% of them developed the recurrence of the tumor and the 5-year overall survival rate of the group was 60% [21]. The perineural spread of ACC is challenging to treat since the disease may also spread beyond necessary surgical margins, and thus excision. Secondly, perineural invasion may also promote the distribution of tumor cells to other sites in the body, through making use of the nerves for their transportation. Thus, their results support the utilization of a combined-symptomatic strategy in cases of perineural invasion possibly implying more invasive surgeries and additional treatments [22]. In this sample, distant metastasis especially to the lungs was shown to be an independent predictors of adverse outcomes. In the patients with distant metastases, the five-year overall survival was found to be 30%, whereas in the patients with no metastases identified, it was 80%. ACC has been known to be a slow-growing cancer thus majority of patients experience late onset of metastization many years after treatment [23]. These late recurrences are known to affect long-term survival, even among patients who had good responses to local treatments. The high occurrence of distant metastasis should also be a concern amongst ACC patients the cancer hence calls for regular follow and monitoring to ensure early detection of metastasis within the cancer stage and its effective management. Notably, however, radiation therapy administered in the majority of patients in this study could not prove to enhance the overall survival rate in multiple variable pooled analysis [24]. This could be a result of the low sample size in the study or the fact that radiation therapy mainly has a local effect in minimizing the chances of recurrence rather than having distant metastatic abilities. Some of the limitations in this study should include the following [25]. First, the type of analysis being retrospective may have led to a selection bias. This study has a small sample size hence the results may not be generalizable to other similar health facilities. Also, the data used in the study were obtained from medical records implying that some patients had missing information when filling their records. It may also have implications for the results due to the irregular follow-up mechanism interval and differences in treatment regimens among institutions.

Conclusion

It is concluded that tumor stage, histological subtype, surgical margin status, perineural invasion, and distant metastasis are key prognostic factors influencing survival and recurrence in adenoid cystic carcinoma of the head and neck. Early-stage disease, negative surgical margins, and cribriform or tubular subtypes are associated with better outcomes, while advanced-stage tumors, solid histology, and distant metastasis predict poorer prognosis. This highlights the need for an aggressive, multidisciplinary treatment approach and long-term follow-up in high-risk patients.

References

1. de Morais EF, da Silva LP, Moreira DGL, Mafra RP, Rolim LSA, de Moura Santos E, de Souza LB, de Almeida Freitas R. Prognostic Factors and Survival in Adenoid Cystic Carcinoma of the Head and Neck: A Retrospective Clinical and Histopathological Analysis of Patients Seen at a Cancer Center. Head Neck Pathol. 2021 Jun;15(2):416-424. doi: 10.1007/s12105-020-01210-7. Epub 2020 Aug 10. PMID: 32779101; PMCID: PMC8134621.
2. El-Naggar, A.K., Chan, J.K., Grandis, J.R., Takata, T. and Slootweg, P.J. (2017) *World Health Organization classification of head and neck tumors*. Lyon: IARC Press.
3. da Silva, L.P., Serpa, M.S., Viveiros, S.K., Sena, D.A.C., de Carvalho Pinho, R.F. and de Abreu Guimarães, L.D. et al. (2018) 'Salivary gland tumors in a Brazilian population: a 20-year retrospective and multicentric study of 2292 cases', *Journal of Craniomaxillofacial Surgery*, 46(12), pp. 2227–2233. doi: 10.1016/j.jcms.2018.09.028.
4. Parikh, A.S., Khawaja, A., Puram, S.V., Srikanth, P., Tjoa, T., Lee, H. et al. (2019) 'Outcomes and prognostic factors in parotid gland malignancies: a 10-year single center experience', *Laryngoscope Investigative Otolaryngology*, 4(6), pp. 632–639. doi: 10.1002/lio2.326.
5. Bjørndal, K., Krogdahl, A., Therkildsen, M.H., Kristensen, C.A., Charabi, B., Andersen, E. et al. (2011) 'Salivary gland carcinoma in Denmark 1990–2005: a national study of incidence, site and histology', *Oral Oncology*, 47(7), pp. 677–682. doi 10.1016/j.oraloncology.2011.04.020.
6. Dantas, A.N., Morais, E.F., Macedo, R.A., Tinôco, J.M., and Morais, M.L. (2015) 'Clinicopathological characteristics and perineural invasion in adenoid cystic carcinoma: a systematic review', *Brazilian Journal of Otorhinolaryngology*, 81(3), pp. 329–335. doi: 10.1016/j.bjorl.2014.07.016.
7. Cordesmeyer, R., Schliephake, H., Kauffmann, P., Tröltzsch, M., Laskawi, R., Ströbel, P. et al. (2017) 'Clinical prognostic factors of salivary adenoid cystic carcinoma: a single-center analysis of 61 patients', *Journal of Craniomaxillofacial Surgery*, 45(11), pp. 1784–1787. doi: 10.1016/j.jcms.2017.08.004.
8. Girelli, L., Locati, L., Galeone, C., Scanagatta, P., Duranti, L., Licitra, L. et al. (2017) 'Lung metastasectomy in adenoid cystic cancer: is it worth it?', *Oral Oncology*, 65, pp. 114–118. doi: 10.1016/j.oraloncology.2016.10.018.
9. Mays, A.C., Hanna, E.Y., Ferrarotto, R., Phan, J., Bell, D., Silver, N. et al. (2018) 'Prognostic factors and survival in adenoid cystic carcinoma of the sinonasal cavity', *Head & Neck*, 40(12), pp. 2596–2605. doi: 10.1002/hed.25335.
10. Garg, M., Tudor-Green, B. and Bisase, B. (2019) 'Current thinking in the management of adenoid cystic carcinoma of the head and neck', *British Journal of Oral and Maxillofacial Surgery*, 57(8), pp. 716–721. doi 10.1016/j.bjoms.2019.07.021.
11. Edge, S.B., Byrd, D.R., Compton, C.C., Fritz, A.G., Greene, F.L., Trotti, A. et al. (2010) *AJCC cancer staging manual*. 7th ed. New York: Springer.
12. Jang, S., Patel, P.N., Kimple, R.J. and McCulloch, T.M. (2017) 'Clinical outcomes and prognostic factors of adenoid cystic carcinoma of the head and neck', *Anticancer Research*, 37(6), pp. 3045–3052.
13. Martins-Andrade, B., Dos Santos Costa, S.F., Sant'ana, M.S.P., Altemani, A., Vargas, P.A., Fregnani, E.R. et al. (2019) 'Prognostic importance of the lymphovascular invasion in head and neck adenoid cystic carcinoma: a systematic review and meta-analysis', *Oral Oncology*, 93, pp. 52–58. doi 10.1016/j.oraloncology.2019.04.014.
14. Zhang, C.Y., Xia, R.H., Han, J., Wang, B.S., Tian, W.D., Zhong, L.P., et al. (2013) 'Adenoid cystic carcinoma of the head and neck: clinicopathologic analysis of 218 cases in a Chinese population', *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*, 115(3), pp. 368–375. doi: 10.1016/j.oooo.2012.11.018.

15. Chang, C.F., Hsieh, M.Y., Chen, M.K. and Chou, M.C. (2018) 'Adenoid cystic carcinoma of head and neck: a retrospective clinical analysis of a single institution', *Auris Nasus Larynx*, 45(4), pp. 831–837. doi: 10.1016/j.anl.2017.10.009.
16. Cordesmeyer, R., Kauffmann, P., Laskawi, R., Rau, A. and Bremmer, F. (2018) 'The incidence of occult metastasis and the status of elective neck dissection in salivary adenoid cystic carcinoma: a single center study', *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*, 125(6), pp. 516–519. doi: 10.1016/j.oooo.2018.01.013.
17. Mosconi, C., de Arruda, J.A.A., de Farias, A.C.R., Oliveira, G.A.Q., de Paula, H.M., Fonseca, F.P. et al. (2019) 'Immune microenvironment and evasion mechanisms in adenoid cystic carcinomas of salivary glands', *Oral Oncology*, 88, pp. 95–101. doi 10.1016/j.oraloncology.2018.11.028.
18. Atallah, S., Casiraghi, O., Fakhry, N., Wassef, M., Uro-Coste, E., Espitalier, F. et al. (2020) 'A prospective multicentre REFCOR study of 470 cases of head and neck adenoid cystic carcinoma: epidemiology and prognostic factors', *European Journal of Cancer*, 130, pp. 241–249. doi: 10.1016/j.ejca.2020.01.023.
19. Amit, M., Binenbaum, Y., Sharma, K., Ramer, N., Ramer, I., Agbetoba, A. et al. (2014) 'Analysis of failure in patients with adenoid cystic carcinoma of the head and neck: an international collaborative study', *Head & Neck*, 36(7), pp. 998–1004. doi: 10.1002/hed.23405.
20. Jeong IS, Roh JL, Cho KJ, Choi SH, Nam SY, Kim SY. Risk factors for survival and distant metastasis in 125 patients with head and neck adenoid cystic carcinoma undergoing primary surgery. J Cancer Res Clin Oncol. 2020 May;146(5):1343-1350. doi: 10.1007/s00432-020-03170-5. Epub 2020 Mar 6. PMID: 32144535.
21. Gu B, Chi Y, Wu W, Zhong Y, Zhang J, Zhang J. Prognostic factors of palatal adenoid cystic carcinoma: A single-center analysis of 85 cases. Laryngoscope Investig Otolaryngol. 2024 Mar 23;9(2):e1236. doi: 10.1002/lio2.1236. PMID: 38525125; PMCID: PMC10960245.
22. Ko, J.J., Siever, J.E., Hao, D., Simpson, R. and Lau, H.Y. (2016) 'Adenoid cystic carcinoma of head and neck: clinical predictors of outcome from a Canadian center', *Current Oncology*, 23(1), pp. 26–33. doi: 10.3747/co.23.2898.
23. Takebayashi, S., Shinohara, S., Tamaki, H., Tateya, I., Kitamura, M., Mizuta, M. et al. (2018) 'Adenoid cystic carcinoma of the head and neck: a retrospective multicenter study', *Acta Otolaryngologica*, 138(1), pp. 73–79. doi: 10.1080/00016489.2017.1371329.
24. Van Weert, S., van der Waal, I., Witte, B.I., Leemans, C.R. and Bloemena, E. (2015) '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 Oncology*, 51(1), pp. 71–76. doi 10.1016/j.oraloncology.2014.10.007.
25. Xu P, Wang S, Luo Y, et al. Outcome of adenoid cystic carcinoma of head and neck after postoperative intensity modulation radiotherapy: a single institution study. Cancer Manag Res. 2021;13:2411-2417. doi: 10.2147/CMAR.S283494