wjpmr, 2023,9(8), 04-09

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

ADENOID CYSTIC CARCINOMA OF SUBMANDIBULAR GLAND: A CASE REPORT AND REVIEW OF THE LITERATURE

Fatima-Zahra Kahouadji*[1], Ouail Benzerouale[1], Hafsa Elouazzani[2], Nadia Cherradi[2], Saber Boutayeb[1], Ibrahim El Ghissassi[1], H. M'rabti[1] and H. Errihani[1].

[1]Medical Oncology Department at the National Institute of Oncology in Rabat Morocco.
[2]Pathological Anatomy Laboratory, Hospital of Specialties, Mohamed V University, Rabat.

***Corresponding Author: Fatima-Zahra Kahouadji**

Medical Oncology Department at the National Institute of Oncology in Rabat Morocco.

Article Received on 31/05/2023 **Article Revised on 20/06/2023** **Article Accepted on 11/07/2023**

ABSTRACT

Adenoid cystic carcinoma (ACC) of submandibular gland is a cancer rarely encountered in clinical practice. Here we presented ACC of submandibular gland in a 57 years old male discovered at a metastatic stage. Distant metastasis from submandibular ACC most commonly involves the lungs, and regional metastasis from submandibular ACC is more common compared to other major salivary glands due to the proximity of the draining lymph nodes. in the absence of metastasis, surgery and adjuvant radiotherapy are the mainstay of curative treatment. Systemic treatments are used for locally recurrent or metastatic disease. The best objective response rates were obtained with cisplatin-vinorelbine dual therapy. Monotherapy with targeted therapies could lead to prolonged stabilization. Two phases II immunotherapy trials were conducted with pembrolizumab, in patients with recurrent or metastatic ACC, one of which showed no objective response and the other is still ongoing. The aim of this case report is to present the particularities of this tumor and to provide a brief overview on systemic treatments for locally recurrent or metastatic diseases.

KEYWORDS: Adenoid cystic carcinoma, malignant salivary gland tumor, submandibular gland, chemotherapy, targeted therapies, immunotherapy.

INTRODUCTION

Adenoid cystic carcinoma is a relatively rare tumor of the minor and major salivary gland.[1] Salivary gland malignancies make up 0.5 to 1.2% of all cancers and 5% of head and neck cancers.[2,3,4] The majority of malignant cases occur in the parotid, followed by the submandibular, sublingual, and minor salivary glands.[5] The submandibular gland harbors 10-15% of all salivary gland tumors with an equal distribution of benign and malignant neoplasms. Adenoid cystic carcinoma is the most common malignant neoplasm in the submandibular gland.[6]

We describe a case of a patient who consulted us for a submandibular swelling associated with dysphonia, and whose clinic-radiological and anatomopathological investigations led to the diagnosis of adenoid cystic carcinoma of submandibular gland. The aim of this case report is to present the particularities of this tumor and to supply a brief information on systemic treatments for locally recurrent or metastatic diseases which is rarely encountered in clinical practice.

CASE REPORT

Mr. K.L. is a 57-year-old patient, a chronic smoker with 5 pack-years weaned 9 years ago, who consulted us for a right submandibular swelling associated with dysphonia. Clinical examination revealed a performance status of 1, a right submandibular mass and facial paralysis. The rest of the examination was unremarkable. A cervical ultrasound showed a right submandibular process with a tumoral appearance, to be compared with the histological data. A cervical-thoracic CT scan revealed a suspicious locally advanced lesion process in the right mandibular region, with diffuse pulmonary lesions and a secondary osteocondensing lesion in C2. A salivary gland biopsy showed the morphological appearance of a cystic adenoid carcinoma. Abdominal ultrasound revealed totally calcified bi-lobar hepatic lesions, suggesting in the first instance hydatid cysts classified as Gharbi V. A bone scan revealed a discretely active right mandibular lesion on bone scan, with no other significant lesions on the rest of the skeleton, and no scintigraphic translation of the C2 lesion described on CT. The patient was deemed inoperable due to local progression: larynx, nerve damage and proximity to the vascular axis and pulmonary metastases. The patient received vinorelbine-

cisplatin-based chemotherapy as 1st-line treatment and the evolution was marked by a partial response.

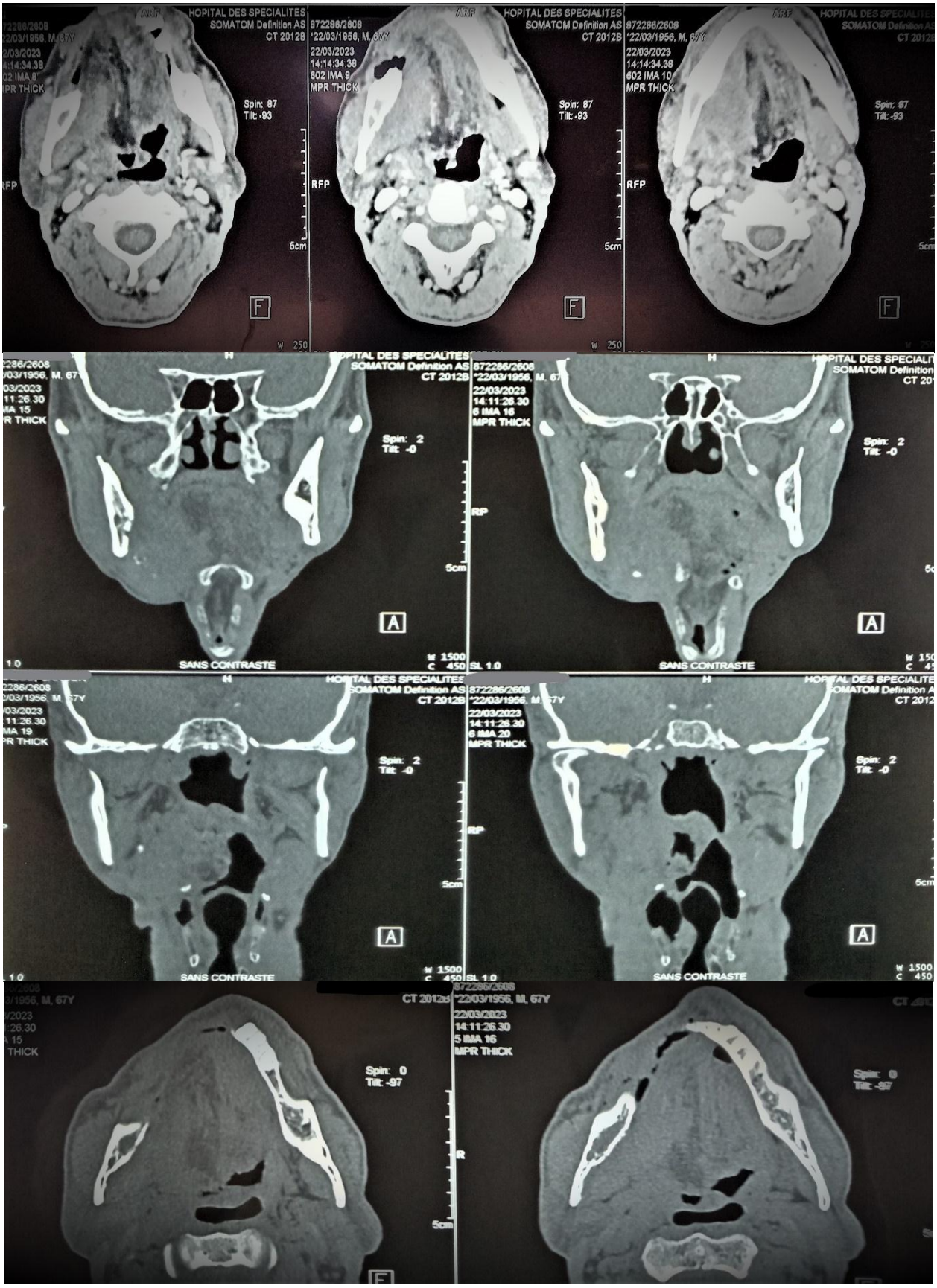

Figure 1: CT images of the patient showing the locally advanced lesion process in the right mandibular region.

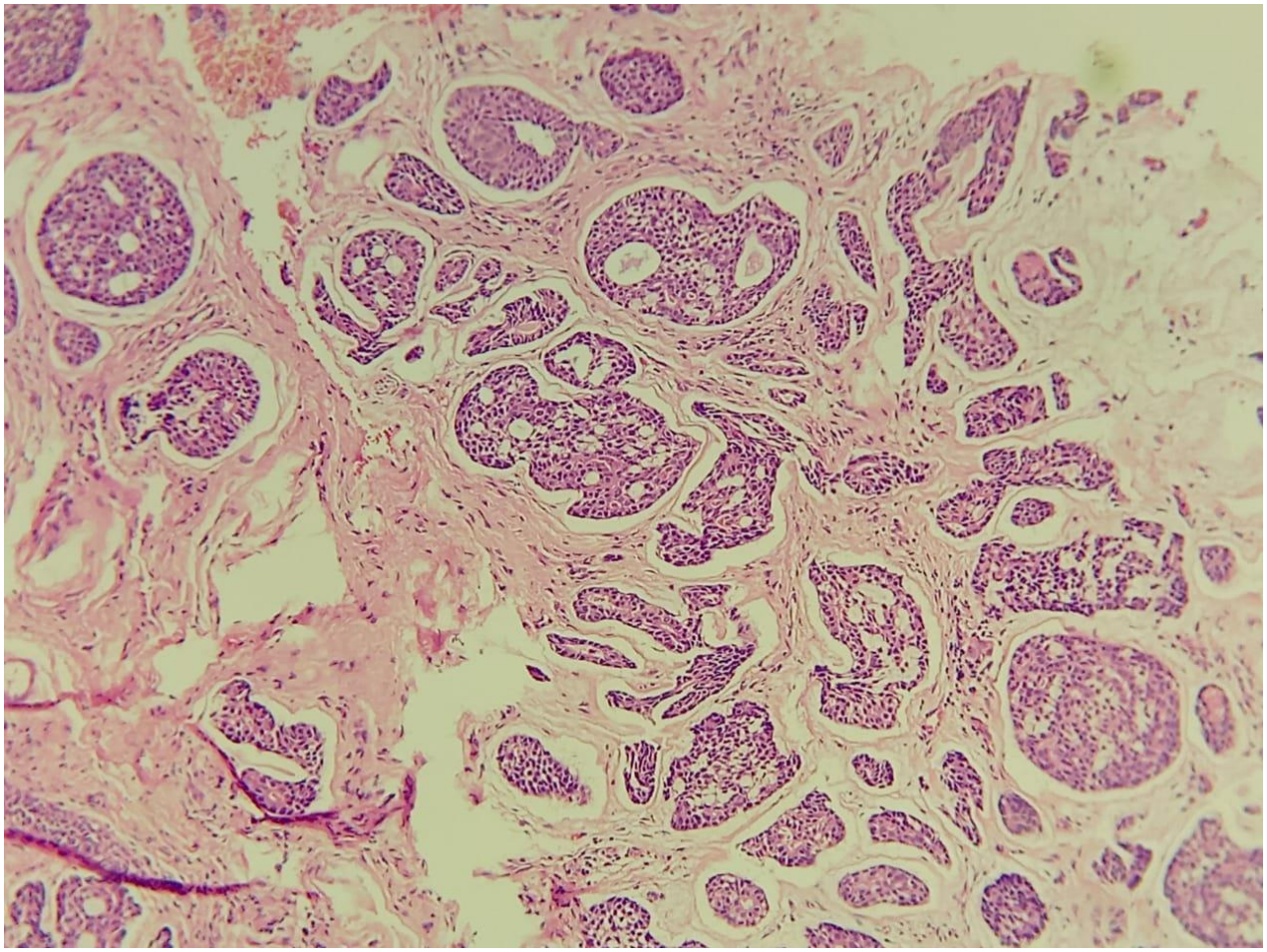

Figure 2: microphotograph showing an ACC made of a biphasic tumor proliferation arranged in cribriform clusters which are bordered by monomorphic cells. HEX10

DISCUSSION

Adenoid cystic carcinoma is a rare malignancy that originates from the salivary glands and other sites in the body, such as the lung and breast.[7] It accounts for about 10% of all salivary gland neoplasms.[17] ACC is the most common malignant neoplasm in the submandibular gland, followed by mucoepidermoid carcinoma and carcinoma Ex-pleomorphic adenoma.[6] The average age of discovery of malignant submandibular tumors is between the 4th and 6th decade with a predilection for men.[12,13,14,15,16] ACC tends to be more common in the submandibular gland in women.[17,18,19] Our patient is male and his age 57 years old, which is in line with the literature. Over 50% of adenoid cystic carcinoma tumors contain the t (6;9) (q22-23; p23-24) translocation, which fuses the *MYB* protooncogene on chromosome 6q to the *NFIB* gene on chromosome 9p, resulting in an overexpression of *MYB-NFIB* fusion oncogene and worse prognosis.[9,10,11] ACC presents as a non-encapsulated, well-circumscribed mass with biphasic ductal and myoepithelial components and three distinct patterns: tubular, cribriform, and solid[17,20], They may occur either separately or together in the same tumor, and the solid subtype is the most aggressive.[8] In this patient's case, biopsy of the submandibular gland showed tube trabeculae and cribriform masses (figure 2). ACC of the submandibular gland presents as a swelling in the submandibular region with pain secondary to perineural and extra-parenchymal invasion.[1,17] One of the most outstanding features of ACC, regardless of its site of origin, is its marked tendency to invade nerves. The involved nerves may be the lingual nerve for submandibular location.[1] In our case the involved nerve is the facial nerve, which caused facial paralysis in this patient. The slow growth and the absence or paucity of symptoms often result in delayed diagnosis and many patients present with advanced disease.[1] ACC is generally recognized for its frequent and often silent distant metastases. They are rare at presentation, but at 10 years they account for approximately 30% to 40%. The commonest sites are lung, bone, liver and brain.[1] Distant metastasis from submandibular ACC most commonly involves the lungs, and regional metastasis from submandibular ACC is more common compared to other major salivary glands due to the proximity of the draining lymph nodes.[26,27] In our case, radiological imaging revealed the locally advanced lesion process in the right mandibular region (figure1) with lung metastases.

In the absence of metastases, surgical excision with negative margins is the mainstay of treatment. Adjuvant radiation therapy (RT) is recommended after surgical excision to improve locoregional control in cases with positive margins, cervical metastases, advanced cancer stage, aggressive histology or grade, perineural invasion, lymph vascular invasion, or extra-glandular extension.[21,22,23,24,25] In patients who are not surgical or radiation candidates, palliative chemotherapy is proposed. In a study of 108 patients with salivary gland tumors (including 63 ACC), suggest treatment with cisplatin or vinorelbine, with similar efficacy but better digestive and renal tolerance for vinorelbine. As the cisplatin-vinorelbine combination is more effective than monotherapy, at the cost of increased toxicity, the choice of treatment is ultimately guided by the patient's general condition and comorbidities. Other options would be polychemotherapy with cisplatin and anthracycline[29] such as cisplatin/doxorubicin/cyclophosphamide (CAP). In our case, we have proposed to the patient vinorelbine cisplatin in the first line chemotherapy. Chemotherapy in ACC management has limited use, and the current evidence does not indicate a substantial clinical benefit from using the most common agents. Despite achieving a stable disease in many cases, the overall results are not satisfying.[7] Recent advances in genomics have made it possible to describe and analyze numerous oncogenic drivers (KIT, MYC, NOTCH, EGFR, FGFR).[30,31], representing potential therapeutic targets. High expression of c-KIT in ACC (>90%) does not appear to be sufficient to predict response to specific inhibitors, and response rates are very low. It is nevertheless useful for diagnostic purposes, providing an additional element for differentiating ACC from other salivary gland tumors.[32,33,34] The majority of ACCs show EGFR overexpression (>80%).[35] Single-agent anti-EGFR treatments (cetuximab, gefitinib, lapatinib) have stabilized the disease, but no complete or partial response has been observed in the metastatic phase.[36] Vorinostat, sorafenib, axitinib, lenvatinib, everolimus and brontictuzumab (NOTCH1 inhibitor antibody) were tested in patients with recurrent or metastatic adenoid cystic carcinoma with very few partial clinical responses and no complete response. Only stabilization of the disease was observed over a prolonged period of time. Some clinical trials are still ongoing, but the available trials are phase I and II only, and they investigated mainly antiangiogenic agents from different generations.[7] The development of immunotherapy, which has shown promise in the treatment of ACC and squamous cell malignancies of the upper aerodigestive tract, has also created new therapeutic options. Two phase II immunotherapy trials were conducted, in patients with recurrent or metastatic adenoid cystic carcinoma, one with pembrolizumab with or without radiation, which they did not observe objective response outside of the radiation treatment field, and the other with lenvatinib plus pembrolizumab which is still ongoing. Current first-line management of locoregionally recurrent disease is based on locoregional treatment whenever possible by surgery or, as a second-line treatment, radiotherapy.[37.38] The local treatment strategy has traditionally been restricted to oligometastatic disease, as opposed to multi-metastatic disease (more than five metastases.[39] Oligo progression could be linked to clonal resistance that escapes systemic treatment, the local strategy thus being complementary strategy, providing ablative treatment of resistant metastases while maintaining quality of life thanks to its excellent tolerability (39). In a recent study on ACC of the head and neck, the overall 5-year, 10-year, and 15-year survival estimates for all stages were 90.34%, 79.88%, and 69.22%, respectively.[1]. Moreover, recurrence and metastasis are often associated with poor long-term prognosis and disease-free survival.[28]

CONCLUSION

Adenoid cystic carcinoma of submandibular gland is rare malignant tumor. Surgery and adjuvant radiotherapy remain the only curative treatment in the absence of metastasis. Systemic treatments are used for locally recurrent or metastatic disease. Local ablative treatment of metastases in oligometastatic ACC situations should be discussed. Inclusion in therapeutic trials should be encouraged in patients with metastatic ACC or locoregionally advanced/recurrent ACC that cannot be treated locally.

REFERENCES

1. Giulio Cantù. Adenoid cystic carcinoma. An indolent but aggressive tumor. Part A: from an etiopathogenesis to diagnosis. ACTA OTORHINOLARYNGOLOGICA ITALICA, 2021; 41: 206-214.
2. Batsakis JG, Regezi JA. The pathology of head and neck tumors: salivary glands, part 1. Head Neck Surg, Sep-Oct, 1978; 1(1): 59-68. [PubMed]
3. Speight PM, Barrett AW. Salivary gland tumors. Oral Dis., Sep, 2002;8(5): 229-40. [PubMed]
4. Ettl T, Schwarz-Furlan S, Gosau M, Reichert TE. Salivary gland carcinomas. Oral Maxillofac Surg, Sep, 2012; 16(3): 267-83. [PubMed]
5. Thomson DJ, Slevin NJ, Mendenhall WM. Indications for Salivary Gland Radiotherapy. Adv Otorhinolaryngology, 2016; 78: 141-7. [PubMed]
6. Ord RA, Ghazali N. Margin Analysis: Malignant Salivary Gland Neoplasms of the Head and Neck. Oral Maxillo-facial Surg Clin North Am., Aug, 2017; 29(3): 315-324. [PubMed]
7. Eyad Saleh and Abdouldaim Ukwas. Adenoid Cystic Carcinoma of Salivary Glands: A Ten-Year Review and an Assessment of the Current Management, Surgery, Radiotherapy, and Chemotherapy. International Journal of Otolaryngology, 2023, Article ID 7401458, 16.
8. Ellis GL, Auclair PL, Gnepp DR. *Adenoid cystic carcinoma, Surgical Pathology of Salivary glands*. Philadelphia: WB Saunders, 1991; 333–346. [Google Scholar]

9. Mitani Y, Li J, Rao PH, Zhao YJ, Bell D, Lippman SM, Weber RS, Caulin C, El-Naggar AK. Comprehensive analysis of the MYB-NFIB gene fusion in salivary adenoid cystic carcinoma: Incidence, variability, and clinicopathologic significance. Clin Cancer Res., Oct 01, 2010; 16(19): 4722-31. [PMC free article] [PubMed]
10. Brill LB, Kanner WA, Fehr A, Andrén Y, Moskaluk CA, Löning T, Stenman G, Frierson HF. Analysis of MYB expression and MYB-NFIB gene fusions in adenoid cystic carcinoma and other salivary neoplasms. Mod Pathol, Sep, 2011; 24(9): 1169-76. [PubMed]
11. Brayer KJ, Frerich CA, Kang H, Ness SA. Recurrent Fusions in MYB and MYBL1 Define a Common, Transcription Factor-Driven Oncogenic Pathway in Salivary Gland Adenoid Cystic Carcinoma. Cancer Discov, Feb, 2016; 6(2): 176-87. [PMC free article] [PubMed]
12. Kukuckova Svec M. Surgical management of submandibulary gland diseases: ten years' experience. *Bratisl Lek Listy*, 2011; 112(5): 264–8. [PubMed] [Google Scholar]
13. Myersen, Ferris RL. *Salivary gland disorders*. 1st ed. New York: Springer; 2007. [Google Scholar]
14. Gott YH, Sethl DS. Submandibular gland excision: a five-year review. *J Laryngol Otol.*, Mar, 1998; 112(3): 69–73. [PubMed] [Google Scholar]
15. Rice DH. Malignant Salivary Gland Neoplasm. *Otolaryngol Clin North Am.*, Oct, 1999; 32(5): 875–86. [PubMed] [Google Scholar]
16. Camilleri IG, Malata CM, McLean NR, Kelly CG. Malignant tumours of the submandibular salivary gland: a 15-year review. Br J Plast Surg, Apr, 1998; 51(3): 181-5. [PubMed]
17. Bradley PJ. Frequency and Histopathology by Site, Major Pathologies, Symptoms and Signs of Salivary Gland Neoplasms. Adv Otorhinolaryngol, 2016; 78: 9-16. [PubMed]
18. Martínez-Rodríguez N, Leco-Berrocal I, Rubio-Alonso L, Arias-Irimia O, Martínez-González JM. Epidemiology and treatment of adenoid cystic carcinoma of the minor salivary glands: a meta-analytic study. Med Oral Patol Oral Cir Bucal, Nov 01, 2011; 16(7): e884-9. [PubMed]
19. Bishop JA, Yonescu R, Batista D, Eisele DW, Westra WH. Most nonparotid "acinic cell carcinomas" represent mammary analog secretory carcinomas. Am J Surg Pathol, Jul, 2013; 37(7): 1053-7. [PMC free article] [PubMed]
20. Ettl T, Schwarz-Furlan S, Gosau M, Reichert TE. Salivary gland carcinomas. Oral Maxillofac Surg, Sep, 2012; 16(3): 267-83. [PubMed]
21. Fu KK, Leibel SA, Levine ML, Friedlander LM, Boles R, Phillips TL. Carcinoma of the major and minor salivary glands: analysis of treatment results and sites and causes of failures. Cancer, Dec, 1977; 40(6): 2882-90. [PubMed]
22. Armstrong JG, Harrison LB, Spiro RH, Fass DE, Strong EW, Fuks ZY. Malignant tumors of major salivary gland origin. A matched-pair analysis of the role of combined surgery and postoperative radiotherapy. Arch Otolaryngol Head Neck Surg, Mar, 1990; 116(3): 290-3. [PubMed]
23. Terhaard CH, Lubsen H, Rasch CR, Levendag PC, Kaanders HH, Tjho-Heslinga RE, van Den Ende PL, Burlage F., Dutch Head and Neck Oncology Cooperative Group. The role of radiotherapy in the treatment of malignant salivary gland tumors. Int J Radiat Oncol Biol Phys., Jan 01, 2005; 61(1): 103-11. [PubMed]
24. Lewis AG, Tong T, Maghami E. Diagnosis and Management of Malignant Salivary Gland Tumors of the Parotid Gland. Otolaryngol Clin North Am., Apr, 2016; 49(2): 343-80. [PubMed]
25. Lin HH, Limesand KH, Ann DK. Current State of Knowledge on Salivary Gland Cancers. Crit Rev Oncog, 2018; 23(3-4): 139-151. [PMC free article] [PubMed]
26. Rinaldo A, Ferlito A, Pellitteri PK, Robbins KT, Shaha AR, Bradley PJ, Kowalski LP, Wei WI. Management of malignant submandibular gland tumors. Acta Otolaryngol, Oct, 2003; 123(8): 896-904. [PubMed]
27. Cohen AN, Damrose EJ, Huang RY, Nelson SD, Blackwell KE, Calcaterra TC. Adenoid cystic carcinoma of the submandibular gland: a 35-year review. Otolaryngol Head Neck Surg, Dec, 2004; 131(6): 994-1000. [PubMed]
28. T. Gao, Z. Shen, C. Ma, Y. Li, X. Kang, and M. Sun, "Te CCL5/CCR5 Chemotactic pathway promotes perineural invasion in salivary adenoid cystic carcinoma," Journal of Oral and Maxillofacial Surgery, 2018; 76(8): 1708–1718.
29. Laurie SA, Ho AL, Fury MG, Sherman E, Pfister DG. Systemic therapy in the management of metastatic or locally recurrent adenoid cystic carcinoma of the salivary glands: a systematic review. Lancet Oncol, 2011; 12: 815–24.
30. Dillon PM, Chakraborty S, Moskaluk CA, Joshi PJ, Thomas CY. Adenoid cystic carcinoma: A review of recent advances, molecular targets, and clinical trials. Head Neck, 2016; 38: 620–7.
31. Chae YK, Chung SY, Davis AA, Carneiro BA, Chandra S, Kaplan J, et al. Adenoid cystic carcinoma: current therapy and potential therapeutic advances based on genomic profiling. Oncotarget, 2015; 6: 37117–34.
32. Jeng Y-M, Lin C-Y, Hsu H-C. Expression of the c-kit protein is associated with certain subtypes of salivary gland carcinoma. Cancer Lett., 2000; 154: 107–11.
33. Penner CR, Folpe AL, Budnick SD. C-kit Expression Distinguishes Salivary Gland Adenoid Cystic Carcinoma from Polymorphous Low-Grade Adenocarcinoma. Mod Pathol, 2002; 15: 687–91.
34. Tariq H, Anjum S, Din HU, Akhtar F. Diagnostic utility of C-kit protein (CD117) expression in differentiating adenoid cystic carcinoma and

polymorphous low-grade Adenocarcinoma. Pak J Med Sci., 2017; 33: 1376–80.
35. Vered M, Braunstein E, Buchner A. Immunohistochemical study of epidermal growth factor receptor in adenoid cystic carcinoma of salivary gland origin. Head Neck., 2002; 24: 632– 6.
36. Agulnik M, Cohen EWE, Cohen RB, Chen EX, Vokes EE, Hotte SJ, et al. Phase II study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non-adenoid cystic carcinoma malignant tumors of the salivary glands. J Clin Oncol Off J Am Soc Clin Oncol, 2007; 25: 3978–84.
37. Iseli TA, Karnell LH, Graham SM, Funk GF, Buatti JM, Gupta AK, et al. Role of radiotherapy in adenoid cystic carcinoma of the head and neck. J Laryngol Otol, 18 2009; 123: 1137–44.
38. Mücke T, Robitzky LK, Kesting MR, Wagenpfeil S, Holhweg-Majert B, Wolff K-D, et al. Advanced malignant minor salivary glands tumors of the oral cavity. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2009; 108: 81–9.
39. Kissel M, Helou J, Thariat J. Nouvelles définitions de la maladie oligométastatique et nouveaux concepts de prise en charge globale de la maladie métastatique. Bull Cancer (Paris), 2018; 105: 696–706.