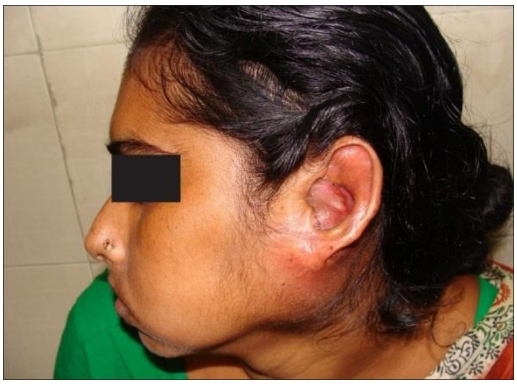
Cancer Association of South Africa (CANSA)

Fact Sheet
on
Adenoid Cystic Carcinoma

Introduction

Adenoid cystic carcinoma (ACC) is a rare type of cancer that can exist in many different body sites. It most often occurs in the areas of the head and neck, in particular the salivary glands; but has also been reported in the breast, lacrimal gland of the eye, lung, brain Bartholin gland, trachea and the paranasal sinuses.

It is also known as adenocyst, malignant cylindroma, adenocystic, Adenocystic Carcinoma, Cribriform Carcinoma, Cylindroma, ACC or AdCC.



[Picture Credit: Adenoid Cystic Carcinoma – Salivary Gland]

Castelnuovo, P. & Turri-Zanoni, M. 2020.

"Sinonasal adenoid cystic carcinoma is a rare malignancy characterized by an insidious growth pattern and a tendency for perineural spread along major and minor nerves, resulting in invasion of the skull base and intracranial extension. Therefore, many patients present with advanced disease and involvement of critical structures, making treatment difficult and potentially associated with high morbidity. Surgery represents the mainstay of treatment of the primary tumor. Complete resection of the tumor with negative margins, whenever feasible, is associated with better survival outcomes. However, in the case of extensive involvement of vital structures (e.g., carotid artery, cavernous sinus, optic nerve, Meckel's cave) or when radical surgery could seriously affect the patient's quality of life, a function-preserving subtotal removal of the tumor followed by irradiation can be proposed. The role of surgery is limited to a biopsy in unresectable lesions that are more suitable for non-surgical treatments (e.g., exclusive chemoradiation). Given the difficulty in obtaining negative margins and the propensity for submucosal and perineural spread, adjuvant radiotherapy is strongly recommended. Recently, heavy-particle radiotherapy using protons or carbon ions has emerged as a promising treatment with improved local control. Local failures (60%) and distant metastases (40%) are common and can occur even decades after definitive treatment. The 5-year overall survival ranges from 55 to 70% and it exceeds that of other sinonasal malignancies, but dramatically drops down at 10 years (40%) and further decreases at 20 years (15%). Therefore, a prolonged follow-up of at least 15 years, and possibly lifelong, is mandatory."

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Armstrong, L.T.D., Subramaniam, S.S. & Borgna, S. 2020.
"Adenoid cystic carcinoma (ACC) is an aggressive salivary gland neoplasm characterized by high rates of local recurrence, early metastasis, and a poor long-term prognosis. Approximately 20-50% of cases result in distant metastasis, commonly involving the lung, bone, liver, and brain. Cutaneous metastasis is a rare occurrence, with a small number of cases reported previously in the context of multiple metastatic sites of involvement. We present a unique case of ACC of the hard palate with isolated cutaneous metastasis. A 36-year-old woman underwent a subtotal maxillectomy and skull base resection for the treatment of a T4N0 ACC of the right maxilla. One year postoperatively, the patient presented with multiple rapidly growing painful nodules on the skin of the scalp, neck, and chest. Biopsy confirmed metastatic poorly differentiated ACC, and positron emission tomography demonstrated cutaneous metastatic lesions without evidence of other tissue involvement. This case highlights the possible rare and aggressive pathways of metastasis of ACC. Currently there is no consensus for the treatment of disseminated disease, due to the poor efficacy of current treatment modalities. Where isolated metastasis is present, surgical resection can be attempted to control disease progression; however the benefit of metastasectomy on survival is not substantiated. As such, the role of newer targeted systemic therapies needs to be further investigated in the hope of achieving disease control."

Ud Din, M.A. & Shaikh, H. 2020.
"Adenoid cystic carcinoma (ACC) is a rare malignancy arising from the secretory glands, most commonly seen 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. The tumor is typically slow-growing compared to other carcinomas and has a tendency for perineural invasion as well as hematogenous spread to distant organs and is most commonly seen in the elderly. Due to its rarity, limited data is available regarding the predisposing risk factors and the management of patients with advanced disease."

Mosconi, C., de Arruda, J.A.A., de Farias, A.C.R., Oliveira, G.A.Q., de Paula, H.M., Fonseca, F.P., Mesquita, R.A., Silva, T.A., Mendonça, E.F. & Batista, A.C. 2019.
OBJECTIVES: The objective of the present study was to investigate the expression of immune checkpoints (PD-L1, PD-L2, PD-1 and CTLA-4), immune inhibitory molecule HLA-G, markers of tumor-infiltrating lymphocytes (TIL) and dendritic cells (DC), as well as its association with clinicopathological features of adenoid cystic carcinomas (ACC) of the salivary glands.
MATERIALS AND METHODS: Thirty-six samples from patients with ACC were analyzed immunohistochemically for the expression of PD-L1, PD-L2, PD-1, CTLA-4, HLA-G, CD8, GrB, CD1a and CD83. Positivity of HLA-G, PD-L1 and PD-L2 expression was defined by cut-offs values. $CD8^+$ TIL was measured semiquantitatively and also using cut-off values obtained by the ROC curve considering recurrence of the lesion.
RESULTS: ACC showed low $CD8^+$, GrB^+ TIL, CD1a and CD83 populations, as well as scarce positivity for CTLA-4 and PD-1. In contrast, PD-L2 and HLA-G expression was increased, while no PD-L1 expression was detected. Interestingly, cases with lower $CD8^+$ TIL density presented greater recurrence rates.
CONCLUSION: Our findings suggest that the ACC microenvironment exhibits low immunogenicity, represented by low TIL and DC density. Moreover, there seems to be activation of the immune inhibitory proteins/PD-L2 and HLA-G, a scenario that may favor tumor escape from the immune system and partially explain the poor prognosis of ACC.

Signs and Symptoms of Adenoid Cystic Carcinoma (ACC)
Signs and symptoms include:

The symptoms of ACC depend on the location of the tumour. Early lesions of the salivary glands may appear as painless, usually slow-growing masses underneath the normal lining of the mouth or skin of the face.

Other symptoms may include:

- A lump on the palate, under the tongue, or in the bottom of the mouth
- An abnormal area on the lining of the mouth
- Numbness of the upper jaw, palate, face, or tongue
- Difficulty swallowing
- Hoarseness
- Dull pain
- A bump or nodule in front of the ear or underneath the jaw
- Paralysis of a facial nerve

Incidence of Adenoid Cystic Carcinoma (ACC) in South Africa
The outdated National Cancer Registry (2016) does not provide information on the incidence of ACC. It only provides information regarding Cancer of the Salivary Gland.

According to the National Cancer Registry (2016) the following number of salivary gland cancer cases was histologically diagnosed in South Africa during 2016:

Group - Males 2016	No of Cases Reported	Estimated Lifetime Risk	Percentage of All Cancers
All males	101	1:1 573	0,26%
Asian males	3	1:2 671	0,31%
Black males	41	1:2 700	0,32%
Coloured males	5	1:2 929	0,13%
White males	51	1:623	0,24%

Group - Females 2016	No of Cases Reported	Estimated Lifetime Risk	Percentage of All Cancers
All females	81	1:2 986	0,19%
Asian females	2	1:2 000	0,16%
Black females	46	1:3 993	0,22%
Coloured females	12	1:1 863	0,26%
White females	21	1:2 041	0,12%

The frequency of histologically diagnosed cases of salivary gland cancer in South Africa for 2016 was as follows (National Cancer Registry, 2016):

Group - Males 2016	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	6	5	10	6	18	30	21	5
Asian males	0	1	0	0	1	1	0	0
Black males	5	2	8	3	5	11	6	0
Coloured males	0	2	1	1	0	1	1	0
White males	0	0	2	4	4	9	14	8

Group - Females 2016	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	6	5	9	15	13	18	13	7
Asian females	0	0	0	0	0	0	2	0
Black females	5	4	7	13	7	7	3	0
Coloured females	0	0	2	2	2	4	2	0
White females	1	1	0	0	4	7	6	2

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Treatment of Adenoid Cystic Carcinoma (ACC)

The most common treatment protocol and "gold standard" for treating initial ACC tumours is surgical resection with follow-up radiation.

Follow-up radiation treatment for any residual tumour left in the surgical area is the most common recommendation for treatment, with some oncologists recommending follow up radiation even with clean margins due to the tendency of ACC for invisible, microscopic spread.

Jeske, S.S., Weissinger, S.E., Veit, J.A., Brunner, C., Huber, U., Theodoraki, M.N., Hoffmann, T.K., Schuler, P.J. & Doescher. J. 2019.

PURPOSE: Adenoid cystic carcinoma (ACC) of the head and neck is a rare and highly malignant tumor, characterized by perineural growth and early distant metastases. The composition of immune cells in the peripheral blood and the tumor microenvironment is critical to tumor growth and control. However, little is known about the frequency and function of the relevant immune cell subsets in this entity.

METHODS: In ACC patients (n = 11) and matched healthy donors (n = 11), the frequency of peripheral blood T and B cells was measured by flow cytometry at different treatment stages of disease (24 samples). Cells were further characterized by their expression of CCR7, PD-1, CD39 and CD73. Tumor-infiltrating lymphocytes (TIL) were analyzed by immunohistochemistry for ten patients and for three patients by flow cytometry.

RESULTS: $CD4^+$ T cells had significantly lower frequency after radiotherapy (RT). All other cell frequencies, including T_{reg}, were stable through course of the disease. In B cells, CD73 was reduced after RT. CCR7 expression on T and B cells in patients with relapse/metastases (R/M) differed significantly from patients with active disease. PD-1 remained stable. T_{reg} were more present in TIL compared to peripheral blood.

CONCLUSION: Composition of lymphocyte subgroups behaves similar to squamous cell carcinoma in the head and neck, except for T_{reg}, which remained stable. Nevertheless, the $CD4^+/T_{reg}$ ratio was lower after RT, which could stand for an immunosuppressive effect in these patients. Therefore, it could be beneficial treating ACC with combined RT and immunomodulatory drugs.

Li, C., Liu, S.M., Zheng, L., Huang, M.W., Sh,i Y., Lv, X.M., Zhang, J.G. & Zhang, J. 2019.

OBJECTIVE: To retrospectively analyze the results of treatment outcome by surgery combined with $_{125}$I brachytherapy and correlative factors of adenoid cystic carcinoma (ACC).

METHODS: In the study, 75 patients with primary ACC of oral and maxillofacial region were treated by surgery combined with $_{125}$I seeds brachytherapy. Radical resection or subtotal resection was applied for the tumor. The brachytherapy treatment planning system was used to create implant plans with the prescribed dose of 60 Gy to 120 Gy. The $_{125}$I seeds were implanted intraoperatively or

postoperatively. The regular follow-up was required. The Kaplan-Meier method was used to assess the tumor control rate and the patients' survival rates. Meanwhile, the Cox regression analysis was used to find out the prognostic factors.
RESULTS: Local control rates at the end of 3 and 5 years were as follows: T1-T2, 92.2% and 82.0%; T3-T4, 82.6% and 82.6%; and overall, 90.0% and 78.8%. The disease-free survival rates were 74.9% and 54.3%, respectively. The overall survival rates for all the patients were 86.0% and 79.6%, respectively at the end of 3 and 5 years and were 91.3% and 91.3% for T1-T2 patients vs. 73.9% and 59.7% for T3-T4 patients. Distant metastasis-free survival rates at the end of 3 and 5 years were 84.4% and 76.7%, respectively. The distant metastasis-free survival rates at the end of 3 and 5 years were 83.4% and 79.6% with T1-T2 lesion compared with 86.0% and 67.8% with T3-T4 lesion. According to the COX univariate analysis and multivariate analysis, the risk of local recurrence would be raised by the age. Tumor stage and tumor site were the prognostic factors of the overall survival rates.
CONCLUSION: $_{125}$I brachytherapy conducted as an adjuvant therapy postoperatively of ACC of oral and maxillofacial region can acquire satisfactory local?regional control, distant metastasis-free survival, disease-free survival and overall survival. Tumors are prone to recur on the older patients. Patients having advanced tumor stage or tumor located in the nasal cavity or sinuses will suffer lower survival rates.

Timoshchuk, M.A., Dekker, P., Hippe, D.S., Parvathaneni, U., Liao, J.J., Laramore, G.E. & Dillon, J.K. 2019. PMID: 30616797.
OBJECTIVES: Radiation therapy is commonly used to treat head and neck malignancies. While there is abundant research regarding photon radiation therapy, literature on neutron radiotherapy (NRT) and oral complications is limited. This study aims to determine: (1) the 6-year and 10-year locoregional control and survival rates, (2) factors associated with locoregional control and survival and (3) the frequency of oral complications in patients undergoing NRT for salivary gland malignancies.
MATERIALS AND METHODS: This is a retrospective cohort study. The sample was composed of patients with salivary gland malignancies treated with NRT between 1997 and 2010. Data were extracted from patient charts, telephone surveys, and social security records. Multivariate competing risk and Cox regression models were used to assess predictors of locoregional control and survival.
RESULTS: The sample was composed of 545 subjects with a mean age of 54.2 years (±16). The predominant tumor and location were adenoid cystic carcinoma (47%) and the parotid (56%). Multivariate analysis indicated that positive surgical margins, biopsied/inoperable malignancies, neck involvement, and lymphovascular invasion were prognostic risk factors associated with decreased survival. The 6- and 10-year locoregional control rates were 84% and 79%. The 6- and 10-year survival rates were 72% and 62%. Osteoradionecrosis developed in 3.4% of subjects.
CONCLUSIONS: The 6- and 10-year locoregional control and survival rates compare favorably to rates reported for conventional photon radiation. Osteoradionecrosis rates were comparable to that of photon radiation treatment (2-7%). Given the potential benefits of NRT, healthcare professionals should be educated regarding its indications and oral complications.

Staging of Adenoid Cystic Carcinoma
The staging of this condition depends on which excretory cells are involved and where in the body the disease is present. Obtaining staging information will assist the physician to determine a treatment plan.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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