Salivary gland tumours in the era of antiretroviral treatment

By

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As the candidate's supervisor I have/have not approved this thesis for submission.

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I. Kerusha Moodley declare that

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Overview

HIV is a global pandemic with an estimated 36.7 million people infected worldwide with HIV in 2015. Sub Saharan Africa remains the region most heavily affected with South Africa being home to the world's largest population living with HIV – which in 2016 was estimated at 7.1 million people. Data released in 2018 by Stats SA placed HIV prevalence rates in South Africa at 13.1% and 19 % for adults aged 15 – 49 years. Anti retroviral therapy has changed the face of the HIV pandemic with people infected with HIV now presenting with a wide variety of conditions including Non – AIDS defining cancers in the Head and Neck region. There are various Head and Neck sites that have been investigated but little data exists regarding the impact of HIV on the Salivary Gland subset of Head and Neck Tumours. In particular there is no data on the topic from South Africa. Kwazulu Natal's high rates of infection make it an excellent region in which to conduct the study. The study will further explore epidemiology and the spectrum pathology of Epithelial Salivary Gland Neoplasms, in HIV positive and negative patients, presenting to our institution and whether our data compares to our local and international counterparts.

This study/ project was conducted by performing a retrospective chart review to determine any differences between patients with HIV presenting with Epithelial Salivary Gland Tumours and their HIV negative counterparts. It further gathers information regarding patient presentation and outcomes between HIV positive patients on ARV's and those not on treatments.

It is hoped that this study will enlighten us to the trends in epidemiology of Salivary Gland Neoplasms at our institution and aspects of Epithelial Salivary Gland Tumours in HIV positive individuals, particularly in those on treatment and in doing so will enable us in future to faster recognize, diagnose and better manage affected individuals.

The purpose of this retrospective study is to compare the presentation and treatment outcomes in patients presenting with Epithelial Salivary Gland Tumours in the Anti retroviral treatment (ART) era presenting to Inkosi Albert Luthuli Hospital from January 2003 to June 2017.

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Chapter 1:

LITERATURE REVIEW

INTRODUCTION

Salivary Gland Neoplasms are an uncommon entity being less than 3% of all tumours and 3 – 10% of all Head and Neck Tumours.[1,2] Despite this, they represent a wide variety of both malignant and benign subtypes. Epithelial salivary gland tumours represent more than 90% of salivary gland tumours and can occur in both the major and minor salivary glands.[3] The occurrence of these tumours within the parotid and submandibular glands (major salivary glands) will be the focus of this study.

To date there are no studies out of Durban describing the spectrum of Parotid and Submandibular Gland pathology. This study will further, in addition, explore the effects of human immunodeficiency virus (HIV) infection on this subset of tumours, knowledge which has not been reported on previously in literature in South Africa or internationally.

ANATOMY OF THE PAROTID AND SUBMANDIBULAR GLANDS

The Parotid Gland

This paired gland has two lobes, a larger superficial lobe and a smaller, deep lobe demarcated from each other by the facial nerve. The facial nerve branches within the substance of the gland and can vary in its branching pattern making each surgical dissection unique and challenging. Around 80% of tumours arising from the parotid gland originate from within the superficial lobe of the gland. Only 20% arise from or grow to involve the deep lobe of the gland.[1]

The Submandibular Gland

This paired gland is located in the anterior part of the submandibular triangle of the neck. Its relation to the mylohyoid muscle determines the superficial and deep parts of the gland. The superficial arm, which is the largest portion of the gland, lies inferior to the posterior half of

the mandible. The deep portion wraps around the posterior margin of the mylohyoid muscle to lie lateral on the surface of the hyoglossus muscle and lateral to the root of the tongue.[1]

PRESENTATION OF SALIVARY GLAND TUMOURS

Majority of tumours that develop within the parotid and submandibular glands commonly develop over a long period of time. In general, they continue to grow slowly and do not cause any further symptoms. Should pain or nerve palsy accompany the mass then a malignant neoplasm should be considered.[1]Parotid tumours commonly present in the retromandibular region, posterior to the angle of the mandible or on the cheek anterior to the tragus of the ear. Submandibular gland tumours present in the submandibular triangle of the neck and constitute 10–15% of all salivary gland tumours. The rest of tumours arise from the remaining glands, which include the paired sublingual salivary glands and the minor salivary glands. Malignant Salivary Gland tumours usually present in the 6th decade of life and benign lesions in the 4th decade of life. There is a slight female predominance when it comes to benign tumours but equal distribution amongst males and females when it comes to malignant lesions.[1,4]

DIAGNOSIS OF SALIVARY GLAND TUMOURS

Fine Needle Aspiration Cytology

Pre–operative diagnosis of salivary gland tumours by fine needle aspiration cytology (FNAC) can be useful in establishing whether a lesion is inflammatory or neoplastic, a lymphoma, an epithelial malignancy, or represents a metastasis or a primary tumour.[5] This is especially true for the submandibular masses as few submandibular triangle masses arise from the submandibular gland. Majority of lesions in this area are secondary to an inflammatory process or represent neoplasms originating from lymph nodes in the area. FNAC can be useful in distinguishing this and assist in directing appropriate therapy.[4,5,6] The use of FNAC in parotid tumours remains controversial.[3,5,6] The area sampled may miss the area of malignant change within the mass. FNAC sampling can reveal the presence of normal lymphocytes which can be found in lymphoma, Warthin's tumour, benign lymphoepithelial disease and tuberculosis, making it difficult to make a conclusive diagnosis on FNAC alone. It is for these reasons that FNAC results rarely alter the management of parotid neoplasms -

that being surgery. Some surgeons feel that it is useful because knowledge of the histologic type may be useful in counseling patients for more extensive surgery should results indicate a high–grade malignancy. FNAC could also rule out some non – neoplastic causes of parotid masses that do not need surgical management. In 2007, Van Lierop et al[7] reported that the accuracy of FNAC in predicting whether a mass is benign or malignant ranges from 81% to 98%.[7] Further the risk associated with seeding of tumours is exceedingly small compared to that of an open biopsy .[1]

Radiology

Radiological investigation in the form of computed tomography (CT) or magnetic resonance imaging (MRI), especially for benign tumours, often does little to add to the diagnosis and management.[5] Majority of tumours arising from both the submandibular and parotid gland are managed without imaging. Imaging can take the form of CT or MRI as both have been proven to be equally sensitive when investigating salivary gland neoplasms.[1] Imaging is undertaken, in the case of the parotid gland, if the mass is arising from or extending to involve the deep lobe of the gland, if there is facial weakness, pain or other neural deficit or symptom suggestive of malignancy and if the mass is a congenital parotid tumour. In the case of the submandibular gland imaging is undertaken if there is a regional neural deficit or if the mass is fixed to the mandible. Imaging is further indicated if there is recurrent disease in either of the glands.[1]

MANAGEMENT OF EPITHELIAL SALIVARY GLAND TUMOURS

Parotid Gland Tumour Management

Management of Benign Salivary Gland Neoplasms involves removal of the mass with the associated part of the gland from which the tumour arises. In the case of a tumour arising from the superficial lobe of the parotid a superficial parotidectomy is adequate. Tumours arising from the deep lobe may need a total parotidectomy with sparing of the facial nerve .[1]

Malignant Parotid Tumours are best managed by primary surgery and where indicated, postoperative radiotherapy. Chemotherapy, at present, has a very limited role in the management of these tumours. The facial nerve should be spared in all cases of low-grade tumours in the parotid gland. There appears to be some controversy with regards to the

management of the facial nerve in high-grade tumours. Some surgeons advocate that the facial nerve should be spared if functioning preoperatively regardless of the histological tumour type unless the nerve passes right through the tumour and cannot be dissected during surgery. However, some surgeons still feel that the nerve should be resected in all cases of high-grade tumours. Radiotherapy is then indicated for all high-grade tumours and indicated for low-grade tumours only if there is a positive margin or it is an advanced stage tumour (T3/T4 tumour).[6]

In the case of a high-grade cancer, if there is concurrent nodal disease then a modified radical neck dissection should be carried out.[6]

In the case of a high-grade cancer with no concurrent nodal disease then elective neck dissection should be performed with clearance of levels 1 -3.[6]

The major complications associated with Parotid Gland Surgery are: [1]

- Facial Nerve injury – may be partial or complete or temporary or permanent. If planned or unplanned sacrifice, then repair or grafting should be undertaken at the same sitting.[6] Van Lierop et al[7] reported that temporary facial nerve palsy occurred post-surgery in 46 – 63% of patients and the rates of permanent facial nerve palsy post-surgery was reported as 3-4 %. In malignant disease where attempts to spare the facial nerve were made, the reported incidence of permanent paralysis was as high as 36%. In South Africa, Van Lierop et al[7] reported a rate of temporary facial nerve palsy related to benign disease as 34% and a permanent palsy rate of 3% for benign disease and 3% for malignant disease – rates well below most series out of the western world.[7] However, it is important to note the series from South Africa was a review of parotidectomies done by a single surgeon who is a specialist head and neck surgeon with years of experience in managing salivary gland disease.
- Hematoma formation – surgical drains are used post operatively to reduce risk of this, but should it occur the wound would have to be explored to locate the source and evacuate the hematoma.
- Sialocoele or Salivary Fistula – this implies a connection between the skin and the salivary gland or duct. The overall incidence of this complication has been reported as 14%.[8,9] They can be managed conservatively with serial aspirations and

compression dressings or botulin toxin type A administration. Techniques involving neurectomy have shown limited success and anticholinergic drugs have fallen out of favor due to their distressing side effects.[10]

- Frey's Syndrome/gustatory sweating - this is the most common long-term complication and results in the patient having sweating and flushing with meals. Usually becomes evident 1 to 12 months post procedure. The incidence of Frey's syndrome has been reported in some studies to be as high as 50% but severe cases have been reported to be around 15%. If problematic to the patient once again botulin toxin is administered, and should this method fail or if contraindicated then surgery to disrupt the aberrant innervation is considered.[10]

Submandibular Gland Tumour Management

All tumours arising from this gland require total resection of the gland.

In the case if a high-grade cancer, if there is concurrent nodal disease then a modified radical neck dissection should be carried out .[6]

In the case of a high-grade cancer with no concurrent nodal disease then elective neck dissection should be performed with clearance of levels 1 -3 with additional clearance of the submental triangle.[6]

Major complications of submandibular gland surgery:[1]

- Damage to the marginal mandibular branch of the facial nerve. Marginal mandibular nerve paresis results in temporary or permanent weakness of the angle of the mouth that will be most noticeable on smiling and puckering the lips. Overall incidence is approximately 7.7%.[11]
- Lingual and Hypoglassal Nerve Damage. The overall incidence of injury has been reported as 2.9 % and 1.4% respectively.[11]

SURGICAL RISK IN HIV POSITIVE PATIENTS

- In 2009, Madiba et al[12] reported that HIV infection should not be considered a significant independent risk factor for major surgical procedures. They further

advised that surgery should be offered to HIV positive patients, as it would to HIV negative patients without the fear of an unfavorable outcome.[12]

CLASSIFICATION OF SALIVARY GLAND TUMOURS

The World Health Organization (WHO) classification of salivary gland cancers published in 2017 listed 11 benign, 1 borderline tumour, 4 other epithelial lesions and 22 malignant epithelial neoplasms.[13] They can further be separated into epithelial tumours, the focus of this study, and stromal tumours.[2]

There are several studies on salivary gland neoplasms from different geographic areas of the world. Table 0.1 represents pathology data from the North American population as reported by Pinkston et al.[14] One would expect variation in incidence and histopathologic types of salivary neoplasms pending the epidemiology of the population being studied.[15] This is probably best highlighted when comparing the incidence of Warthin's tumour in a European and African study population, where the incidence of Warthin's tumour is reduced in the African population.[15] The African population has also been found to have an increased malignant to benign ratio of parotid tumours when compared to the western world.[7,15] In 2009, Mejía-Velázquez et al,[16] demonstrated that in the Mexican population malignant tumours were found in younger age brackets than what was reported in the American and European literature.[16]

Table 0.1: Common Parotid Gland Tumours [4]

Histopathology	Incidence (%)	
	Parotid Gland	Submandibular
Pleomorphic Adenoma	59	36
Mucoepidermoid Carcinoma	7.9	25
Warthin's Tumour	7.3	12
Carcinoma Ex – Pleomorphic Adenoma	4.4	10
Acinic Cell Carcinoma	3.5	7.0

Adenoid Cystic Carcinoma	3.1	7.0
Squamous Cell Carcinoma	2.0	1.0

Chung et al[17], in 1999, reported on parotid gland tumours in an Asian population over a period of 10 years. The racial distribution of Warthin's tumours exhibited an increased incidence among Chinese patients and a reduced incidence amongst the Malay and Indian populations.[17,18]

Bello et al[19], in 2012, reported that majority of malignant tumours occurred in the parotid gland in the Finnish centers reviewed, whereas among the Israeli population reviewed, malignant tumours were more commonly seen in the minor salivary glands, further illustrating the differences that can occur.[19]

With regards to Africa, there are a number of significant differences in various parts of the continent. An example of this is the proportion of malignant tumours arising from the salivary gland which varies from as high as 46% in Uganda to as low as 16.7% in Senegal.[15]

In South Africa there are currently only four studies describing the spectrum of Parotid Gland pathology and only two of those studies include the disease spectrum of the submandibular gland. These are reviewed in the Table 0.2.[7,20-22]

In a review of these studies the rates of malignancy in the parotid gland ranged from 24 – 29 % and 10 – 19 % in the submandibular gland.[7,20-22] In the recent study by Van Lierop et al[7] that looked exclusively at Parotid tumours excised by a single surgeon in Cape Town, South Africa, they hypothesized that the possible reason for their higher rate of metastatic cutaneous squamous cell carcinoma (SCC) was due to there being a high rate of skin cancer in South Africa. Their hypothesis was confirmed with metastatic cutaneous SCC (22%) being the most common malignant tumour reported from their study. These results were echoed by similar trends in the Australian literature. Overall, studies from Uganda and Tanzania, on parotid malignancy reported much higher rates of malignancy, 46% and 47% respectively. Most series from the western society report parotid malignancy rates as between 11% and 28%.[7]

As mentioned above, no studies out of South Africa have looked at what effect HIV infection or anti–retroviral therapy has on salivary gland disease. Sub-Saharan Africa remains the region most heavily affected with South Africa being home to the world's largest population living with HIV – which in 2016 was estimated at 7.1 million people making this the ideal area in which to conduct such a study. [23]

Table 0.2: Salivary gland lesions in South Africa. PG – parotid gland, SG – submandibular gland, and MG – minor salivary gland. *ca* – cancer and NR – not reported

Type of Tumor Cancer	Type of Gland Incidence [7,20-22]						
	Van Lierop et al[7]	Lakhoo et al[20]	Schoeman et al[21]		*Theron et al[22]		
	PG	PG	PG	SG	PG	SG	MG
Number	196	60	97	30	138	31	48
BENIGN EPITHELIAL NEOPLASMS	54	72	75	90	75		
Pleomorphic Adenoma	42	63	68	90	63		
Whartins Tumour	8	2	3	0	7		
Monomoprhic Adenoma	4	7	2	0	2		
Other benign epithelial neoplasms	0	0	2	0	3		
BENIGN NON-EPITHELIAL NEOPLASMS	7	NR	0	0	NR		
MALIGNANT EPITHELIAL NEOPLASMS	20	28	24	10	25		
Mucoepidermoid *ca*	5	3	12	0	5		
Acinic cell *ca*	4	0	4	0	2		
Adenoid cystic *ca*	1.5	15	3	7	3		
Squamous cell *ca*	1	3	1	3	5		

Epithelial Myoepithelial *ca*	0	0	1	0	0
Adenocarcinoma	0.5	0	1	0	2
Metastatic *ca*	7	0	0	0	0
Carcinoma ex Pleomorphic adenoma	0	0	1	0	5
Undifferentiated/other	1	7	1	0	3
MALIGNANT NON-EPITHELIAL NEOPLASMS	7	NR	1	0	NR
NON-NEOPLASTIC LESIONS	12	NR	NR	NR	NR

* IN THIS STUDY THE DETAILS OF PATHOLOGY ORIGINATING FROM EACH GLAND WERE NOT CLEARLY OUTLINED.

THE LINK BETWEEN HIV AND EPITHELIAL SALIVARY GLAND NEOPLASMS.

The devastating effect of the global HIV epidemic has been significantly reduced largely due to the administration of antiretroviral therapy (ART). HIV infection has now become a chronic disease with people living with HIV (PLHIV) now surviving, aging and requiring lifelong care and treatment. [24]

Across all age groups, PLHIV have increased risk of chronic complications and comorbidities (non-communicable diseases and mental, neurological and substance-use disorders) which can be pre-existing, HIV associated, or due to aging.[25-27]

Benign Parotid Lymphoepithelial Disease and Mucocoeles are well documented to be associated with HIV infection.[28,29] Studies have also shown that the incidence of AIDS-defining malignancies has been on the decline.[26,27] However, deaths due to non-AIDS-defining illnesses have been on the rise. These so-called non-AIDS-defining cancers (NADCs) include cancers of the lung, liver, kidney, anus, head and neck, and skin, as well as Hodgkin's lymphoma.[27] The reasons for PLHIV having an increased risk of cancer is perhaps their

susceptibility to immunosuppression, opportunistic and viral infections which render them at higher risk for cancers that are caused by oncogenic viruses.[29,30]

Literature has demonstrated an increased risk associated with HIV positivity and development of squamous cell carcinoma in the head and neck region.[31] In particular, for salivary gland cancers, Purgina et al[31], in 2011, showed in their review of the literature on head and neck carcinomas in HIV positive patients, the cancer risk for patients with HIV was greatest for developing Lymphoepithelial carcinoma and further determined that patients with HIV also had a significant risk of developing Squamous cell carcinoma. In this study they also reported that when patients with HIV did have confirmed primary squamous cell carcinoma of the salivary gland it histologically was high grade and keratinizing in nature.[31] The WHO classification of salivary gland tumours defines Lymphoepithelial carcinoma as an undifferentiated carcinoma with prominent non–neoplastic lymphoplasmalytic infiltrate. It occurs in less than 1% of the salivary gland tumours in the general population. It is seen more commonly in the Asian and in the Inuit (Eskimo) populations. There is almost a 100% association with lymphoepithelial carcinomas and Epstein Barr Virus (EBV) in endemic areas but it is absent from Lymphoepithelial carcinomas in the salivary glands in non–endemic areas. What was found particularly interesting is that LEC is morphologically indistinguishable from the more common nasopharyngeal carcinoma (NPC), which has also been found to be elevated in patients with HIV.[30,31,32] It has also been reported that individuals with acquired immunodeficiency syndrome (AIDS) in the American population had strongly elevated risks for lymphoepithelial carcinoma along with squamous cell carcinoma.[30, 31] This was mirrored in India where it has been shown that there is also a moderately increased risk of developing a non-AID's defining salivary gland cancer in patients with HIV infection.[32]

RESEARCH QUESTION

This particular area of study has not previously been undertaken in Southern Africa, which in no doubt is the heart of the pandemic and home to the world's largest Anti-retroviral Treatment (ART) programme.[33]

Further, the apparent variable distribution of salivary gland tumors in South Africa and Africa as a whole makes it imperative for the need to evaluate the pattern in in this part of the world, as data from other parts of the world do not represent patterns of disease found here in South Africa or in Africa at large. The paucity of data on this group of tumours in South Africa makes this retrospective review even more relevant. This study therefore aims to document the pattern of salivary neoplasms in Durban, Kwazulu Natal, South Africa and further evaluate if HIV infection has had any impact on the presentation and treatment outcomes of Salivary Gland Tumours in the ART era.

The results of the study will inform the body of knowledge on the aspects of this subset of Head and Neck Tumours in HIV positive and negative individuals in an area with high rates of HIV infection. In doing so, this will, in future, enable faster recognition, diagnosis and hence better management of affected individuals.

Furthermore, this is the first study of this nature on salivary gland pathology from South Africa and it is believed it will serve as a platform for further research and development in the area.

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Chapter 2: Salivary gland tumours in the era of antiretroviral treatment

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Summary

Objectives. Determine and compare the demographics and presentation of salivary gland tumours in two groups of patients infected with human immunodeficiency virus (HIV): those on antiretroviral therapy (ART), those not on ART, and uninfected patients, (ii) Ascertain if HIV infection and access to ART has altered the histopathological presentation of salivary gland tumours in the patient population, (iii) Determine if HIV infection and its treatment is associated with a change in morbidity, compared to uninfected patients following definitive treatment of salivary gland neoplasms.

Method. A retrospective chart analysis was conducted of all the submandibular and parotid gland surgeries undertaken by the Department of Otorhinolaryngology at Inkosi Albert Luthuli Hospital, a quaternary state hospital. This review was done for surgeries completed from July 2008 to June 2017 (data for 2003 to 2008 could not be located on site).

Results. Between July 2008 and June 2017, a total of 185 surgeries had been undertaken: 100 parotidectomies and 85 submandibular gland excisions. HIV-positive patients are likely to present with malignant epithelial parotid gland tumours at a younger age than their HIV-negative counterparts, p=0.032. *Conclusion.* HIV-positive patients are likely to present with a malignancy of the parotid gland at a younger age. As clinicians, we need to have a high index of suspicion when assessing and

Introduction

The link between HIV and epithelial salivary gland neoplasms

The devastating effect of the global human immunodeficiency virus (HIV) epidemic has been significantly reduced, largely due to the administration of antiretroviral therapy (ART). HIV infection has now become a chronic disease, and people living with HIV (PLHIV) are now surviving, ageing and requiring lifelong care and treatment.[1-3]

Studies have shown that the incidence of acquired immunodeficiency virus (AIDS) - defining malignancies has been on the decline and deaths due to non-AIDS-defining illnesses, such as non-AIDS defining cancers (NADC), have been on the rise. These so-called NADCs include cancers of the lung, liver, kidney, anus, head and neck, and skin, as well as Hodgkin's lymphoma.[3] The reasons why

PLHIV have an increased risk of cancer could be their susceptibility to immunosuppression, and opportunistic and viral infections, which render them at higher risk of cancers that are caused by oncogenic viruses.[4]

The literature demonstrates an increased risk associated with HIV positivity and the development of squamous cell carcinoma in the head and neck region.[5-7] Regarding salivary gland cancers, in particular, it has recently been reported that individuals with AIDS in the North American population had strongly elevated risks for lymphoepithelial carcinoma and squamous cell carcinoma.[5,7] This finding was mirrored in India, where there was found to be a moderately increased risk of developing non-AIDS-defining salivary gland cancer in patients with HIV infection.[8]

It has also been postulated that combination ART (cART) may have a role in the development of certain cancers. A review of cART and cancer risk by Borges in 2017 reported that, when cART is initiated immediately, the risk of developing an NADC might be reduced by 29% compared to patients for whom cART initiation is deferred. However, Borges does admit that further study in this area is required.[9]

From Durban, South Africa, Madiba *et al.* reported in 2009 that HIV-infected patients without AIDS-defining criteria have a surgical course similar to that of uninfected patients.[10] In the same study by Madiba *et al.*, the outcome of all surgery except anorectal surgery, including post-procedural complications, is similar for HIV-infected and uninfected patients, regardless of the site of surgery.[10]

In our study, we wanted to determine if our findings echoed the findings of the studies mentioned above, if our patient population differed and, if so, how they differed. These particular areas of study have not been investigated before in southern Africa, which is the epicentre of the HIV pandemic and home to the world's largest ART programme.[11] This study, therefore, endeavoured to document the pattern of salivary neoplasms in Durban, KwaZulu-Natal, South Africa, and, furthermore, evaluate if HIV infection has had any impact on the presentation and treatment outcomes of salivary gland tumours in the ART era.

The results of the study will enlighten us about aspects of this subset of head and neck tumours in HIV-positive and -negative individuals in an area with high rates of HIV infection and, in doing so, the study will enable us to recognise, diagnose and, hence, manage affected individuals better and faster in the future.

Materials and methods

Ethical clearance for the study was

obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal and the KwaZulu-Natal Health Research Committee (BE464/16).

A retrospective chart analysis was planned for data from 2003, when the Inkosi Albert Luthuli Hospital (IALCH) Department of Otorhinolaryngology service started, to June 2017. This involved analysing theatre records and treatment charts of patients who presented with submandibular or parotid salivary gland tumours requiring surgery. Unfortunately, charts for patients from 2003 to July 2008 could not be traced, so the analysis was undertaken for data from July 2008 to June 2017.

All patients who presented for surgical removal of their parotid or submandibular gland tumours at IALCH during the designated period, with documented HIV results, were included in the study. Patients with undocumented HIV results, or with non-epithelial and non-neoplastic disease, were excluded. Patients with metastatic disease were not included, as they were often operated on in conjunction with additional surgical disciplines, in other theatres, which made it difficult to trace these patients accurately.

Data analysis

Continuous variables were expressed as mean ± standard deviation (SD) or medians (interquartile range) and compared using the Student's t-test or the Wilcoxon test, as appropriate. Proportions and categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. All analyses were performed using SPSS Version 25 (IBM Corp. Released 2018. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Our study included 184 surgeries performed between July 2008 and June 2017:142 parotidectomies and 42 submandibular gland (SMG) removals. Patient ages ranged from 1 to 88 years, with an average age of 44.14 (SD ± 18.70 years). Using Shapiro-Wilk's test for normality, patient age was found to be normally distributed (p=0.191) (Table 1). In our patient population, 30 (16.30%) patients were HIV-positive and 102 (55.43%) were HIV-negative; the HIV results of a further 52 (28.26%) patients were unknown.

Of the 25 HIV-positive patients who had undergone parotid surgery, 22 (88.0%) were found to have epithelial salivary gland neoplasms (ESGN). In the SMG, 3 (60.0%) of a total of 5 HIV-positive patients were found to have ESGN. All 3 of the HIV-positive patients presenting with ESGN in the SMG were found to have

benign disease. There was no significant difference in the mean age of presentation in HIV-positive (34.3 years) compared to HIV-negative (31 years) patients with ESGN in the SMG (p=0.48). There was a statistically significant difference between the mean age of patients presenting with malignant epithelial parotid gland neoplasms (MEPGN) who were HIV-positive (38.7 years), and that of patients who were HIV-negative (47.9 years) (p=0.032). However, there was no statistically significant difference between the mean ages of HIV-positive patients (40.9 years) and HIV-negative (39.3 years) patients with benign epithelial parotid gland neoplasms (BEPGN) (p=0.74) (Table 4). There appears to be an overall increased risk for an HIV-positive patient to develop a malignant tumour in the parotid gland (relative risk 1.41, 95% confidence interval (CI) 0.75 to 2.66, p=0.29).

Among the study group there were 100 (54.31%) female and 84 (45.65%) male patients. More female patients (25, 60.98%) than male patients (16, 39.02%) presented with malignant epithelial tumours in the parotid gland and this difference was found to be statistically significant (p=0.0162). The mean age of male HIV-positive patients presenting with parotid ESGN was 41.63 years (SD ± 6.97), which was higher than the mean age of their female counterparts, which was 38.41 years (SD ±13.53). However, using a Welch's t-test that corrected for the difference in numbers of male and female patients, this difference was found to be not statistically significant (p=0.44). The mean age of HIV-positive female patients presenting with MEPGN was 37.40 (SD ± 8.82), and the mean age of HIV-positive male counterparts was 40.25 years (SD ± 10.18). Again, the Welch's t-test found that this difference was not statistically significant (p=0.67).

Out of a total of 74 pleomorphic adenomas found arising from the parotid gland, 12 (16.2%) were in HIV-positive patients. Only 1 (33.33%) of the 3 patients presenting with basal cell adenoma in the parotid gland was HIV-positive. The total number of patients presenting with pleomorphic adenoma arising from the SMG was 14, and only 3 (21.43%) of those patients were HIV-positive (Tables 2 & 3 respectively).

In our patient population, HIV-positive patients with epithelial malignancies had a mean CD4 count of 385.89 cells/mm^3 (SD ± 161.72). This CD4 count is lower than the mean CD4 count of 407.92 cells/mm^3 (SD ± 119.04) found in HIV-positive patients presenting with benign epithelial salivary gland tumours; however, this difference was not found to be statistically significant (p=0.72) – this was determined using the Welsch's t-test, because we had different sample sizes and variances.

The World Health Organization defines immunosuppression by its classification for

established HIV-infection in adults.[12] We considered the CD4 counts of HIV-positive patients with benign and malignant disease in the parotid gland and grouped them according to this classification, using the Fischer's exact test. When comparing the CD4 ranges of these two groups, the p-value was found to be 0.55 (Table 5). No patients in either group presented with severe immunosuppression (CD4<200).

Of the 30 HIV-positive patients, 14 (46.67%) were on highly active antiretroviral therapy (HAART); 15 (50%) of the HIV-positive patients were not on HAART, and this information was not documented for 1 (3.33%) patient. Three (33.33%) of the 9 patients with MEPGN were on HAART, and 7 (53.85%) of the 12 patients presenting with benign epithelial salivary gland neoplasms were on HAART.

Of the 184 patients who underwent surgery, the final histology reports of 144 (78.26%) reported that they had ESGN (Tables 3 & 4). Patients' final histology reports showed only 3 types of benign epithelial tumours arising from the parotid gland, and 1 type of benign epithelial tumour from the SMG. Malignant epithelial disease was more varied, with 6 different pathologies reported in the parotid gland and 4 in the SMG.

Epithelial-myoepithelial carcinoma was the most common malignant epithelial tumour found in the SMG, representing 3 (50%) of total malignant tumours identified. The most common MEPGN was mucoepidermoid carcinoma, in 10 (24%) patients, followed closely by epithelial-myoepithelial carcinoma, representing 9 (22%) malignancies (Tables 2 & 3).

After surgical excision, normal glands were reported in 3 patients; however, for 1 of those in the parotid gland, an adjacent lymph node was reported positive for carcinoma of possible cutaneous origin, and for 1 of those in the SMG, an adjacent lymph node was reported positive for adenocarcinoma. Of the 42 patients who underwent SMG excision, 1 (3.45%) HIV-negative patient had no documented post-operative pathology report. We believe this patient was subsequently registered under a different name or number.

Post-operative complications

In our study population, HIV-positive patients did not show any increased risk of complications related to salivary gland surgery.

Discussion

In this study, 47 (32.64%) patients, out of a total number of 144, had malignant epithelial tumours. The number of patients with epithelial malignancy in the parotid gland was 41

(33.03%), which is higher than the rates reported in large population studies for northern Europe and northern America, in which parotid malignancies accounted for only 11 to 17% of parotid tumours.[13-17]

Pleomorphic adenoma was found in 74 (59.68%) of patients with epithelial parotid neoplasms. Warthin's tumour accounted for 6 (7.23%) of BEPGN in our series, which is less than the 15 - 22% reported in Western literature.[17] The reason may be because Warthin's tumour has been found to be uncommon in Black African populations.[18]

In our study, the rate of malignancy in the SMG was 30%, and appears to be lower than rates reported by large American and European studies, which report rates of malignancy of the SMG between 40 and 66%.[19-22] In the SMG, all 6 (100%) of our patients who presented with epithelial malignancy were female. Benign disease occurred with equal frequencies in male and female patients. None of the patients presenting with epithelial malignancies in the SMG were HIV-positive.

The most common benign and malignant epithelial neoplasms in our population group were pleomorphic adenoma and epithelial-myoepithelial carcinoma, identified in 88 (90.72%) and 12 (25.53%) of patients respectively, out of a total number of 144 patients. The second-most-common epithelial malignancy was mucoepidermoid carcinoma, with 11 (23.40%) patients identified in our population group. Epithelial-myoepithelial carcinoma is a rare salivary gland malignancy that represents <1% of all salivary gland malignancies. It has been reported to have a slight female predominance, which was echoed in our study population.[23,24] This could further explain the higher rates of MEPGN in females compared to males in our study population compared to other studies from the rest of the world, including Africa.(13-15,17,25-17)

The most common primary MEPGN was mucoepidermoid carcinoma; this was in keeping with other population-based studies from the rest of the world, including Africa.[13-17,19,20,25-27)

Studies have confirmed that the incidence of AIDS-defining cancers (ADC) has been on the decline; however, deaths due to non-AIDS-defining illnesses have been on the rise.[3] These so-called NADCs include cancers of the lung, liver, kidney, anus, head and neck, and skin, as well as Hodgkin's lymphoma.[3] The reasons for PLHIV having an increased risk of cancer could be their susceptibility to

immunosuppression, and opportunistic and viral infections, which render them at higher risk for cancers that are caused by oncogenic viruses, such as human papillomavirus and Epstein Barr virus.[4,5]

Deeken *et al.* (2012), in a review of various epidemiological studies from France, the United Kingdom, Switzerland and the United States, observed increased rates of NADCs, whilst ADCs were found to have declined in some areas, up to threefold from 1995 to 2005. They also report that the risk of a PLHIV older than 40 years developing an NADC of any kind, is 12 times higher than the risk of the general population. They state that the duration of HIV infection is associated with an increased risk of developing an NADC, with a reported increased risk ratio of 1.20 for every year of HIV infection. Furthermore, in the United States, NADCs have been found to occur more commonly in men, with women displaying no higher rates of NADCs than the general population.[3] This finding regarding malignant disease was not replicated in this study's population of HIV-positive patients. Malignant disease was found more commonly in female patients, with 5 (55.56%) female patients found to have a malignant neoplasm arising from the parotid gland, and only 4 (44.44%) HIV-positive male patients presenting with a malignancy.

In this study, the mean age of patients presenting with benign epithelial disease and malignant epithelial disease was 42.77 (SD ± 17.68 years) and 53.13 (SD ± 15.53 years) respectively. We found that HIV-positive patients presenting with MEPGN presented significantly younger than their HIV-negative counterparts (p=0.032). The mean age of the HIV-positive group was 38.67 (SD ± 8.94 years), and that of the HIV-negative group, 47.89 (SD ± 11.23 years) (Table 4). This finding appears to be in keeping with results reported by Purgina *et al.* (2011) in a review article on carcinomas arising from the head and neck region of HIV-positive patients. They found that mucosal squamous cell carcinoma, nasopharyngeal carcinoma, lymphoepithelial carcinoma of the salivary glands and Meckel cell carcinoma in the head and neck region presented at a younger age in HIV-positive patients. They report, furthermore, that HAART did not appear to alter the incidence of head and neck carcinomas in HIV-positive patients, as it did in HIV-positive patients with Kaposi sarcoma, but acknowledge that this is an area in which further study is required.[7] The number of HIV-positive patients with

malignancy, and on HAART, identified in our study was 3 (12%); this number is too small to draw any of the above conclusions and, hence, no further calculations were carried out in this area.

The most common benign epithelial salivary gland neoplasm amongst all 25 HIV-positive patients in this study was pleomorphic adenoma, which was found in 16 (64.00%) patients. The most common malignant epithelial salivary gland neoplasm amongst our HIV-positive patient population, in the parotid gland, was shared by mucoepidermoid and epithelial-myoepithelial carcinoma, with 4 patients each presenting with the above representing (44.44% with each malignancy). The remaining 1 (11.11%) HIV-positive patient presented with acinic cell carcinoma. This finding is in contrast with findings reported by Purgina *et al.* (2011), whose study found that lymphoepithelial carcinoma and squamous cell carcinoma were the most common salivary gland tumours in their HIV-positive population.[7] A 2010 study by Shebl *et al.* in India found a moderately elevated risk for developing a malignant salivary gland tumour for PLHIV.[5] In our series, none of the HIV-positive patients presented with lymphoepithelial carcinoma or squamous cell carcinoma of the parotid or SMG.

One HIV-positive patient with a benign epithelial neoplasm had documented postoperative sepsis; however, due to this small number it was evident that HIV infection did not play a role in the development of postoperative sepsis or wound breakdown in our patient population, in keeping with findings by Madiba *et al.* (2009) in Durban, South Africa.[10]

Conclusion

From the discussion above, we conclude that HIV-positive patients are more likely to present with a malignancy of the parotid gland at a younger age than their HIV-negative counterparts. As clinicians, we need to have a high index of suspicion when assessing such patients and avoid any unnecessary delays in management.

To the best of our knowledge, this is the first study of this nature on salivary gland pathology in South Africa, and it will serve as a platform for further research and development in this important and relevant area.

Table 1: Demographic data

	Parotid		Submandibular	
	N (%)	95% CI	N (%)	95% CI
AGE				
<20	15 (10.1)	5.01-15.06	6 (14.3)	3.7-24.9
21 – 30	18 (12.7)	7.22-18.18	9 (21.4)	9.0-33.8
31 – 40	22 (15.5)	9.55-21.45	6 (14.3)	3.7-24.9
41 - 50	32 (22.5)	15.63-29.37	10 (23.8)	10.9-36.7
51 – 60	22 (15.5)	9.55-21.45	6 (14.3)	3.7-24.9
61 - 70	20 (14.1)	8.38-19.82	3 (7.1)	0.7-14.9
>70	13 (9.2)	4.45-13.95	2 (4.8)	1.7-11.3
Total	**142 (100.0)**		**42 (100.0)**	
GENDER				
Male	62 (43.7)	35.54-51.86	22 (52.4)	37.3-67.5
Female	80 (56.3)	48.14-64.46	20 (47.6)	32.5-62.7
Total	142 (100.0)		42 (100.0)	
HIV STATUS				
Positive	25 (17.6)	11.34-23.86	5 (11.9)	2.1-21.7
Negative	73 (51.4)	43.18-59.62	29 (69.0)	55.0-83.0
Unknown	44 (30.1)	22.56-37.64	8 (19.0)	7.1-30.9
Total	142 (100.0)		42 (100.0)	
***CD4**				
None	4 (16.0)	1.63-30.37	1(20.0)	15.1-55.1
Mild	8 (32.0)	13.71-5029	0(0.0)	0.0-0.0
Advanced	11 (44.0)	24.54-63.46	2(40.0)	2.9-82.9
Severe	0 (0.0)	0.0-0.0	1(20.0)	15.1-55.1
Unknown	2 (8.0)	2.63-18.63	1(20.0)	15.1-55.1
Total	25 (100.0)		5(100.00	
ART				
Yes	11 (44.0)	24.54-63.46	3 (60.0)	17.1-102.9
No	13 (52.0)	32.42-71.58	2 (40.0)	2.94-82.94

Unknown/not documented	1 (4.0)	3.68-11.68	0 (0.0)	0.00-0.00
Total	25 (100.0)		5 (100.0)	

* CD4 classification/grade of immunodeficiency[12]

Table 2: Histology and Distribution of Parotid gland Neoplasms

Tumour type/ pathology reported	N	Gender		HIV status			Age groups						
		Male	Female	Positive	Negative	Unknown	≤20	21-30	31-40	41-50	51-60	61-70	>70
Benign epithelial neoplasms	83	36	47	13	44	26	8	14	12	18	15	9	7
Pleomorphic adenoma	74	30	44	12	41	21	8	14	11	16	14	6	5
Warthin's tumour	6	5	1	0	2	4	0	0	0	1	1	3	1
Monomorphic adenoma	3	1	2	1	1	1	0	0	1	1	0	0	1
Malignant epithelial neoplasms	41	16	25	9	18	14	0	3	9	10	6	7	6
Epithelial – myoepithelial carcinoma	9	2	7	4	3	2	0	2	1	2	2	0	2
Mucoepidermoid carcinoma	10	4	6	4	4	2	0	1	4	4	0	1	0
Adenoid cystic carcinoma	2	0	2	0	1	1	0	0	0	0	0	1	1
Adenocarcinoma	5	2	3	0	4	1	0	0	0	1	2	2	0
Acinic cell-carcinoma	6	2	4	1	4	1	0	0	3	1	1	1	0
Carcinoma ex – pleomorphic adenoma	3	1	2	0	1	2	0	0	1	1	1	0	0
Squamous cell carcinoma	5	4	1	0	1	4	0	0	0	1	0	2	2
Metastatic carcinoma	1	1	0	0	0	1	0	0	0	0	0	0	1
Benign non-epithelial neoplasms	4	2	2	0	2	2	2	0	0	1	0	1	0

Tumour type/ pathology reported	N	Gender		HIV status			Age groups						
		Male	Female	Positive	Negative	Unknown	≤20	21-30	31-40	41-50	51-60	61-70	>70
Spindle cell Lipoma	1	1	0	0	0	1	0	0	0	0	0	1	0
Lipoma	1	0	1	0	1	0	0	0	0	1	0	0	0
Calcifying fibrous pseudotumor	1	1	0	0	1	0	1	0	0	0	0	0	0
Giant cell fibroma	1	0	1	0	0	1	1	0	0	0	0	0	0
Malignant non-epithelial neoplasms	6	4	2	2	4	0	4	1	0	1	0	0	0
Lymphoma	2	1	1	1	1	0	2	0	0	0	0	0	0
Rhabdomyosarcoma	2	1	1	0	2	0	2	0	0	0	0	0	0
Parotid synovial sarcoma	1	1	0	0	1	0	0	1	0	0	0	0	0
Neuroendocrine carcinoma	1	1	0	1	0	0	0	0	0	1	0	0	0
Non-neoplastic lesions	9	4	5	2	5	2	1	0	1	3	1	3	0
Fatty infiltration	0	0	0	0	0	0	0	0	0	0	0	0	0
Chronic sialadenitis	1	1	0	0	1	0	0	0	0	1	0	0	0
Adipose metaplasia	1	0	1	0	0	1	0	0	0	0	0	1	0
Chronic inflammation	1	1	0	0	1	0	0	0	0	0	1	0	0
Cyst	3	2	1	1	2	0	1	0	0	1	0	1	0
Reactive lymphoid hyperplasia	1	0	1	0	0	1	0	0	1	0	0	0	0
Normal gland	2	0	2	1	1	0	0	0	0	1	0	1	0

Table 3: Histology and Distribution of Submandibular gland Neoplasms

Tumour type/ pathology reported	N	Gender		HIV status			Age groups						
		Male	Female	Positive	Negative	Unknown	≤20	21-30	31-40	41-50	51-60	61-70	>70
Benign epithelial neoplasms	14	7	7	3	8	3	1	6	4	1	2	0	0
Pleomorphic adenoma	14	7	7	3	8	3	1	6	4	1	2	0	0
Malignant epithelial neoplasms	6	0	6	0	5	1	0	0	0	2	0	3	1
Epithelial-myoepithelial carcinoma	3	0	3	0	2	1	0	0	0	1	0	1	1
Mucoepidermoid carcinoma	1	0	1	0	1	0	0	0	0	1	0	0	0
Adeno carcinoma	1	0	1	0	1	0	0	0	0	0	0	1	0
Squamous cell carcinoma	1	0	1	0	1	0	0	0	0	0	0	1	0
Benign non-epithelial neoplasms	2	1	1	0	2	0	1	0	1	0	0	0	0
Schwannoma	1	1	0	0	1	0	0	0	1	0	0	0	0
Teratoma	1	0	1	0	1	0	1	0	0	0	0	0	0
Malignant non-epithelial neoplasms	0	0	0	0	0	0	0	0	0	0	0	0	0
Non-neoplastic lesions	20	14	6	1	14	5	4	3	1	7	3	1	1
Fatty infiltration	1	1	0	0	0	1	0	0	0	0	1	0	0
Chronic sialadenitis	11	8	3	1	8	2	1	2	1	5	1	1	0
Chronic inflammation	1	0	1	0	1	0	0	0	0	0	0	0	1
Cyst	2	1	1	0	2	0	1	1	0	0	0	0	0
Ranula	1	1	0	0	0	1	0	0	0	0	1	0	0

Mucocoele	1	1	0	0	0	1	1	0	0	0	0	0	0
Reactive lymphoid hyperplasia	1	0	1	0	1	0	0	0	0	1	0	0	0
Normal gland	1	1	0	0	1	0	0	0	0	1	0	0	0
*No result	1	1	0	0	1	0	0	0	0	0	1	0	0

*No pathology report found/located

Table 4: Mean age of HIV positive and HIV negative individuals presenting with an ESGN in the PG and SMG

Epithelial neoplasms		Frequency (%)		p-value	Mean age ± (SD)		p-value
		HIV+	HIV-		HIV+	HIV-	
Parotid gland	Benign	13 (59.1)	44 (71.0)	0.31	40.9 (13.1)	39.3 (15.8)	0.74*
	Malignant	9 (40.9)	18 (29.0)	0.012	38.7 (8.9)	47.9 (11.2)	0.032*
Submandibular gland	Benign	3	8	0.20	34.3 (2.5)	31.0 (12.1)	0.48*
	Malignant	0	5	0.5	0	55.6 (9.6)	0.000*

*The Welsch's t-test is an adaptation of the Student's t-test, which is used when two samples have unequal variances and unequal sample sizes.

Table 5: Immunosuppression vs benign and malignant epithelial neoplasms

Parotid gland	None (CD4>500)	Mild immunosuppression (CD4 350 – 499)	Advanced immunosuppression (CD4 200 – 349)	p-value
Benign epithelial neoplasms	3	5	4	0.55
Malignant epithelial neoplasms	1	3	5	

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Appendix 1:

Protocol Title of the study:

Salivary Gland Tumours in the era of Antiretroviral Treatment

Aim of the Study:

To evaluate the presentation and treatment outcomes of Salivary Gland Tumours in the antiretroviral treatment (ART) era

Objectives:

- To describe and compare the demographics and presentation of Salivary Gland Tumours in HIV infected patients on ART, patients not on ART and uninfected patients

- To determine if HIV infection and access to antiretroviral treatment has altered the histopathological presentation of salivary gland tumours

- To determine if HIV infection and its treatment is associated with a change in morbidity when compared with uninfected patients following definitive treatment of Salivary gland tumours

Background and Literature:

HIV is a global pandemic with an estimated 43 million people infected worldwide.[1] Sub Saharan Africa remains the region most heavily affected. South Africa is home to the world's largest population living with HIV – which in 2010 was estimated at 5.6 million people.[1] Kwazulu Natal has the highest burden of disease in the country with an estimated 37.4% of people living with HIV followed closely by the Gauteng province.[2,3]An estimated 16.9% of our adult population ages 15 – 49 years are HIV positive.[3]

The Link and Impact of HIV on Epithelial Salivary Gland Neoplasms.

- The devastating effect of the global HIV epidemic has been significantly reduced largely due to the administration of Antiretroviral therapy (ART). HIV infection has now become a chronic disease with people living with HIV (PLHIV) now surviving, aging and requiring lifelong care and treatment. Across all age groups, PLHIV have increased risk of chronic complications and comorbidities (non communicable diseases and mental, neurological and substance---use disorders), which can be pre-existing, HIV associated, or due to aging.[4] Benign Parotid Lymphoepithelial Disease and Mucocoeles are well documented to be associated with HIV infection in the literature.[5,6] People living with HIV also manifest an increased risk of cancer. Their susceptibility to opportunistic and viral infections render them at higher risk for cancers that are caused by oncogenic viruses.[7]

Literature regarding this topic has demonstrated an increased risk associated with HIV infection and the development of squamous cell carcinoma in the head and neck region.[7,8]

In particular for salivary gland cancers, it has recently been reported that individuals with AIDS, in the American population had strongly elevated risks for lymphoepithelial carcinoma along with squamous cell carcinoma.[8.9]

This study will enlighten us to aspects of this group of tumours in HIV positive individuals, particularly in those on treatment and in doing so will enable us in future to faster recognize, diagnose and better manage affected individuals.

Key References:

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Study Design:

Retrospective Chart Review

Study Population:

All patients who have presented with Parotid or Submandibular Glands tumours to Inkosi Albert Luthuli Hospital (IALCH) and have been tested for HIV will be included in the study.

Sampling Strategy:

This is a retrospective chart review. All patients with salivary gland tumours who have been tested for HIV will be included in the sample. Patients with no documented HIV results will be excluded.

Statistical Planning (variables/confounders):

- HIV status
- CD4
- HAART
- Gender
- Age at presentation
- Primary site of tumour (Parotid/ Submandibular Gland)
- Pre – operative histology
- Post operative/Final Histology
- Infective post operative complications

Sample Size:

It is estimated that approximately 200 patients have been assessed with salivary gland tumours during but it is unclear how many of these patients had documented HIV results.

Inclusion/ Exclusion Criteria:

Inclusion Criteria All patients presenting with Submandibular or Parotid Salivary Glands tumours at IALCH during the study period, with documented HIV results.

Exclusion Criteria

Patients without a documented HIV result will be excluded

Data Collection Methods and Tools:

A retrospective chart analysis will be undertaken commencing from 2003 (when the IALCH ENT service began) to the present. This will involve analyzing theatre records and treatment charts of patients presenting with Submandibular or Parotid Salivary Gland tumours. A database will be created with the aforementioned data variables. The data collected will be simplified into a numerical binary code and entered into a SPSS data collection spreadsheet. SPSS statistics will be used to analyze the data as captured on the SPSS spreadsheet.

Data Analysis Techniques:

This will be done using SPSS statistics programme with the assistance of Mr. Boikhutso Tlou, who has already been consulted

prior to writing this protocol. Descriptive statistics such as frequencies, percentages, mean, median, standard deviation and interquartile range will be used to summarize results. There will be three groups i.e HIV positive on treatment, HIV positive not on treatment and HIV negative. Data summaries will be given for each group separately. Depending on the distribution parametric or non---parametric tests will be used. If the data is normally distributed ANOVA testing will be used and if nonparametric Kruskal Wallis or Friedmans ANOVA will be used for comparisons between two groups such as T---tests or Mann--- Whitney tests will be used depending on distribution. . A P value of <0.05 will be accepted as indicating that the difference between groups is significant. A P value of >0.05 will considered as evidence in favour of the null hypothesis indicating that the groups compared were from the same population and the difference was not significant.

The following calculations will be conducted:

1. The occurrence of HIV infection in the study population expressed as a percentage

2. The mean age/year of the study group, HIV negative and Positive (ART vs Not on ART) groups

3. Overall occurrence of disease amongst genders --- HIV negative and positive (ART vs Not on ART) groups

4. Comparison of malignant/ benign lesions in the HIV positive (ART vs Not on ART) and negative groups

5. The mean CD4 count (cells/mm3) of the HIV positive (ART vs Not on ART) group

6. The number of patients receiving HAART

7. A comparison of infective post---operative complications in the

HIV positive group receiving HAART and those not yet initiated on HAART

8. Comparison of all tumour subtypes in the HIV positive group (ART vs Not on ART) and HIV negative group

Study Location:

Inkosi Albert Luthuli Hospital (IALCH)

Study Period:

Since records began to the present

Limitations of the Study:

No limits were identified to the study

Ethical Considerations:

The author is the principal investigator in this study.

The author/principal investigator will be primarily responsible for maintaining the confidentiality of the data collected from the study. The study will only commence once prior approval from BREC, IALCH and the Department of Health has been achieved.

The data for each patient will be numerically stored with names omitted. Each patient will be allocated a code identification number, the key of which will be known only to the principal investigator/author. Further the data will be stored on a password---protected computer to which access is restricted to only the principal investigator/author. No personal data (like patients file numbers and identity numbers) will be published in the study. Any forms from the initial data collection will be secured in a locked department office. There will be no direct contact with the patients:

Therefore the study will not require consent from the participants. The author /principal investigator is responsible for the running of the study and will ensure that the study will not interrupt the running of the ENT Department with regards to Service Delivery.

Appendix 2: The Guidelines for Authorship for the Journal selected for submission of the manuscript

South African Journal of Surgery

Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on substantial contribution to:

(i) conception, design, analysis and interpretation of data;

(ii) drafting or critical revision for important intellectual content; and

(iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written

consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Original articles not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to surgery. References should preferably be limited to no more than 15. Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results,* and *Conclusion.*

Scientific letters/short reports, which include case reports, side effects of drugs and brief or negative research findings should preferably be 1500 words or less, with 1 table or illustration and no more than 6 references. Please provide an accompanying abstract not exceeding 150 words.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the SAJS peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Obituaries should be about 400 words and may be accompanied by a photograph.

MANUSCRIPT PREPARATION Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as **'supplementary files'**. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must

be of **high resolution/quality**: 300 dpi or more is preferable but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as '**supplementary files**' upon submission (not embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

REFERENCES Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software. Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given. **Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID).** Authors are encouraged to use the DOI lookup service offered by **CrossRef**.

Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health

Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

PROOFS A PDF proof of an article may be sent to the corresponding author before publication to resolve remaining queries. At that stage, **only** typographical changes are permitted; the corresponding author is required, having conferred with his/her co-authors, to reply within 2 working days in order for the article to be published in the issue for which it has been scheduled.

CHANGES OF ADDRESS Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

CPD POINTS Authors can earn up to 15 CPD CEUs for published articles. Certificates may be requested after publication of the article.

CHARGES There is no charge for the publication of manuscripts.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.

3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted as 'supplementary files' (not in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).
11. Authors' details, included full names, current position, department and place of work as well as email addresses attached as a supplementary file

Appendix 3: Ethical approvals

3.1 Biomedical research eithics committee

3.2 Inkosi Albert Luthuli Hospital approval of study

3.3 Department of Health approval

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI
RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

28 November 2017

Dr K Moodley (201293314)
Discipline of Otorhinolaryngology
School of Clinical Medicine
NRMSM
kerushamoodley@yahoo.com

Dear Dr Moodley

Title: Salivary gland tumours in the era of antiretroviral treatment. **Degree:** MMed
BREC REF NO: BE464/16

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	28 November 2018
Expiration of Ethical Approval:	27 November 2019

I wish to advise you that your application for Recertification received on 26 November 2018 for the above protocol has been **noted and approved** by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 11 December 2018.

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc supervisor: samany@ukzn.ac.za

cc administrator: konar@ukzn.ac.za

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

Physical Address: 800 Bellair Road, Mayville, 4058
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Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ ialch.co.za
www.kznhealth.gov.za

Office of The Medical Manager
IALCH

21 August 2017

Dr K Moodley
Discipline of Ophthalmology
School of Clinical Medicine

Dear Dr Moodley

Re: Approved Research: Ref No: BE 464/16: Salivary gland tumors in the era of antiretroviral treatment.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

.....

Dr L P Mtshali
Medical Manager

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

HRKM Ref: 375/17
NHRD Ref: KZ_201709_043

Date: 10 October 2017
Dear Dr K. Moodley
UKZN

Approval of research

1. The research proposal titled **'Salivary Gland Tumours in the era of Antiretroviral Treatment'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge

Chairperson, Health Research Committee

Date: 12/10/17

Appendix 4: Data collection sheet

CASE ID	AGE	GENDER	GLAND	INITIAL HISTOLOGY	FINAL HISTOLOGY	RVD STATUS	CD4 COUNT	POST OP WOUND BREAKDOWN/INFECTION

Appendix 5: Raw data – see attachment 1

PATIENT ID	AGE	GENDER	GLAND	INITIAL HISTOLOGY	FINAL HISTOLOGY	RVD STATUS	CD4 COUNT /HAART	POST OP WOUND BREAKDOWN/INFECTION
163807	53	M	P	PLEO	PLEO	NEG	N/A	NIL
165407	76	M	P	UNKNOWN	METASTATIC CA	U	N/A	NIL
135810	11	M	S	UNKNOWN	MUCOCOELE	U	N/A	NIL
169171	24	F	P	PLEO - FNAC	PLEO	POS	273/N	NIL
170459	29	M	P	PLEO-FNAC	PLEO	NEG	N/A	NIL
138040	88	M	P	MALIGNANT	SCC	U	N/A	NIL
171408	43	F	S	PLEO	RLH	NEG	N/A	UNKNOWN
176388	24	M	S	PLEO	PLEO	NEG	N/A	NIL
174863	39	F	P	SPINDLE CELLS	PLEO	U	N/A	NIL
68255	47	M	S	INCONCLUSIVE	CS WITH S	NEG	N/A	NIL
184113	67	F	P	PLEO	PLEO	U	N/A	NIL
185069	23	M	S	PLEO	PLEO	U	N/A	NIL
186765	44	F	P	PLEO	PLEO	NEG	N/A	NIL
193026	72	M	P	MIXED INFL CELLS	WHARTINS	U	N/A	NIL
191214	41	M	S	UNKNOWN	CS WITH S	NEG	N/A	NIL
186930	47	F	P	RLH	ACINIC CELL CA	NEG	N/A	NIL
187185	54	F	P	PLEO	PLEO	U	N/A	NIL
197218	70	M	P	ATYPICAL CELLS	WHARTINS	U	N/A	MM PARESIS
198385	DAY 1	F	S	NOT DONE	TERATOMA	NEG	N/A	NIL
194226	61	F	S	NIL	ADENO CA	NEG	N/A	NIL
198744	48	M	P	NIL	CS	NEG	N/A	NIL
200726	51	F	S	PLEO	PLEO	NEG	N/A	NIL
205795	51	F	P	INCONCLUSIVE	PLEO	U	N/A	NIL

207918	52	F	P	PLEO	EM CA	POS	358-N0	UNKNOWN
208466	51	F	P	BLOOD ONLY	LG ADENO CA	NEG	N/A	NIL
207903	69	F	P	ADENOID CYSTIC CA	ADENOID CYSTIC CA	U	N/A	MM PARESIS
209700	45	M	P	MIXED CELLS - BENIGN	PLEO	NEG	N/A	NIL
212702	52	F	P	HAEMORRHAGIC CELLS	EM CA	NEG	N/A	NIL
211285	49	F	P	UNKNOWN	EM CA	NEG	N/A	NIL
213774	45	F	P	PLEO	PLEO	NEG	N/A	NIL
214819	37	F	S	INCONCLUSIVE	PLEO	POS	307 - NO	MM PARESIS
214508	67	M	P	ATYPICAL CELLS	ADENO CA	U	N/A	NIL
215709	30	F	P	PLEO	LG MUCO CA	POS	348 - NO	NIL
218095	60	M	P	PLEO	PLEO	NEG	N/A	NIL
218027	48	F	P	AMORPHOUS	LIPOMA	NEG	N/A	NIL
218678	51	F	P	INCONCLUSIVE	ADENO CA	NEG	N/A	NIL
218123	46	F	P	PLEO	PLEO	U	N/A	MM PARESIS
217535	85	F	P	PLEO	BASAL CELL ADENOMA	U	N/A	FREYS
221988	43	M	P	UNKNOWN	PLEO	NEG	N/A	MM PARESIS
224572	40	F	P	INCONCLUSIVE	HG MUCO CA	NEG	N/A	NIL
220097	70	M	P	PLEO	SPINDLE CELL LIPOMA	U	N/A	TEMPORAL PARESIS
220439	8	F	P	BLOOD ONLY	GIANT CELL FIBROBLASTOMA	U	N/A	NIL
226525	64	M	P	ATYPICAL CELLS	HG MUCO CA	U	N/A	NIL
221210	27	M	S	AMORPHOUS	EPIDERMOID CYST	NEG	N/A	NIL
230189	55	F	P	ATYPICAL CELLS	PLEO	NEG	N/A	NIL
226622	30	M	S	NIL	CS WITH S	U	N/A	NIL
205149	35	F	P	PLEO	PLEO	POS	568 - YES	NIL
232312	33	M	P	PLEO	PLEO	U	N/A	MM PARESIS
234733	41	M	P	UNKNOWN	PLEO	U	N/A	GRADE 1 CNVII PARESIS
233401	22	M	S	PLEO	PLEO	NEG	N/A	MM PARESIS

227842	15	F	P	PLEO	PLEO	NEG	N/A	NIL
235456	76	F	P	PLEO	EM CA	U	N/A	NIL
229044	46	M	S	NOT DONE	CS WITH S	NEG	N/A	HYPOGLOSSAL NERVE PARESIS
229541	38	M	P	PLEO	PLEO	NEG	N/A	NIL
236857	27	F	S	ATYPICAL CELLS	PLEO	NEG	N/A	MM PARESIS
236554	38	M	P	BENIGN DUCTAL CELLS	BASAL CELL ADENOMA	NEG	N/A	NIL
239709	25	M	P	ATYPICAL CELLS	PAROTID SYNOVIAL SARCOMA	NEG	N/A	NIL
163921	47	F	S	NIL	CS WITH S	NEG	N/A	NIL
241949	32	F	S	PLEO	PLEO	POS	717-YES	NIL
241584	58	F	P	PLEO	PLEO	U	N/A	NIL
242611	39	F	P	PLEO	PLEO	NEG	N/A	MM PARESIS
130341	69	M	S	NIL	CS WITH S	NEG	N/A	NIL
243152	29	F	P	ATYPICAL CELLS	EM CA	NEG	N/A	NIL
215024	11	F	P	NIL	RHABDO	NEG	N/A	NIL
240070	26	F	S	NIL	CS	POS	322-NO	POST OP SEPSIS
210661	37	M	S	INCONCLUSIVE	CS	NEG	N/A	NIL
248006	39	F	P	INCONCLUSIVE	RLH	U	N/A	MM PARESIS
231469	56	F	P	PLEO	PLEO	POS	305-NO	NIL
249709	49	F	P	DUCTAL CELLS	LG MUCO CA	NEG	N/A	NIL
227847	25	F	P	PLEO	PLEO	NEG	N/A	NIL
246782	29	F	P	PLEO	PLEO	NEG	N/A	NIL
250287	56	F	P	PLEO	CA EX PLEO	U	N/A	NIL
229529	32	F	P	INCONCLUSIVE	MUCO CA	POS	449-U	MM PARESIS
253868	53	F	S	NIL	CS	U	N/A	NIL
254601/621	72	F	S	PLEO	EM CA	U	N/A	NIL
257477	66	F	P	PLEO	PLEO	U	N/A	MM PARESIS

256943	45	F	P	PLEO	CA EX PLEO	U	N/A	MM PARESIS
14955	83	M	P	SCC	SCC	U	N/A	NIL
258567	41	F	P	INCONCLUSIVE	PLEO	U	N/A	MM PARESIS
260521	34	M	P	INCONCLUSIVE	PLEO	NEG	N/A	MM PARESIS
264767	24	M	P	PLEO	PLEO	NEG	N/A	MM PARESIS
261057	26	M	P	ATYPICAL CELLS	PLEO	NEG	N/A	LMN CNVII PARESIS
265910	26	F	S	ATYPICAL CELLS	PLEO	U	N/A	NIL
174799	49	M	P	SCC	SCC	NEG	N/A	NIL
239601	15	F	P	INCONCLUSIVE	PLEO	POS	373-NO	NIL
268723	16	M	S	DUCTAL CELLS	PLEO	NEG	N/A	NIL
265648	47	F	S	PLEO	PLEO	NEG	N/A	NIL
269874	19	M	P	NIL	PLEO	U	N/A	NIL
270409	43	M	S	ADENO CA	NORMAL GLAND	NEG	N/A	MM PARESIS
268716	57	F	P	PLEO	PLEO	NEG	N/A	MM PARESIS
269371	30	M	P	PLEO	PLEO	NEG	N/A	MM PARESIS
246284	32	F	P	PLEO	PLEO	U	N/A	LMN CNVII PARESIS
271493	48	F	P	UNKNOWN	PLEO	U	N/A	MM PARESIS
269386	40	M	P	PLEO	CA EX PLEO	NEG	N/A	LMN CNVII PARESIS
122192	52	M	P	ACINIC CELLS	WHARTINS	U	N/A	MM PARESIS
250811	35	F	P	EMMYO COMPONT	PLEO	POS	534-YES	NIL
275161	33	M	P	ATYPICAL CELLS	MUCO CA	POS	258-YES	MM PARESIS
275200	46	F	P	PLEO	PLEO	NEG	N/A	MM PARESIS
250285	46	M	P	INCONCLUSIVE	WHARTINS	NEG	N/A	NIL
271472	11	M	S	NIL	CS WITH S	NEG	N/A	NIL
273494	39	M	P	MIXED INFL CELLS	LG MUCO CA	U	N/A	LMN CNVII PARESIS
275316	59	M	P	PLEO	PLEO	NEG	N/A	LMN CNVII PARESIS
277875	55	M	P	PLEO	CHRONIC INFLAMMATION	NEG	N/A	MM PARESIS
27896	34	M	P	ACINIC	ACINIC CELL CA	NEG	N/A	NIL

7				CELLS				
2292	34	M	P	ACINIC CELL CA	ACINIC CELL CA	NEG	N/A	NIL
121548	76	F	P	ADENOID CYSTIC	ADENOID CYSTIC CA	NEG	N/A	NIL
12310	88	M	P	ATYPICAL CELLS	PLEO	U	N/A	NIL
143408	63	F	P	ACINIC CELLS	ADIPOSE METAPLASIA	U	N/A	NIL
284286	72	F	S	UNKNOWN	CHRONIC INFLAMMATION	NEG	N/A	NIL
281106	29	F	P	DUCTAL CELLS	PLEO	NEG	N/A	NIL
279777	25	F	P	PLEO	PLEO	NEG	N/A	FREYS +MM PARESIS
282418	49	F	P	BLOOD ONLY	BASAL CELL ADENOMA	POS	257-YES	WOUND BREAKDOWN
285328	54	M	P	PLEO	PLEO	NEG	N/A	LMN CNVII PARESIS
292833	34	M	S	PLEO	PLEO	POS	132-YES	NIL
264048	11	M	S	NIL	RANULA	POS	U-YES	NIL
295486	18	M	P	PLEO	PLEO	NEG	N/A	LMN CNVII PARESIS
295468	54	F	P	DUCTAL CELLS	PLEO	NEG	N/A	NIL
299499	47	M	S	NIL	CS WITH S	NEG	N/A	NIL
269347	14	M	P	DUCTAL CELLS	CALCIFYING FIBROUS PSEUDOTUMOUR	NEG	N/A	NIL
290981	69	F	P	PLEO	PLEO	U	N/A	NIL
302067	17	F	P	MIXED LYMPHOCYTES	HG HODGKINS	POS	U-YES	NIL
302594	33	M	S	INCONCLUSIVE	SCHWANNOMA	NEG	N/A	NIL
303072	65	M	P	LYMPHOCYTES	LE CYSTS	NEG	N/A	NIL
303066	75	F	P	PLEO	PLEO	NEG	N/A	NIL
303797	49	F	P	BENIGN DUCTAL CELLS	LG MUCO CA	NEG	N/A	NIL
204257	56	M	S	INCONCLUSIVE	FATTY INFILTRATION	U	N/A	NIL
308759	31	F	P	PLEO	PLEO	U	N/A	NIL
309292	49	M	P	PLEO	LG MUCO CA	POS	300-YES	NIL
307696	15	F	S	NIL	KERATINOUS CYSTS	NEG	N/A	NIL

303844	46	F	P	INCONCLUSIVE	LG ADENO CA	NEG	N/A	LMN CNVII PARESIS
310874	45	M	P	BLOOD ONLY	PLEO	NEG	N/A	NIL
311448	64	F	P	PLEO	PLEO	U	N/A	MM PARESIS
275676	41	M	P	MALIGNANT CELLS ? LYMPHOMA	NEUROENDOCRINE CA	POS	258-NO	NIL
306143	49	F	P	PLEO	PLEO	NEG	N/A	NIL
290663	65	M	P	NOT DONE	SCC	U	N/A	NIL
314034	49	M	P	PLEO	EM CA	POS	216-NO	NIL
313541	51	M	P	PLEO	PLEO	NEG	N/A	NIL
305642	68	F	P	INCONCLUSIVE	NORMAL GLAND-ADJACENT ADENOCA ? PRMARY	NEG	N/A	NIL
143168	43	M	P	PLEO	PLEO	POS	430-NO	MM PARESIS
315521	75	M	P	ATYPICAL CELLS	PLEO	U	N/A	NIL
318762	60	F	S	BLOOD ONLY	EM CA	NEG	N/A	NIL
187503	48	F	P	INCONCLUSIVE	NORMAL GLAND-ADJACENT METASTATIC LN	POS	288-NO	NIL
297018	47	F	S	CS	LG MUCO CA	NEG	N/A	NIL
317167	72	F	P	BLOOD ONLY	PLEO	U	N/A	NIL
318801	25	M	P	INCONCLUSIVE	PLEO	NEG	N/A	MM PARESIS
320332	32	F	P	INCONCLUSIVE	PLEO	NEG	N/A	MM PARESIS
334387	64	F	P	?ACINIC /?ADENO CA	ACINIC CELL CA	U	N/A	NIL
322868	66	M	P	MIXED INFL CELLS	WHARTINS	U	N/A	NIL
322368	23	F	P	DUCTAL CELLS	PLEO	NEG	N/A	NIL
119578	63	F	P	?PLEO	SCC	U	N/A	NIL
330148	67	M	P	?PLEO	PLEO	NEG	N/A	NIL
336920	8	M	P	BLOOD ONLY	ALL	NEG	N/A	NIL
329113	20	M	P	INCONCLUSIVE	PLEO	NEG	N/A	MM PARESIS
317510	29	M	S	PLEO	PLEO	NEG	N/A	NIL

323412	58	M	S	PLEO	NO RESULT	NEG	N/A	MM PARESIS
330139	45	F	P	BENIGN LESION	PLEO	POS	U-YES	NIL
335828	77	M	P	LG MUCO CA	PLEO	U	N/A	MM PARESIS
338438	55	F	S	BLOOD ONLY	PLEO	U	N/A	NIL
220125	60	F	P	PLEO	ACINIC CELL CA	NEG	N/A	LMN CNVII PARESIS
367018	30	M	P	UNKNOWN	EM CA	POS	329-NO	NIL
328151	82	F	P	BLOOD ONLY	EM CA	U	N/A	NIL
331765	17	F	P	PLEO	PLEO	U	N/A	NIL
331702	64	F	P	PLEO	PLEO	POS	610-NO	NIL
339408	64	M	P	INCONCLUSIVE	ADENO CA	NEG	N/A	NIL
342409	34	F	P	PLEO	EM CA	NEG	N/A	NIL
319394	31	M	P	PLEO	PLEO	NEG	N/A	NIL
314773	44	F	S	PLEO	EM CA	NEG	N/A	LINGUAL NN PARESIS
341372	23	F	P	PLEO	PLEO	NEG	N/A	NIL
269362	57	M	P	PLEO	PLEO	NEG	N/A	NIL
344395	66	F	S	INCONCLUSIVE	SCC	NEG	N/A	NIL
346946	66	F	P	SCC	WHARTINS	NEG	N/A	NIL
349143	42	F	P	MIXED INFL CELLS	LG MUCO CA	NEG	N/A	NIL
339571	39	F	P	PLEO	ACINIC CELL CA	POS	451-NO	NIL
345801	52	F	P	PLEO	PLEO	NEG	N/A	NIL
361046	12	M	P	INCONCLUSIVE	RHABDO	NEG	N/A	NIL
343165	48	F	P	PLEO	PLEO	POS	400-YES	NIL
363664	11	M	P	PLEO	PLEO	NEG	N/A	NIL
360519	11	M	P	INCONCLUSIVE	SALIVARY DUCT CYST	NEG	N/A	NIL
294516	32	M	S	PLEO	PLEO	NEG	N/A	MM PARESIS
367403	26	M	P	PLEO	PLEO	NEG	N/A	LMN CNVII PARESIS
234729	46	M	P	PLEO	PLEO	POS	290-YES	NIL

297551	42	M	P	PLEO	PLEO	POS	480-NO	NIL
370080	30	F	P	PLEO	PLEO	POS	375-YES	NIL
265913	16	F	P	BLOOD ONLY	PLEO	NEG	N/A	NIL