SINONASAL TUMORS IN ADULT PATIENTS: CLINICOPATHOLOGICAL PERSPECTIVE FROM CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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Declaration

I, **Dr Lungile Precious Setoaba**, declare that this research report is my own work. It is submitted for the degree of MMed (Otorhinolaryngology) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Dr Lungile Precious Setoaba

On this 30th day of January 2021

Dedication

I would like to dedicate this paper to my late mother, Thembekile Agnes Setoaba, who passed away in 2002. She has always been my pillar of strength. I will forever hold her shining smile in my heart.

Publications and presentations

This paper has not been published nor presented at a congress.

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ABBREVIATIONS AND DEFINITIONS OF TERMS

CHBH - Chris Hani Baragwanath Hospital

DLBCL - Diffuse large B-cell lymphoma

DWI - Diffusion Weighted Imaging

EBV- Epstein Barr Virus

EBV ISH - Epstein Barr Virus In Situ Hybridization

ENT- Ear Nose and Throat

HIV - Human Immunodeficiency Virus

NHLS - National Health Laboratory Service

NPC - Nasopharyngeal Carcinoma

ORL - Otorhinolaryngology

SNOMED - Systematized Nomenclature of Medicine

SCC - Squamous Cell Carcinoma

SNUC - Sinonasal Undifferentiated Carcinoma

IMRT- Intensity Modulated Radiation Therapy

WHO - World Health Organization

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Abstract

Sinonasal tumors are rare tumors of the nasal cavity and paranasal sinuses. Demographics of adult patients with sinonasal tumours who presented at the Otorhinolaryngology (ORL) department at Chris Hani Baragwanath Academic Hospital between July 2013 and July 2016 were reviewed. The spectrum of these sinonasal tumours and the influence of concomitant pathology such as Epstein Barr Virus (EBV) were evaluated. Presenting symptoms of benign and malignant tumors were compared. This record review study evaluated a spectrum of histopathological types of sinonasal tumors by using SNOMED codes to access the histopathology reports at National Health Laboratory Service (NHLS) at CHBAH. Patient demographics, presenting signs and symptoms and associated concomitant pathology were reviewed. Lymphoma was the most prevalent tumor at 45% and was followed by invasive poorly differentiated squamous cell carcinoma at 19%. The average age range of patients was 30-39 years. The nasal cavity was found to be the most common site for these tumours in 66% of the cases, followed by the maxillary sinus at 25%. Human Immunodeficiency Virus infection was documented in 45% of the cases and these were mostly associated with malignant tumours. There was a significant association between malignant tumor subtype, particularly lymphoma and EBV. EBV was present in 26% of the cases that were assessed for the virus. Nasal obstruction was the most common presenting symptom. Lymphoma is the most common sinonasal tumour in adult patients at the CHBAH Otolaryngology department. HIV and EBV were found to be important viruses that influenced their development. Squamous cell carcinoma was found to be less common compared to what has been described in the literature, and, perharps HIV has contributed to this shift in the trend.

1. INTRODUCTION

1.1 Background

The paranasal sinuses and the nasal cavity in the human body occupy a relatively limited anatomical space, yet these sites may harbor complex and diverse neoplasms. These neoplasms may develop form a variety of structures that are indigenous to these regions. While some of the tumors may be similar to those occurring elsewhere in the human body such as squamous cell carcinoma and adenocarcinoma, a few of the tumors such as the olfactory neuroblastoma are unique to this region. (1) It is essential to appreciate the complex anatomical structure displayed by the paranasal sinuses to appreciate the extent of the tumors outlined in this study.

1.2 Anatomy

1.2.1 The nasal cavity

The nasal cavity is formed by the bony and cartilaginous skeleton. It extends anteriorly from the nasal vestibule to terminate posteriorly at the choanae. It is separated in the midline by the nasal septum. The bony framework is formed by the nasal bones, the frontal process of the maxilla and the nasal part of the frontal bone. The cartilaginous frame work is formed by the septum, lateral nasal cartilage, major and minor alar cartilages. The nasal septum is formed by the septal cartilage anteriorly, the vomer posterior inferiorly, and the perpendicular plate of the ethmoid bone posteriorly. The floor is formed by the palate which is formed by the palatine processes of the maxillae and the horizontal portions of the palatine bones. The roof is formed by the very thin cribriform plate. The lateral walls are formed by the superior, middle and inferior turbinates. The turbinates are attached anteriorly and have a free edge posteriorly. The ethmoid and the maxillary ostia are also found on the lateral wall and open into the nasal cavity. The nasal fossa is related laterally to the superior turbinate and medially to the

nasal septum. The nasal fossa houses the olfactory recess which appears as yellowish mucosal epithelium. The mucosa houses olfactory bipolar olfactory epithelium which crosses through the cribriform plate and terminate at the olfactory bulb. The nasal cavities and paranasal sinuses are lined by pseudostratified columnar ciliated epithelium with goblet cells. The blood supply to the nasal septum is from the external and internal carotid artery. The septum is supplied by the branch of the internal carotid artery which is the ophthalmic artery that gives off the anterior and posterior ethmoidal arteries which supply the septum. Posteriorly the septum receives blood supply from the sphenopalatine and greater palatine arteries which are branches of the maxillary artery, a branch of the external carotid artery. The facial artery gives off the septal branch which also supplies the septum. The venous drainage is via the sphenopalatine, facial and ophthalmic veins. The lymphatic drainage is via the submandibular and upper deep cervical nodes. The blood supply to the lateral wall of the nasal cavity is via the anterior, posterior ethmoidal artery, the sphenopalatine artery, the lateral nasal branch which is the branch of facial artery, and the greater palatine artery. (52,54)

1.2.2 The posterior nasal space (PNS)

This area is also referred to as the chaonae. It is formed by the two oval openings between the nasal cavities and the nasopharynx. The rigid openings are completely surrounded by bone. Inferiorly, it is formed by the posterior border of the horizontal plate of the pterygoid process. Medially it is formed by the posterior surface of the vomer. The roof of the choanae is formed anteriorly by the ala of the vomer and the vaginal process of the medial plate of the pterygoid process. Posteriorly it is formed by the body of sphenoid bone.(52)

1.2.3 The paranasal sinuses

The paranasal sinuses develop as outgrowths from the nasal cavities and erode into the surrounding bones. Sinuses are absent at birth. They are lined by respiratory mucosa,

which is ciliated and secretes mucous. The paranasal sinuses are formed by the bilateral paired frontal and maxillary sinuses, the ethmoidal sinuses which are divided into anterior, middle and posterior air cells and the sphenoid sinus. All paranasal sinuses open into the nasal cavities. Paranasal sinuses are innervated by the branches of the trigeminal nerve.

1.2.4 The ethmoid sinus complex

The ethmoidal sinuses are thin walled cavities in the ethmoidal labyrinth. They are formed by 3 large and 18 small sinuses. The ethmoidal sinuses are divided into anterior, middle, and posterior air cells according to the location of their ostia. The posterior air cells are larger and fewer than the anterior air cells. The anterior group which is referred to as the infundibular group is made up of about 11 air cells open at the infundibulum. The middle group which is referred to as bullar sinuses and is usually made up of 3 cells, opens on or above the ethmoid bulla. The posterior group which is usually made up of between one and seven cells opens into the superior meatus. This air cell complex lies between the orbit and upper nasal fossa. The cribriform plate connects the left and right group of ethmoidal complex. The cribriform plate is an essential landmark with regards to sinonasal tumors. Cribriform plate erosion signifies erosion of the skull base and extension of the tumor to the intracranial cavity. The medial wall of the ethmoids is formed by the lamina from which the middle and superior turbinates are attached. The lateral ethmoid wall is formed by a thin lamina papyracea that separates ethmoid cells from the orbit. The roof of the ethmoids is formed by the fovea ethmoidalis which is the medial extension of the orbital plate of the frontal bone. (1) The blood supply to the ethmoid sinuses is via the sphenopalatine artery and the anterior and posterior ethmoidal arteries. The nerve supply is via the orbital branches pterygopalatine, the anterior and posterior ethmoidal nerves. The lymphatic drainage is via the submandibular nodes and the retropharyngeal group of lymph nodes. (52)

1.2.5 The frontal sinus

The frontal sinuses are paired sinuses located between the anterior and posterior cranial tables. They are prominent in males and rarely symmetrical. The floor of the frontal sinus forms the roof of the orbit. It is bounded posteriorly by the anterior cranial fossa. The frontal sinus drains into the frontal recess. The frontal recess is occupied by the cells that determine the drainage pathway of the sinus. The frontal sinus ostium is the narrowest region between the frontal sinus and the frontal recess. The anterior part is formed by the frontal sinus beak and the skull base posteriorly. The frontal sinus is sometimes associated with Kuhn (frontal) cells namely:

I – Type I frontal cell (one air cell superior to agger nasi)
II – Type II frontal cell (multiple air cells superior to agger nasi and inferior to orbital roof)
III – Type III frontal cell (reaches the frontal sinus and is continuous with agger nasi cell)
IV – Type IV frontal cell is located within the frontal sinus

The Agger nasi cell is the anterior most air cell found anterolateral and inferior to the frontal recess. (54) The arterial supply to the frontal sinus is via the supraorbital and anterior ethmoidal arteries. (53) The nerve supply is from the supraorbital nerve. The lymphatic drainage to these sinuses is via the submandibular nodes. (52)

1.2.6 The sphenoid sinus

The sphenoid sinus is located at approximately the center of the skull above the nasopharynx. It is paired and lies within the body of sphenoid. Its posterior wall is formed by the clivus. It relates laterally to the cavernous sinus, the internal carotid artery and cranial nerves II–VI, and it is intimately related to the optic canal. The optic nerve and internal carotid artery may run directly beneath the mucosa of the lateral wall of the sphenoid sinus, without a bony covering. The sphenoid sinus is bordered superiorly by the sella turcica, the pituitary and by the anterior and middle cranial fossae. Inferiorly it is related to the nasal cavities. It opens at the sphenoethmoidal recess. The sphenoid sinus has 3 types of cells which signify the extent of pneumatization:

I. Conchal type - It is commonly found in children. The area of inferior to the sella turcica is a solid block of bone that has no pneumatization.
II. Presellar type – With the type, pneumatization does not extend beyond the coronal plane defined by the anterior sellar wall.

III. Sellar type - pneumatization extends into the body of the sphenoid and extends to the clivus

The blood supply to the sphenoid sinus is via the posterior ethmoidal artery. (52,55) The nerves supply the posterior ethmoidal nerves and orbital branches. The lymphatic drainage is via the retropharyngeal group of nodes.

1.2.7 The maxillary sinus

The maxillary sinuses are paired sinuses that lie within the body of the maxilla. Each sinus is pyramidal in shape consisting of the base, apex, roof and the floor. The superolateral surface (roof) is related above to the orbit. The anterolateral surface is related below to the roots of the upper molar and premolar teeth and in front of the face. The posterior wall is related posteriorly to the infratemporal fossa. The maxillary sinus opens into the hiatus semilunaris. It borders the nasal cavity laterally. Behind the maxillary sinus is the pterygopalatine fossa, which is traversed by the maxillary artery along with branches of the trigeminal nerve and autonomic nervous system. The variation of the maxillary sinus is the presence of the Haller cell, commonly known as the infraorbital cell. They are the extension of the anterior ethmoidal cells along the floor of the orbit. (56) The blood supply to the maxillary sinus is via the facial artery, the greater palatine artery, and the infraorbital vessels. The nerve supply is via the infraorbital nerve, and superior alveolar nerves. The lymphatic drainage is via the submandibular lymph nodes. (52)

1.3 Epidemiology and etiology

Sinonasal tumors occur in the nasal cavity and paranasal sinuses. In the literature, it is noted that 3% of sinonasal tumors are malignant. (1,2) With regards to the anatomical site, 60% of sinonasal tumors originate in the maxillary sinus, 20-30% in the nasal cavity, 10-15% in the ethmoid sinus and 1% in the sphenoid and/or frontal sinuses. (3) The most common (70-80%) malignant sinonasal histological type is the squamous cell carcinoma, followed by adenocarcinoma and adenoid cystic carcinoma (10% each). (4) These tumors are seen more commonly in males than females and are frequently seen in the fourth and eighth decades of life. (5)

The annual incidence of cancer of the nasal cavity and paranasal sinuses is reported to be low in most populations (1 in 100 000 per annum). (6) However, higher rates are recorded in Japan and certain parts of China and India. Squamous cell carcinoma is the most common. Over time, a stable incident rate and a slight decline has been reported in recent decades.

Benign sinonasal tumors have been associated with exposure to certain viruses such as the Human Papillomavirus (HPV) 6 and 11. HIV infection often presents as an association in certain patients with these tumors, but its role has not been entirely determined. Exposure to allergens, air pollution and industrial carcinogens influences the development of benign tumors. (6,7,8) Tobacco, alcohol and industrial exposure to heavy metal particles (such as nickel and chromium), particularly for workers in the leather, textile, furniture and wood industries, are considered carcinogenic and are associated with various types of malignant sinonasal tumors. Adenocarcinoma is known to be associated with exposure to wood dust and leather tanning. (8)

1.4 Classification of sinonasal tumors

The World Health Organization (WHO) has a broad classification for sinonasal tumors. This classification divides sinonasal tumors according to the tissue of origin and whether they are benign or malignant. The histological types include epithelial tumors, hematolymphoid tumors, skin and muscle tumors, bone and cartilage tumors, neuroectodermal tumors, germ cell tumors and metastatic tumors. (1)

1.4.1 Benign neoplasms

Epithelial tumors

The benign epithelial tumors consist of papillomas, salivary gland adenomas and mixed tumors known as pleomorphic adenomas. Papillomas in the sinonasal tract may have an inverted growth pattern. These are termed inverted papilloma and categorized as

sinonasal Schneiderian papilloma. These neoplasms are known to have high recurrence rates and can be locally aggressive. HPV has been implicated in the development of this tumor. Treatment is complete surgical resection. Incomplete resection results in tumour reoccurrence. (1,36)

Soft tissue tumors

Soft tissue tumours are very rare tumours of the sinonasal tract and consist of nerve sheath tumours, hemangioma, angiofibroma, meningioma, myxoma, and leiomyoma. Neurofibroma is a peripheral nerve tumour and it is very rare in the sinonasal tract. It is associated mainly with neurofibromatosis. Associated with this tumour are schwannomas which arise from the nerve sheath and are associated with Neurofibromatosis 2 (NF2). Malignant transformation of these tumours is very rare and often associated with neurofibroma. (9) Juvenile angiofibroma is a vascular tumour that originates from the sphenopalatine foramen and grows towards the nasal cavity, or may extend into the nasopharynx or extend laterally into the pterygopalatine foramen. It is more common in males and if found in females genetic mosaicism should be considered. (10) It commonly presents in a young male with nasal obstruction and epistaxis. Preoperative embolization prior to surgical excision is performed to minimize the risk of intra-operative bleeding.

Bone and cartilage tumors

Bone and cartilage tumours may affect the sinonasal tract and present with disfigurement of the face and compression of the cranial nerves and other vital structures. They consist of osteoma, fibrous dysplasia, and ossifying fibroma. Fibrous dysplasia is the most common of the tumours and commonly involves the craniofacial skeleton. Osteoma is most commonly found in the frontal and ethmoid sinuses. They are often found incidentally and are asymptomatic. These may present as multiple tumours in multiple sites in Gardner syndrome. (11) Ossifying fibroma consists of mattered bone originating from mesenchyme of peridontal ligament and commonly occurs in the mandible and less commonly in the sinus walls and the maxilla. They are seen mostly in young females and can be locally aggressive**.** (12)

1.4.2 Malignant neoplasms

Squamous cell carcinoma is the most common epithelial malignancy followed by adenocarcinoma. These are both commonly found in males. Occupational exposure to irritants such as wood dust, chrome and nickel are considered significant risk factors for the development of these tumors**.** (5,6,8,13) Sinonasal undifferentiated carcinoma (SNUC) is an aggressive neoplasm without evidence of squamous or glandular differentiation. It is often considered a neuroendocrine tumor due to the similarities it shares with those tumors. It is commonly seen in males and often presents with nodal disease and distant metastasis. This tumor has a poor prognosis with a 5-year survival rate of less than 20%. (14)

Adenoid cystic carcinoma is the most common salivary gland tumor and is found predominantly in men. It has the potential for perineural spread and intracranial extension affecting most commonly the maxillary division of the Trigerminal nerve. (15)

Non-Hodgkin lymphoma is the most common hematolymphoid neoplasm of the sinonasal tract. (16) Sinonasal lymphoma tends to occur more commonly in the nasal cavity compared to the paranasal sinuses. Other types of hematolymphoid neoplasms include plasmacytoma, myeloid, histiocytic sarcomas and Langerhans cell histiocytosis.

Neuroectodermal malignancies

Esthesioneuroblastoma is a neuroendocrine tumor arising from the olfactory nerve. It commonly occurs in males and has no known associated risk factors to date. It is a highly vascular tumor and epistaxis is often a commonly presenting symptom. Intracranial and intra-orbital extension is often seen at presentation. Nodal disease occurs in 15-20% of the cases and it is often associated with recurrence. (17)

Sinonasal melanoma is a very rare mucosal melanoma. (22) It is a very aggressive sinonasal tumor and caries a very poor prognosis. The lesion tends to be vascular and epistaxis is a common presentation.

Malignant tumors of soft tissue, bone and cartilage

Mesnchymal tumors originate from muscle, bone and cartilage. Osteosarcoma and chondrosarcoma occur commonly in adults, while rhabdomyosarcoma is seen mostly in children. These tumors tend to be aggressive with a 5-year survival rate of 47%. (23)

1.5 Imaging of sinonasal tumors

Imaging is key to the evaluation and diagnosis of the sinonasal tumors. It is helpful in assessing the precise location of the lesion and assists with identifying involved local and distant structures. Imaging is also essential in planning surgical and oncological treatment. The computed tomography scan (CT scan) provides detailed bone anatomy and involvement of surrounding structures, the vascularity of the lesion and texture. In sinonasal pathology, essential anatomical structures such as the anterior and middle cranial fossa, orbit, pterygopalatine fossa, palate, or infratemporal fossa (masticator and parapharyngeal space) are of importance to evaluate as their involvement influences surgical planning.

A CT scan is the most commonly used imaging modality because of its wider availability, easy access, lower cost, and potential to offer greater anatomic detail. In comparison to MRI, CT is particularly effective in delineating calcifications and evaluating the pattern of bone invasion. In addition, certain lesions on imaging are typical of a specific diagnosis, though histological diagnosis is still required. Bone changes such as bone erosion and destruction can give information with regards to tumor aggression. High grade malignancies such as lymphoma and the squamous cell carcinoma show extensive bony destruction, whereas small round cell tumors show permeative invasion and lack of bone destruction. Benign lesions and low grade malignancies may cause bone expansion due to their slow and expansive growth. Calcifications are observed in some sinonasal disorders, such as adenocarcinoma, olfactory neuroblastoma, inverted papilloma, fibrous dysplasia, osteoma, osteosarcoma, cartilaginous tumor, fungal sinusitis, and dentigerous tumor. Characteristic patterns of

bone invasion help predict the tumor histology. Contrast-enhanced CT is invaluable for the identification of the feeding artery and for the diagnosis of highly vascular tumors.

The magnetic resonance imaging (MRI) provides significant information with regards to the soft tissue involvement and neural structures. Malignant tumors usually exhibit nonspecific hyper intensity on T2-weighted images (T2WI) and hypo- to isointensity on T1-weighted images (T1WI). On T2WI, mucinous or cartilaginous tumors show marked hyperintensity, hypercellular tumors show slight hyperintensity and tumors with fibrosis, calcification, or flow void show hypointensity. On T1WI, hyperintensity within a tumor is indicative of the presence of methemoglobin, melanin, lipid, protein, and mineral elements. Diffusion-weighted image (DWI) with measurement of apparent diffusion coefficient (ADC) captures the degree of Brownian movement of the water molecules in tissues, which serves as a useful imaging biomarker. Low-ADC lesions with strong diffusion restriction indicate hypercellularity, abscess, or hemorrhage, whereas high-ADC lesions indicate hypocellularity, mucus, cartilage, or fluid. Therefore, DWI with ADC measurement is can be useful to differentiate between benign and malignant tumors. (18, 19, 20, 21)

Tumor location plays a significant role in arriving at a differential diagnosis. Tumors involving the region of the cribriform plate and upper nasal cavity suggest diagnoses such as olfactory neuroblastoma or meningioma. Inverted Schneiderian papilloma occurs predominantly along the lateral wall of cavity and the medial wall of the maxillary sinus.(36) In the lower maxilla, odontogenic lesions should be considered. Such lesions arise in the bone of the alveolar process and during their growth elevate the floor of the maxillary sinus. Fibroosseous lesions typically arise from bone and follow the contour of the bone. On imaging it is seen as a radiodense lesion. Correlation of imaging studies with histologic appearance is crucial in the evaluation of bony lesions.

1.6 Tumor staging

Staging of the sinonasal tumors is complex. The tumors are staged according to the

tumors that start in the nasal cavity or ethmoids, and maxillary sinus. Tumor stage is not characterized by size, but the extent of sites and local structures involved. The late stage of the tumor is characterized by invasion of adjacent structures such as the orbit, base of skull, cranial nerves, brain and facial skin. Below is the detailed staging for sinonasal tumors:

TX- Primary Tumour cannot be assessed

T0 -No evidence of primary Tumour
Tis =Carcinoma *in situ*

Maxillary Sinus

T1 Tumor limited to the maxillary sinus mucosa with no erosion or destruction of bone.

T2 Tumor causing bone erosion or destruction, including extension into the hard palate and/or middle nasal meatus, except extension to the posterior wall of the maxillary sinus and pterygoid plates.

T3 Tumor invades any of the following: bone of the posterior wall of the maxillary sinus,subcutaneous tissues, or medial wall of the orbit, pterygoid fossa, or ethmoid sinuses.

T4a Moderately advanced local disease
Tumour invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses.

T4b Moderately advanced local disease
Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve. (V2), nasopharynx, or clivus.

Nasal cavity and ethmoid sinus

T1 Tumor restricted to any one subsite, with or without bony invasion

T2 Tumor invades two subsites in a single region or extending to involve

an adjacent region within the nasoethmoidal complex, with or without bony invasion

T3 Tumor extends to invade the medial wall or oor of the orbit, maxillary sinus, palate, or cribriform plate

T4a Moderately advanced local disease. Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses

T4b Moderately advanced local disease
Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus.

Regional lymph nodes

NX Regional lymph nodes cannot be assessed.

N0 regional nodes metastasis.

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension.

N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in its greatest dimension; or in multiple ipsilateral lymph nodes, no more that 6 cm in its greatest dimension; or in bilateral or contralateral lymph nodes, none greater than 6 cm in their greatest dimensions.

N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension.

N2b Metastasis in multiple ipsilateral lymph nodes, none more that 6 cm in greatest dimension.

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension .

N3 Metastasis in a lymph node more than 6 cm in greatest dimension.

Stage grouping

Stage 0	**Tis**	**N0**	**M0**
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M

	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Clinical stage grouping by T and N status

N	T1	T2	T3	T4a	T4b
N0	I	II	III	IVa	IVb
N1	III	III	III	IVa	IVb
N2	IVa	IVa	IVa	IVa	IVb
N3	IVb	IVb	IVb	IVb	IVb

Sinonasal tumor staging adapted from: Deschler DG, Moore MG, Smith RV, eds. Quick Reference Guide to TNM Staging of Head And Neck Cancer and Neck Dissection Classification, 4th ed. Alexandria, VA: American Academy of Otolaryngology-Head and Neck Surgery Foundation, 2014.

1.7 Presentation and management

Malignant neoplasms of this region may lead to morbidity and disfigurement. Patients with sinonasal tumors present to the ENT surgeon with nonspecific complaints such as epistaxis, nasal obstruction, headache, nasal congestion, nasal discharge, swelling, and facial pain or numbness. (25) Loss of vision and diplopia is most often as a result of the tumor compressing or invading the orbital nerve or direct involvement of occulomotor nerve. Epiphoria is due to the obstruction or infiltration of the lacrimal duct. Trismus heralds an advanced tumor invading the muscles of mastication and at times, the invasion of the pterygoid plates. A neck mass is also a sign of advanced disease in the setting of carcinoma due to the likelihood of nodal metastases. Hearing loss may result from nasopharyngeal extension of the tumor obstructing the Eustachian tube with resultant middle ear effusion. What is noted further is that 9-12% of patients are frequently

asymptomatic and this further contributes to a delay in diagnosis and therefore an advanced stage at presentation. (25,26)

Diagnosis begins with a thorough clinical history and physical examination. Computed tomography/magnetic resonance imaging (CT/MRI) scans are done to stage the tumor locally and to evaluate for the presence of metastasis. Biopsy of the tumor is necessary to make a final diagnosis. Tumor proximity to vital structures such as the brain, optic nerves, and internal carotid artery pose significant challenges for their treatment and may be the source of the significant morbidity of the patients. Almost all the benign tumors have a tendency to recur with locally destructive capability and have a 5–15% likelihood of progressing to malignancy. Surgery (open or endoscopic) is the mainstay of treatment with or without radiation therapy and/or chemotherapy. (26) Sinonasal tumors carry a poor prognosis, despite an early diagnosis, radical surgical resection and strict follow-up.

1.8 Rationale

A number of patients present to the ENT division at CHBAH with sinonasal tumors of varying subtypes. A retrospective assessment of the clinical and histopathological spectrum of sinonasal tumors allowed for comparison with documented published literature and brought to our attention the burden of sinonasal disease and the prominent histological subtypes presenting to the unit. This is important, as there had been a notable difference in the most common histological type presenting in the CBHAH ENT unit in comparison to what has been documented in the literature. In addition, the role of the human immunodeficiency virus (HIV) infection in sinonasal tumors will be evaluated.

1.9 Aims and objectives

1.9.1 Aim of the research

To document the clinical and pathological spectrum of benign and malignant sinonasal tumors in an HIV-seroprevalent South African setting

1.9.2 Objectives

- To describe the demographic details of adult patients (age and gender) and the topographic site of biopsy sampled at Chris Hani Baragwanath Academic Hospital (CHBAH) over a three year time frame, July 2013 to July 2016.
- To describe the pathological spectrum of sinonasal tumour subtypes occurring in HIV positive and negative patients.
- To describe the presence of concomitant pathology such as cytomegalovirus infection, granulomatous inflammation or parasites.
- To compare the presenting symptoms of benign and malignant tumours.

2. Methodology

A record review study was conducted to document the spectrum of benign and malignant sinonasal tumors in patients who presented at the ENT clinical unit at CHBAH between July 2013 and July 2016. Ethics approval of this study was obtained from the Human Research Ethics Committee, Medical, at the University of the Witwatersrand (clearance certificate number M170668).

2.1 Study population

This study included 53 adult male and female patients, above the age of 18 years, who presented with a sinonasal mass at CHBAH, ORL department between July 2013 and July 2016. These patients were clinically assessed between the time frame of July 2013 and July 2016. Biopsies were performed with the intent of establishing a histopathological diagnosis at the National Health Laboratory Service (NHLS). HIV positive and negative patients were included in this study.

2.2 Sampling strategy

The histopathological reports of all patients included in this study were retrieved from the NHLS following a SNOMED (Systematized Nomenclature of Medicine) search of the laboratory database. The following codes were used to retrieve cases (T-code represents the anatomical topography and M-code represents neoplastic subtype): T-2200 (nasal sinus structure), T-21002/3 (nasal region), T-22100 (maxillary sinus), T-22200 (frontal sinus), T- 22300 (ethmoid sinus), T22400 (sphenoid sinus), M-80000 (benign neoplasm), M-80001 (neoplasm: uncertain whether benign or malignant) and M-0003 (neoplasm malignant). The histopathological reports were retrieved. The patient's demographic information, the clinical features and the pathological details were documented from the reports. The HIV status and CD4 count were documented from the NHLS database. Concomitant pathology was also documented.

2.3 Data collection

Data was collected using the SNOMED electronic records from the NHLS Corporate Data Warehouse and patient records were retrieved using episode numbers. A data collection sheet (Appendix A) was utilized to detail age, gender, HIV status, CD4 count, nasal symptoms, tumor site/topographic region, gross appearance and histopathological findings. There was no mention of other concomitant symptoms either than nasal obstruction and therefore, nasal obstruction was selected as the commonest symptom. Concomitant pathology was also documented.

2.4 Statistical analysis

The data was analysed using IBM SPSS Statistics. Descriptive statistics were run to produce and present basic features of the study sample in the form of frequencies and percentages as well as measures of central tendency. Normality of the sample data was tested in order to determine if parametric or non-parametric methods would be more suitable for the main analysis. Among the inferential methods used were the Pearson's Chi square, the Mann-Whitney test and binomial logistic regression. All the multivariate and statistical significance testing was done at a 95% confidence interval.

2.5 Descriptive statistics

2.5.1 Normality tests

The data was first tested for normality to determine if parametric or non-parametric methods would be more appropriate for the subsequent inferential analysis. Skewness is a measure of symmetry in a distribution and a value between -0.5 and 0.5 is regarded as indicative of approximately symmetric distribution. Table 1 shows that skewness for gender (0.79), age (0.74) and tumor type (1.64) were all above the recommended threshold for parametric testing. Tests suitable for analysis of data that is not sufficiently normally distributed were therefore utilised.

Table 1: Normality of sample distribution

		Statistic	Std. Error
Gender	Mean	1.68	0.06
	Median	2.00	
	Variance	0.22	
	Std. Deviation	0.47	
	Skewness	0.79	0.33
Age	Mean	44.64	1.85
	Median	42.00	
	Variance	182.35	
	Std. Deviation	13.50	
	Skewness	0.74	0.33
Tumour type	Mean	1.19	0.05
	Median	1.00	
	Variance	0.16	
	Std. Deviation	0.39	
	Skewness	1.64	0.33
HIV	Mean	1.58	0.08
	Median	2.00	
	Variance	0.32	
	Std. Deviation	0.57	
	Skewness	0.30	0.33

3. Results

The collected data comprised a total of 53 cases, of these, 36 (68%) were male and 17 (32%) were female patients (Figure 1). The largest concentrations were in the 30-39 age range (29%) and 40-49 age range (30%), with about 6 in 10 (59%) of the patients falling in the 30-49 range. (Figure2) The nasal cavity was specified as the site of the tumor in two thirds (66%) of the cases. The second most common site was the maxillary sinus at 25% (Table 3). There was a total of 43 (81%) malignant tumor and 10 (19%) benign tumor cases in the study. (Figure 3) Lymphoma was the most prevalent tumor subtype at 45% and was followed by invasive poorly differentiated squamous cell carcinoma (SCC) at 19% (Table 4). The most common benign tumor was inverted papilloma and tumor-like inflammatory polyps. The presenting concomitant pathology is described in Figure 4. Two thirds (66%) of the cases did not have any accompanying pathology while EBV was demonstrated in 26% of cases tested for EBV and choanal atresia in 2% of the cases. HIV testing was non-reactive in 27 of the 53 cases (51%) and reactive in 24 cases (45%). The HIV status of two of the patients in this sample was not specified. (Figure 4) The CD4 count was recorded in 18 of the 24 cases that tested positive for HIV. The recorded CD4 count ranged widely between a minimum of 5 cells/uL and a maximum of 787 cells/uL, with a mean of 336 cells/uL as shown in Table 5. The relationship between benign and malignant tumors and HIV was examined, first, using the Chi-square test and then using the logistic regression method. The percentage of cases testing positive for HIV was higher amongst patients with malignant tumors at 56% compared to only 10% amongst patients with benign tumors (Table 10). The differences in HIV results between malignant and benign tumor cases were statistically significant (Chi-square=6.857, p=0.01). Therefore, cases with malignant tumors tended to be significantly more associated with HIV reactive results compared to those with benign tumors (Table11). The results showed a significant association between malignant tumors and HIV positive results, the analysis further examined if the HIV association varied between the different diagnosed malignant tumor subtypes (viz. lymphoma, SCC and other less prevalent subtypes). As shown in Table 12, the percentage of cases testing positive for HIV among

patients with lymphoma was 83% compared to 40% amongst patients with SCC, while none of the 8 patients diagnosed with other tumor subtypes tested positive for HIV. The differences in HIV results between patients with lymphoma, SCC and other malignant tumor subtypes were statistically significant (Chi-square=17.838, p=0.00).

The percentage of HIV reactive results was significantly higher in lymphoma cases compared to cases with SCC as well as those with other types of malignant tumors. (Table 13) The logistic regression model explained 53% of the variance in HIV test results based on malignant tumor subtypes as reflected by the Nagelkerke R^2 value = 0.53. A malignant tumor subtype was thus a significant predictor of HIV test results in patients (Wald chi-square 11.703, p=0.00) with a strong association between lymphoma and reactive HIV test results.

EBV was tested in certain types of lymphomas. Table 20 shows the types of lymphomas associated with EBV, those that were EBV negative , and those that were not specifically tested for EBV. As shown in Table 23, 33% of malignant tumor cases had EBV. Table 24 shows that the EBV prevalence was associated with patients with malignant tumors (Chi-square = 4.425, p=0.04). The results showed a significant association between malignant tumors and EBV. The analysis extended to examine the association between EBV and specific malignant tumor subtypes namely, lymphoma and SCC. The differences in EBV between patients with Lymphoma and SCC and were statistically significant (Chi-square=7.528, p=0.02). The percentage of cases with EBV was significantly higher in lymphoma cases. Binomial logistic regression was then performed to determine if EBV could be predicted from the presenting malignant tumor subtypes. In this instance malignant tumor subtypes were analysed as the predictor variables of EBV as shown in the omnibus tests table, the logistic regression model was statistically significant (Chi-square=7.163, p=0.01). A malignant tumor subtype was thus a significant predictor of EBV in patients (Wald chi-square 4.975, p=0.03), with a strong association between lymphoma and positive EBV status.

The presenting nasal and other symptoms were not described in 24 of the 53 cases (45%). Where the symptoms were described, nasal obstruction was the most common at 34%, a figure about twice that of nasal mass, the next most common symptom. At least 12 of the cases presented with more than one nasal symptom. (Table 2) Proptosis was present in 9% of the patients. Cranial nerve fallout, sinusitis and facial numbness were equally distributed in 4% of the patients. The less commonly presenting symptoms included epistaxis and cervical lymphadenopathy, facial asymmetry, hearing loss, nasal bridge deformity, otitis media with effusion and skin involvement

3.1 Results in tables and figures

The collected data had a total of 53 cases of which 36 (68%) were male and 17 (32%) female patients

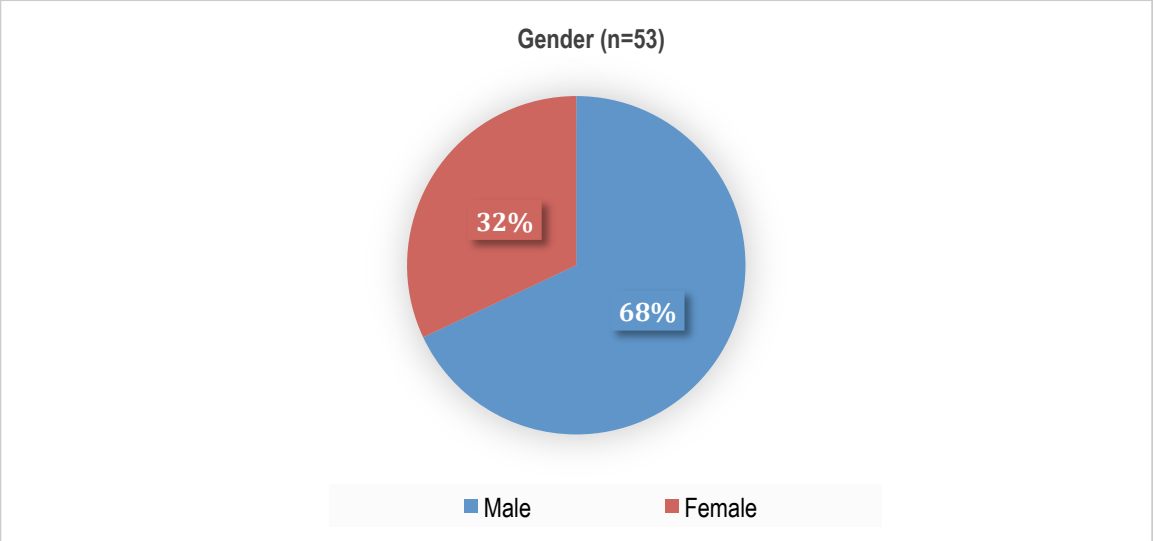

Figure 1: Gender

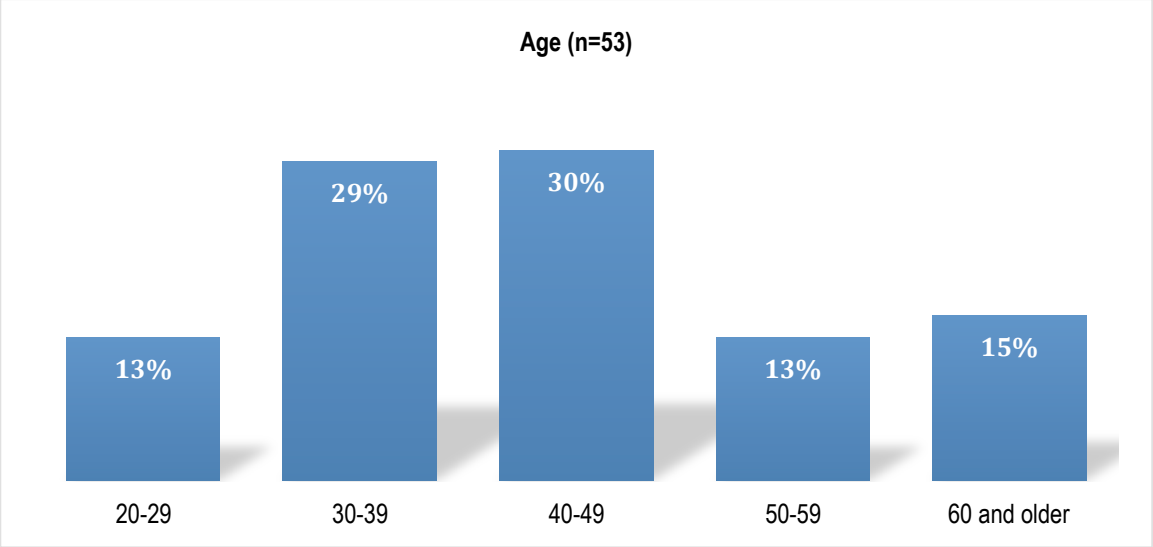

Figure 2: Age

Figure 2 shows the age brackets and the largest concentrations were in the 30-39 age range (29%) and 40-49 age range (30%), with about 6 in 10 (59%) of the patients therefore falling in the 30-49 range

Presenting symptoms

The presenting nasal and other symptoms were not described in 24 of the 53 cases (45%). Where the symptoms were described, nasal obstruction was the most common at 34%, a figure about twice that of nasal mass, the next common symptom. At least 12 of the cases presented more than one nasal symptom, hence the count exceeding 100% in the results table.

Table 2: Percentage of presnting symptoms

Symptoms	Number of patients	Percentage
Not described	24	45%
Nasal obstruction	18	34%
Nasal mass	8	15%
Visual symptoms/Proptosis	5	9%
Associated tonsillar mass/hypertrophy	2	4%
Cranial nerve fallout	2	4%
Facial numbness	2	4%
Sinusitis	2	4%
Cervical lymphadenopathy	1	2%
Epistaxis	1	2%
Facial asymmetry	1	2%
Hearing loss	1	2%
Nasal bridge deformity	1	2%
Otitis media with effusion	1	2%
Premaxillary mass extension	1	2%

Semter's triad	1	2%

Tumor sites

The nasal cavity was given as the site of the tumour in two thirds (66%) of the cases. The second most common site was the maxillary sinus at 25% as shown in the table below. Notably, the tumour covered more than one specific site in many of the patients, hence the counts that in excess of 100% .

Table 3: Percentage of tumor sites

Tumour site	Number of patients	Percentage
Nasal cavity	35	66%
Maxillary sinus	13	25%
Posterior nasal cavity	7	13%
Ethmoids	6	11%
Posterior nasal space	6	11%
Nasopharynx	3	6%
Orbit	3	6%
Frontal sinus	2	4%
Nasal mass	2	4%
Base of tongue	1	2%
Bilateral nasal cavity	1	2%

Cribriform	1	2%
Lateral pharyngeal wall	1	2%
Middle meatus	1	2%
Nasal skin	1	2%
Oral cavity	1	2%
Palate	1	2%
Parapharyngeal space	1	2%
Posterior nasal mass	1	2%
Skull base	1	2%

Tumor types

There was a total of 43 (81%) malignant tumor and 10 (19%) benign tumor cases in the study.

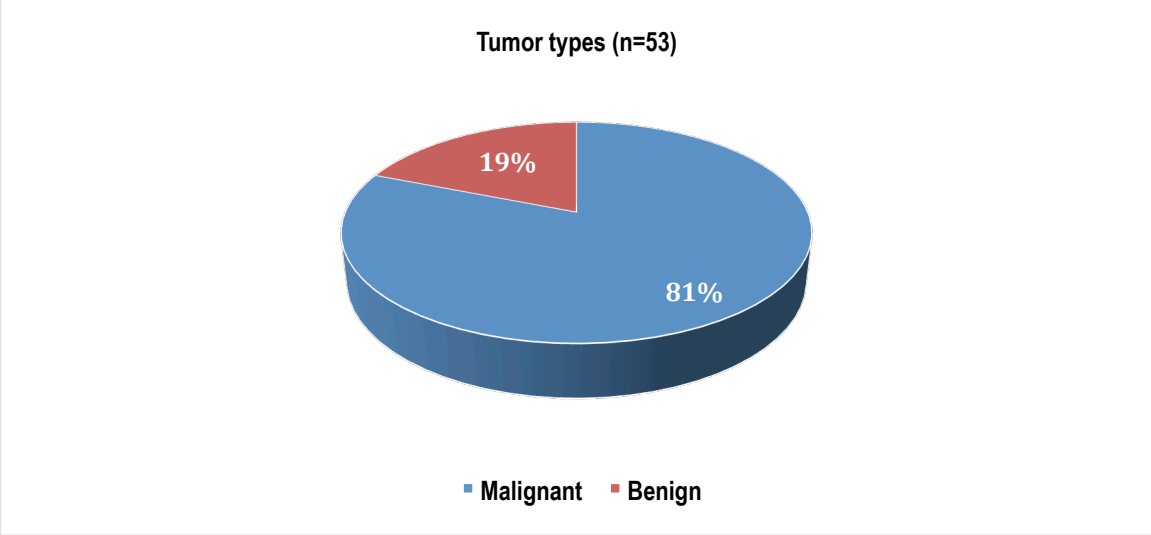

Figure 3

Concomitant pathology

The presenting concomitant pathology is described in Figure 4. Two thirds (66%) of the cases did not have any accompanying pathology while EBV was diagnosed in 26% of the cases tested for EBV and choanal atresia in 2% of the cases.

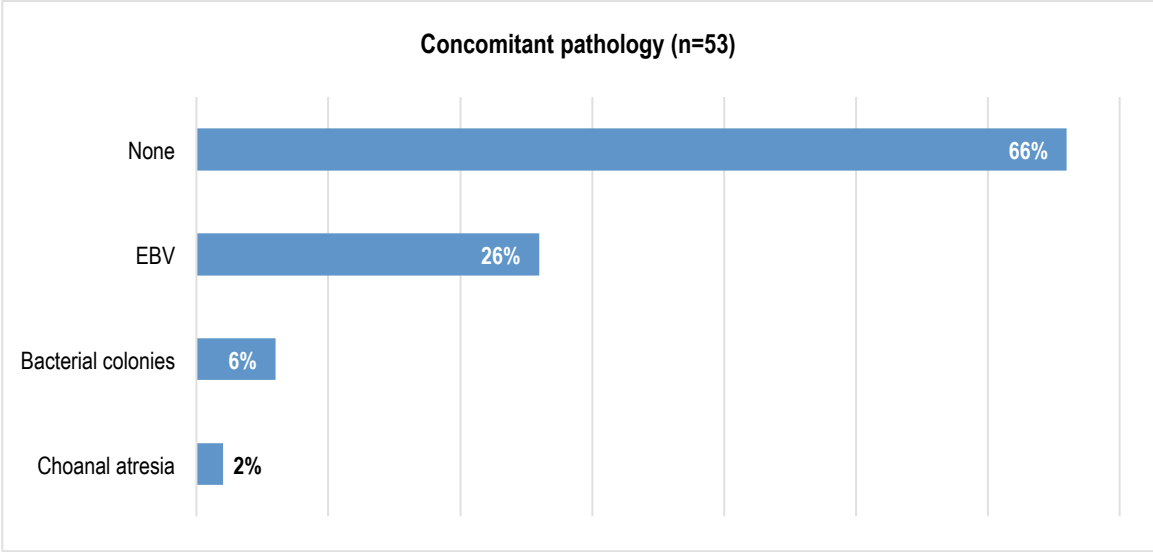

Figure 4

Tumor and tumor-like subtypes

Lymphoma was the most prevalent tumour subtype at 45% and was followed by Invasive poorly differentiated squamous cell carcinoma (SCC) at 19%. (Table 4)

Table 4

Tumor and tumor-like subtypes	Number of patients	Percentage
Lymphoma	24	45%
SCC	10	19%
Inflammatory polyp	3	6%
Inverted papilloma	3	6%
Adenoid cystic carcinoma	2	4%
Lymphoid hyperplasia	2	4%
Melanoma	2	4%
Vascular tumours	2	4%
Alveolar Rhadomyosarcoma	1	2%
Chondrosarcoma	1	2%
Nasopharyngeal carcinoma	1	2%
Sinonasal Adenocarcinoma	1	2%
Spindle cell carcinoma	1	2%

HIV status

HIV testing was non-reactive in 27 of the 53 cases (51%) and reactive in the other 24 cases (45%). The HIV status of two of the patients in the sample was not specified.

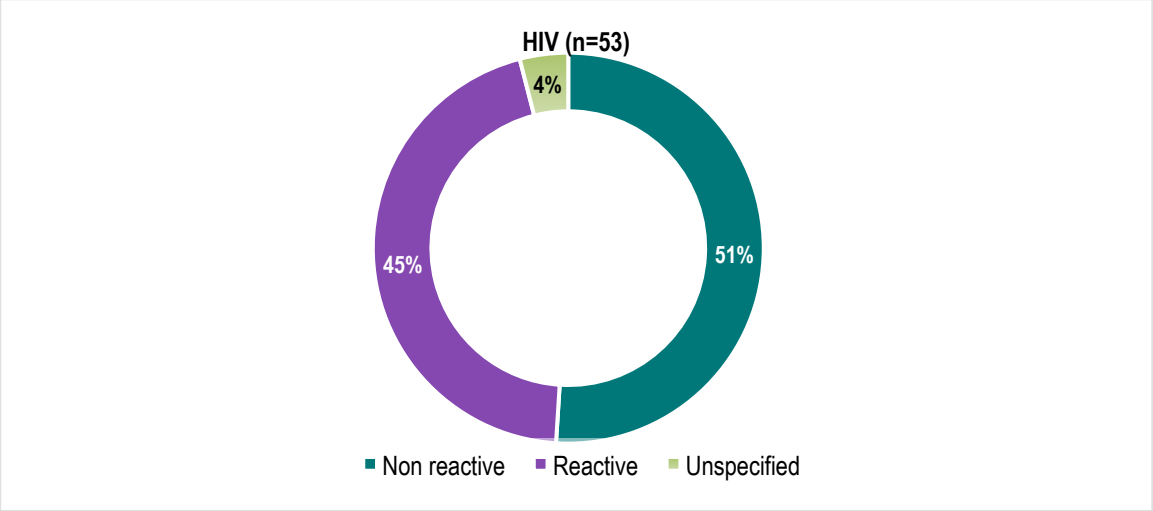

Figure 5

CD4 count (cells/uL)

The CD4 count was recorded in only 18 of the 24 cases that tested positive to HIV. The recorded CD4 count ranged widely between a minimum of 5 to a maximum of 787cells/uL, with a mean of 336 as shown below.

Table 5

			Statistic	**Std. Error**
CD4 count	Mean		335.72	62.01
	95% Confidence Interval for Mean	Lower Bound	204.89	
		Upper Bound	466.56	
	5% Trimmed Mean		329.02	
	Median		240.00	
	Variance		69220.45	
	Std. Deviation		263.10	
	Minimum		5	
	Maximum		787	
	Range		782	
	Interquartile Range		490.25	
	Skewness		0.64	0.54
	Kurtosis		-1.18	1.04

Tumor types by gender

The Pearson's Chi square test was run to compare the prevalence of tumor types by gender and 65% of female patients had malignant tumors compared to 89% among male patients as shown below

Table 6

Type of tumor	**Gender**	
	Female (n=17)	**Male (n=36)**
Malignant tumors	65%	89%
Benign tumors	35%	11%

Chi-square tests on benign and malignant tumors by gender

The results in Table 7 show that prevalence in benign and malignant tumors differed significantly by gender (Chi Square=4.411, p=0.04), with the proportion of malignant tumour cases markedly higher amongst males compared to females.

Table 7

	Value	**df**	**Asymptotic Sig. (2-sided)**
Pearson Chi-Square	4.411	1	**0.04***
Likelihood Ratio	4.146	1	0.04
N of Valid Cases	53		

p<0.05* = statistically significant

Tumor types by age

Table 8 shows how benign and malignant tumours were distributed across the different age groups. The Mann-Whitney test was used to compare the differences in tumour types by patient age and the test statistics in Table 9 show that differences in tumour types by age were not statistically significant (U=32.00, p=0.39).

Table 8

Type of tumor	**Age**				
	20-29	**30-39**	**40-49**	**50-59**	**>60**
	n=7	n=15	n=16	n=7	n=8
Malignant	57%	80%	94%	71%	88%
Benign	43%	20%	6%	29%	13%

Table 9: Mann-Whitney test statistics

	Type of tumour
Mann-Whitney U	32.00
Wilcoxon W	123.00
Z	-0.87
Asymp. Sig. (2-tailed)	0.39

p<0.05* = statistically significant

HIV results by tumor types

The Pearson's Chi square test was run to compare differences in HIV status between patients with benign and malignant tumors. The two cases whose classification in terms of HIV was unknown were excluded from this analysis, leaving 51 cases. As shown in Table 10, the percentage of cases testing positive to HIV was higher amongst patients with malignant tumours at 56% compared to only 10% amongst patients with benign tumors.

Table 10

Tumour types	**N**	**HIV**	
		Reactive	**Non-reactive**
Malignant	41	56%	44%
Benign	10	10%	90%
Total	51	47%	53%

Chi-square tests on HIV results by benign and malignant tumors

Table 11 shows that these differences in HIV results between malignant and benign tumor cases were statistically significant (Chi-square=6.857, p=0.01). Therefore, cases with malignant tumors tended to have significantly more HIV reactive results compared to those with benign tumors.

Table 11

	Value	**df**	**Asymptotic Sig. (2-sided)**
Pearson Chi-Square	6.857	1	**0.01***
Likelihood Ratio	7.796	1	0.01
N of Valid Cases	51		

p<0.05* = statistically

HIV results by malignant tumor subtypes

With the results showing a significant association between malignant tumors and HIV positive results, the analysis extended to examining if the HIV association varied between the different diagnosed malignant tumor subtypes (viz. Lymphoma, SCC and other less prevalent subtypes). As shown in the table below, the percentage of cases testing positive to HIV among patients with Lymphoma was 83% compared to 40% amongst patients with SCC, while none of the 8 patients diagnosed with other tumour subtypes tested positive to HIV.

Table 12

Malignant tumour subtypes	**N**	**HIV**	
		Reactive	**Non-reactive**
Lymphoma	23	83%	17%
SCC	10	40%	60%
Other	8	0%	100%
Total	41	56%	44%

Chi-square tests on HIV results by malignant tumor subtypes

Table 13 shows that the above differences in HIV results between patients with Lymphoma, SCC and other malignant tumour subtypes were statistically significant (Chi-square=17.838, p=0.00). The percentage of HIV reactive results was significantly higher in Lymphoma cases compared to cases with SCC as well as those with other types of malignant tumours.

Table 13

	Value	**df**	**Asymptotic Sig. (2-sided)**
Pearson Chi-Square	17.838	2	**0.00***
Likelihood Ratio	21.513	2	0.00
N of Valid Cases	41		

p<0.05* = statistically significant

Predicting HIV status from malignant tumor subtypes

Binomial logistic regression was then performed to determine if HIV test results could be predicted from the presenting malignant tumor subtypes. In this analysis malignant tumor subtypes were allocated as the predictor variables and HIV results as the outcome variable. As shown in the omnibus tests table, the logistic regression model was statistically significant (Chi-square=20.543, p=0.00).

Table 14: Omnibus tests of model coefficients

		Chi-square	**df**	**Sig.**
Step 1	Step	20.543	1	0.00
	Block	20.543	1	0.00
	Model	20.543	1	**0.00***

p<0.05* = statistically significant

Table 15: Logistic regression model summary

Step	-2 Log Likelihood	Cox & Snell R Square	Nagelkerke R Square
1	35.684	0.394	0.53

Malignant tumor subtype was thus a significant predictor of HIV test results in patients (Wald chi-square 11.703, p=0.00), with a strong association between Lymphoma and reactive HIV test results.

Table 16: Variables in the Equation

	B	S.E.	Wald	df	Sig.	Exp(B)
Malignant tumor subtype	2.376	0.695	11.703	1	**0.00***	10.764
Constant	-4.044	1.132	12.755	1	0.00	0.018

p<0.05* = statistically significant

The logistic regression model explained 53% of the variance in HIV test results based on malignant tumour subtypes as reflected by the Nagelkerke R^2 value = 0.53 in Table 17

Table 17: Logistic regression model summary

Step	-2 Log Likelihood	Cox & Snell R Square	Nagelkerke R Square
1	35.684	0.394	0.53

Malignant tumor subtype was thus a significant predictor of HIV test results in patients (Wald chi-square 11.703, p=0.00), with a strong association between Lymphoma and reactive HIV test results.

Table 18: Omnibus tests of model coefficients

		Chi-square	df	Sig.
Step 1	Step	7.796	1	0.01
	Block	7.796	1	0.01
	Model	7.796	1	**0.01***

p<0.05* = statistically significant

The logistic regression model explained 19% of the variance in HIV test results as reflected by the Nagelkerke R^2 value = 0.19 in Table 19.

Table 19: Logistic regression model summary

Step	-2 Log Likelihood	Cox & Snell R Square	Nagelkerke R Square
1	62.73	0.14	0.19

Table 20: Lymphoma cases associated with EBV in the study

Different types of lymphoma were encountered in the study. EBV ISH was performed in certain lymphomas.

Lymphoma subtype	Number of lymphoma cases	EBV ISH +ve	EBV ISH -ve	EBV ISH not performed
Diffuse Large B-cell Lymphoma	9	4	1	4
Peripheral T-cell Lymphoma	1	-	-	
Plasmablastic Lymphoma	11	5	2	4
Burkitt Lymphoma	1			1
Total:	22	9	2	11

Table 21 shows that EBV prevalence was significantly high in patients with lymphoma and SCC (Chi-square = 11.518, p=0.00).

Table 21: Chi-square tests on EBV and malignant tumors

	Value	**df**	**Asymptotic Sig. (2-sided)**
Pearson Chi-Square	11.518	2	**0.00***
Likelihood Ratio	11.809	2	0.00
N of Valid Cases	53		

p<0.05* = statistically significant

Table 22: Omnibus tests of model coefficients

		Chi-square	**df**	**Sig.**
Step 1	Step	0.996	1	0.32
	Block	0.996	1	0.32
	Model	0.996	1	0.32

p<0.05* = statistically significant

As shown in Table 23, 33% of malignant tumors were associated with EBV

Table 23: EBV by tumor types

Tumor types	N	EBV	
		Positive	None
Malignant	43	33%	67%
Benign	10	-	-
Total	53	33%	67%

Table 24 shows that EBV is prevalent in patients with malignant tumors (Chi-square = 4.425, p=0.04).

Table 24: Chi-square tests on EBV and malignant tumors

	Value	df	Asymptotic Sig. (2-sided)
Pearson Chi-Square	4.425	1	**0.04***
Likelihood Ratio	6.933	1	0.01
N of Valid Cases	53		

p<0.05* = statistically significant

EBV according to malignant tumor subtypes

The analysis examined the association between EBV and specific malignant tumor subtypes (viz. Lymphoma, and SCC).

Predicting EBV from malignant tumor subtypes

Binomial logistic regression was then performed to determine if EBV could be predicted from the presenting malignant tumor subtypes. In this instance malignant tumor subtypes were analysed as the predictor variables and EBV and as shown in the omnibus tests table, the logistic regression model was statistically significant (Chi-square=7.163, p=0.01).

Table 25: Omnibus tests of model coefficients

		Chi-square	df	Sig.
Step 1	Step	7.163	1	0.01
	Block	7.163	1	0.01
	Model	7.163	1	**0.01***

p<0.05* = statistically significant

The logistic regression model explained 21% of the variance in EBV across the malignant tumour subtypes as reflected by the Nagelkerke R^2 value = 0.21 in Table 26.

Table 26: Logistic regression model summary

Step	-2 Log Likelihood	Cox & Snell R Square	Nagelkerke R Square
1	47.104	0.153	0.21

Malignant tumor subtype was thus a significant predictor of EBV in patients (Wald chi-square 4.975, p=0.03), with a strong association between Lymphoma and positive EBV.

Table 27: Variables in the Equation

	B	S.E.	Wald	df	Sig.	Exp(B)
Malignant tumour subtype	-1.346	.604	4.975	1	**0.03***	0.260
Constant	1.268	.870	2.123	1	0.15	3.553

p<0.05* = statistically significant

4. Discussion

In this study, 53 histopathological reports of sinonasal biopsies of patients presenting at the CHBAH ORL department between July 2013 and July 2016 were analysed. The study aimed to evaluate the demographic details of these patients, the spectrum of sinonasal tumors, concomitant pathology and the presenting symptoms of benign and malignant tumors. 68% of the cases were male and 32% were female of age range 30-49 years. Malignant tumors were found to be the highest in males (89%) compared to females (65%) ($p=0.04$). The most common site of presentation was the nasal cavity followed by the maxillary sinus. The most common tumors were malignant tumors (81%). Lymphoma was found to be the most prevalent tumor subtype (45%), which is contrary to what has been previously described in the literature. The squamous cell carcinoma (SCC) is known in the literature to be the most common sinonasal tumor, followed by adenoid cystic carcinoma. (4) In this study, however, lymphoma was found to be the most common sinonasal tumor, followed by the SCC.

The SCC is classified as keratinizing and non-keratinizing. It is then further classified into SCC variants such as papillary, verrucous, spindle, basaloid, to mention but a few. The subtypes encountered in this study were basaloid and spindle cell variants.
Treatment for sinonasal SCC varies depending on the stage, patient physical well-being and comorbidities, tumor type and staging of the tumor. Basic principles are surgical resection followed by radiotherapy. Recently, endoscopic surgical approaches have superseded the conventional open approaches for tumor excision. Directed radiotherapy, such as intensity modulated radiation therapy (IMRT) and gamma knife radiotherapy have improved treatment outcomes and decreased morbidity, especially for those patients with tumors adjacent to vital structures such as the orbit, skull base, and brain. For advanced stage tumors, especially those that are inoperable, targeted treatments have not been practiced. Palliative chemotherapy is reserved for advanced irresectable tumors. (40)
Adenoid cystic carcinoma is the most common salivary gland tumor of the sinonasal tract and has been described in the literature as the third most common tumor. The current

study demonstrated similar findings. It is a slow growing tumor with a tendency for recurrence, local and regional spread with a predilection for perineural spread and distant metastasis. Surgery and postoperative radiation/photon therapy is the mainstay treatment, however, it is associated with high recurrence rate. (41) Sinonasal melanoma is described in the literature as a rare mucosal melanoma accounting for less than 1% of the malignant sinonasal tumors. It is seen in adult patients with the average age of 64. (22) In this study, this tumor was found in a young 27-year-old female. Its presentation demonstrated malignant aggression with skull base erosion. Vascular tumors in this study constituted 4% of the sinonasal tumors. These were the lobular capillary haemangioma and cavenous hemangioma. The cavenous hemangioma was associated with a unilateral choanal atresia on a CT scan. Interestingly, this was a finding in a 49 year old patient.

The alveolar rhabdomyosarcoma is a rare mesenchymal tumor involving skeletal muscles, often seen in children. In this study it was found in a 53 year old male patient. Overall, this tumor constituted 2% of the cases in this review. Chondrosarcoma is an uncommon neoplasm that accounts for between 1% and 4% of all primary bone neoplasms. The most common origin of this tumor is the sacrum, however, 28% to 36% are seen in the clival region of the skull. It is very rare in the sinonasal tract. (27) Our study included a case of low grade chondrosarcoma. Nasopharyngeal carcinoma was found in one patient and was associated with EBV. Genetic, environmental and dietary factors together with Epstein Barr Virus (EBV) infection are implicated as the causative factors of NPC. (28)

Sinonasal adenocarcinoma (non-intestinal type) in this study constitutes 2% of the tumors encountered. These tumors are divided into two types: intestinal and non-intestinal sinonasal adenocarcinoma. These constitute 10-20% of malignant tumors of the sinonasal tract. Histologically, these resemble adenocarcinoma or adenoma of the intestines, or exceptionally normal small intestinal mucosa. Spindle cell carcinoma constitutes about 2% of the sinonasal tumors reviewed in this study. This tumor is a variant of squamous cell carcinoma and exhibits spindled and pleomorphic tumor cells. This tumor has commonly been seen in the larynx especially the glottis, then the oral

cavity, it is however very rare in the sinonasal tract with only a few cases having been reported. (29)

Benign tumors-like lesions such as the inflammatory polyps and lymphoid hyperplasia constitute 6% of all tumors in this review. These patients presented with mild symptoms of nasal obstruction, Samter's triad and otitis media with effusion. The malignant tumors had some of the severe symptoms and signs. Nasal obstruction, nasal mass and visual disturbance/proptosis constitute the most common clinical presentations. Other less common associated clinical symptoms were cranial nerve fallout, facial numbness, sinusitis, epistaxis and skin involvement. These severe features were mostly associated with malignant tumors.

The role of concomitant infection was evaluated and HIV was found to be of importance. In this study, 45% of the patients were HIV reactive. The percentage of cases testing positive for HIV was higher amongst patients with malignant tumors at 56% compared to only 10% amongst patients with benign tumours. This means that a higher percentage of malignant tumors were associated with HIV ($p=0.01$). This study further demonstrated that HIV was highly associated with Lymphoma (83%) and SCC (40%) ($p=0.00$). EBV was associated with 33% of the malignant tumors ($p=0.04$). EBV was associated with 50% of the lymphoma cases compared to SCC (10%) ($p=0.02$). EBV is a gamma-herpesvirus first discovered by Epstein and Barr over half a century ago with the aid of electron microscopy. It is known to infect 90–95% of people worldwide. The virus enters the human body at a young age and remains persistent for years. Transmission occurs primarily through saliva. Infection occurs first within oropharyngeal epithelial cells where the IgA:EBV complex is formed at the IgA receptor and enters the cell. (41) The nearby circulating B cells that come close to the vicinity of the infected epithelial cells become infected through viral attachment to CD21 and then enter into the nucleus. (42) Once it has gained nuclear entry, the EBV viral genome becomes circular and starts to express EBV nuclear antigen leader protein (EBNA-LP) and EBNA-2. Within 24–48 hours additional EBNAs and latent membrane proteins (LMPs) are produced, leading to cell growth, transformation and suppression of apoptosis through increase in BCL2 expression. Full expression of all EBV proteins transforms the naive B cells into

activated lymphoblasts. EBV-infected lymphoblasts continue to differentiate within the germinal center into memory B cells, the reservoir of EBV infection. For the duration of latent infection, EBV expresses nuclear antigens, membrane proteins, small non-coding RNA and cell transcripts that contribute to genomic maintenance and evasion of host immunosurveillance. EBV lymphomagenesis is dependent on expression of viral gene products that may inhibit apoptosis and promote proliferation via MYC activation or through inhibition of tumor suppressor genes.(43)

EBV is not only associated with malignancy, but there are certain benign syndromes which are linked to this virus. Infectious mononucleosis is one such syndrome, which affects adolescents and adults. Symptoms manifest as fever, lymph node enlargement, and inflammation of the pharynx. Enlargement of the liver and spleen, and, associated petechial lesions of the palate are present in most of the patients. Other associated less common complications include blood dyscrasias, inflammation of the myocardium, liver dysfunction, ulcers of the genitalia, splenic rupture and neurological complications such as Guillain-Barre, encephalitis and meningitis. Chronic EBV infection is another syndrome associated with EBV. It is characterized by severe illness of more than six months that starts as a primary EBV infection with abnormal EBV antibody titers, presence of organ disease evidenced by a confirming histologic report, such as hepatitis, pneumonitis, bone marrow hypoplasia or uveitis. This is accompanied by demonstration of EBV antigens or DNA tissue. (48) X-linked lymphoproliferative disease is also a syndrome associated with EBV. It is an inherited disease of males, who are unable to control infection with EBV. The gene found on the X chromosome known as SAP (signaling lymphocyte activation molecule associated protein), encodes a protein located on the surface of Tcells that interacts with proteins on the surface of Tcells and natural killer cells. When this gene is absent in these patients results in impairment of normal interaction of T and B cells which results in unregulated growth of EBV infected cells. (48)

EBV was the first virus associated with the development of malignant lymphoma, and has been reported to play a role in the development of a variety of HIV-related lymphomas. According to a different series, EBV has been identified in the HIV positive setting in 30–90% of DLBCL, between30–40% in Burkit Lymphoma, 70–80% in

Plasmablastic Lymphoma, and almost 100% Hodgkin Lymphoma. The lymphoma subtypes observed in the HIV positive setting can be grouped in 3 different categories:

1. Immunocompetent patients with lymphoma
    a. Burkitt lymphoma
    b. Diffuse large B-cell lymphoma
    c. Classical Hodgkin lymphoma
    d. MALT lymphoma
    e. Peripheral T-cell lymphoma

2. Lymphoma associated with HIV
    a. Primary effusion lymphoma
    b. Plasmablastic lymphoma
    c. HHV8 positive diffuse large B-cell lymphoma, not otherwise specified
3. Lymphoma associated with other immunodeficiency syndromes :
    - Polymorphic B cell lymphoma(PTLD-like)

Plasmablastic lymphoma was the commonest lymphoma encountered in our study at CHBAH. It was first described in 1997 as a HIV related lymphoma affecting young male patients involving the jaw and oral cavity. Subsequent studies have also shown its association with other forms of immunosuppression such as organ transplant immunosuppression. It is known to be an aggressive form of non-Hodgkins lymphoma with diffuse proloferation of malignant clones resmbling immunoblasts, but have plasma cell immunophenotype with associated absence of B-cell antigens. HIV associated plasmablastic lymphoma is an AIDS defining illness. (44) EBV is positive in 70-80% of the cases and our study depicted a similar finding.

Diffuse large B-cell lymphoma (DLBCL) is a subtype of high grade B cell non Hodgkins lymphoma which was the second most commonly encountered lymphoma in our study.

DLBCL has various subtypes such as the central nervous system lymphoma affecting the brain, and primary mediastinal B cell lymphoma occurring in the chest typically in young patients. Most cases of DLBCL do not fall in any category and are termed not otherwise specified (DLBCL-NOS). Diagnosis requires tissue biopsy and imaging for staging. Bone marrow may also be included and, a lumbar puncture is often performed to determine the presence of cancer cells in the brain and spine. DLBCL is treated with a combination of chemotherapy and the monoclonal antibody rituximab. The treatment regimen is referred to as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). (45)

Burkitt lymphoma was found in our study. It is a high grade malignant lymphoma of small, noncleaved B cells. In central Africa, Burkitt's lymphoma is associated with Plasmodium falciparum malaria. These tumors usually present in the jaw, and, over 90% of the cases are associated with EBV. Infection with malaria is associated with diminished ability of the T-cell to control of proliferating EBV infected B-cells and, enhance their proliferation. The cells contain a chromosomal translocation involving chromosomes 8 and 14, 22, or 2. The translocations result in the positioning of the c-myc oncogene (chromosome 8) near the immunoglobulin heavy chain (chromosome 14) or light-chain (chromosome 2 or 22) constant region, leading to abnormal regulation of the c-myc gene. This results in increased tumorigenicity**.** High titers of antibody to EBV structural proteins are associated with high risk for Burkitt's lymphoma (46)

Lymphoblastic lymphoma, which was seen in this review, is a rare lymphoma and almost 100% of the cases were found to be associated with EBV infection. It is a type of non-Hodgkin lymphoma associated with immunosuppression due to exposure to pesticides or radiation. It arises from immature T cells in the majority of cases and immature B cells in the remainder of cases. It can affect individuals who are HIV negative who have immunosuppression secondary to organ transplants. (30,31) The associated concomitant pathology namely the bacterial colony was insignificant, however, it may have contributed to sinusitis as the presenting symptom in some cases. EBV is implicated in the pathogenesis of other tumors such as the lymphomatoid

granulomatosis, central nervous system lymphomas, nasal T-cell/ natural killer cell lymphomas, smooth cell tumors in immunocompromised patients and gastric carcinomas.

EBV and HIV

A vast association between HIV and EBV was noted in this review, and it is the author's opinion that these viruses seem to support each other in some way that is not currently understood. T cells from patients with AIDS suppress EBV-infected B cells less effectively than do cells from normal controls and results proliferation of EBV infected cells. EBV is found in substantial amounts in oropharyngeal secretions of patients with HIV, and this is also associated with high antibody titers. EBV associated non-Hodgkins's lymphoma in HIV patients is associated with a reduction in EBV-specific cytotoxic T cells and an elevated EBV viral load (49,51)

EBV diagnostics

The diagnostic strategies used to detect EBV differ between immunocompromised and immunocompetent persons as a result of distinct therapeutic intervention required. Serology offers a dependable criteria for interpretation of results despite a high degree of variability with EBV. EBV genome encodes a number of different unique genes. The important ones are the viral capsid antigens (VCA), the early antigens (Eas), and the EBNAs: EBNA-1 and EBNA-2. There are only three essential serological markers for detection of EBV namely VCA immunoglobulin G (IgG), VCA IgM, and EBNA-1 IgG. Interpretation of serological findings should allow EBV infection stage specific diagnoses. This means that diagnosis should correlate with the clinical picture. In immunocompetent persons, three diagnosis are relevant: primary or acute infection (mononucleosis), a past infection that excludes monocucleosis, and the absence of EBV specific antibodies. In the case of positive results for VCA IgG and EBNA-1 IgG and in the absence of VCA IgM, a past infection is considered. If the results for VCA IgG, VCA IgM and EBNA-1 are negative, the patient is EBV susceptible. If tests for VCA IgM and VCA IgG are positive and those for EBNA-1 are negative then acute or primary

infection can be considered to be present. EBER in situ hybridization (EBRER-ISH) has been promoted as the most successful test in picking up and localizing latent EBV in tissue samples (50). This test was used in our study to detect presence of EBV in the selected submitted specimens. It was an essential diagnostic test especially in tumors that were borderline such as the plasma cell neoplasm which overlaps with plasmablastic lymphoma, where a considered differential was multiple myeloma, plasmacytoma or plasmablastic lymphoma. The detection of EBV using EBER-ISH , tumor morphology and high proliferation index of the tumor, in context of HIV infection, leads to the confirmation of plasmablastic lymphoma.

5. Current application

This review has revealed how HIV has influenced the sinonasal disease spectrum and completely changed what has been described in the literature for many years, this being the fact that SCC is the most common malignant sinonasal tumor and, osteoma the most common benign tumor of the sinonasal tract. Researchers and clinicians can now approach sinonasal pathology with knowledge in mind that the most common pathology is a malignat tumor and this should allude the treating clinician of the need to test for HIV as the strong association between malignant tumors and HIV has been demonstrated. The clinician should also treat this pathology with some urgency because of the nature of progression of the disease and the tendency to spread to essential adjacent structures such as the orbit, skull base and cranial nerves.

6. Limitations of the current study

As predicted, there were limitations with regards to certain patients whose HIV status was unknown and records were not found. Another limitation was the fact that this was a retrospective study, the researchers were unable to assess the outcomes in the patients selected for the study. Presenting symptoms were not specified in the request forms and patients were not interviewed with regards to these. Due to financial factors, EBV status was not routinely assessed in all tumors.

7. Conclusion

Sinonasal tumors in adult patients at the CHBAH ORL Department are a very diverse spectrum and demonstrate very interesting characteristics. Male patients younger than 50 years of age tend to have more aggressive malignant tumors and these tumors are noted to be lymphoma and SCC. These malignant tumors showed a strong association with HIV and EBV. The most common site for the presentation of these tumours was the nasal cavity and the maxillary sinus respectively. As a result, the most common presenting symptoms were a nasal mass and nasal obstruction. The sinonasal tumors known to affect older patients, such as melanoma were seen to affect even younger patients in this study.

Expanding on this research, it would be interesting to evaluate if ARV treatment influences the disease outcome in terms of tumor aggression as compared to patients who are not initiated on HAART. It is absolutely essential for primary health care clinicians to refer patients with nasal obstuction promptly to prevent delay in diagnosis of such aggressive nasal tumors as seen in this study.

For the practicing ORL specialist, it is worth remembering that even the rarest tumors occuring in other sites can be found in the sinonasal tract. Indeed, a varying degree disease spectum in CHBH of sinonasal tumors was demonstrated in this study.

Appendix A : Data collection sheet

Hospital No:

Study No:

Male □

Female □

Age

HIV :

Reactive □

Non reactive □

CD4 Count:

Date of CD4 count:

Nasal symptoms

Tumor site

Gross appearance

Date of biopsy:

Histological findings:

Tumor subtype:

Concomitant pathology:

Appendix B: Ethics clearance certificate

R14/49 Dr Lungile Precious Setoaba et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170668

NAME: (Principal Investigator)	Dr Lungile Precious Setoaba et al
DEPARTMENT:	ENT-Head and Neck Surgery, School of Nueroscienes Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Sinonasal Tumours in Adult Patients: Clinicopathological Perspective from Cihris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	30/06/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Sugeshnee Pather
APPROVED BY:	Professor P. Cleaton-Jones Chairperson, HREC (Medical)
DATE OF APPROVAL:	23/08/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/3rd floor, Philip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially review June and will therefore be due in the month of June each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 30/08/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: Turn it in receipt

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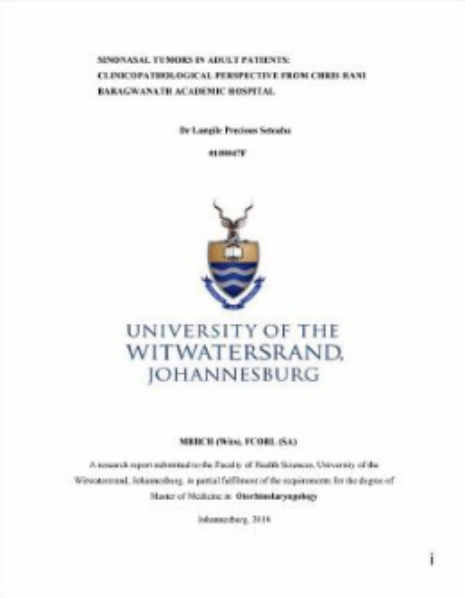

SINONASAL TUMORS IN ADULT PATIENTS:
CLINICOPATHOLOGICAL PERSPECTIVE FROM CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

Dr Lungile Precious Setoaba

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

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