ROLE OF HUMAN PAPILLOMA VIRUS IN THE ETIOLOGY OF PRIMARY MALIGNANT SINONASAL TUMORS

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF M.S BRANCH –IV (OTORHINOLARYNGOLOGY) EXAMINATION OF THE TAMILNADU DR.MGR MEDICAL UNIVERSITY TO BE HELD IN APRIL 2016

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CERTIFICATE

This is to certify that the dissertation entitled **'ROLE OF HUMAN PAPILLOMA VIRUS IN THE ETIOLOGY OF PRIMARY MALIGNANT SINONASAL TUMORS'** is a bonafide original work of Dr Miria Mathews, carried out under my guidance, in partial fulfilment of the rules and regulations for the MS Branch IV, Otorhinolaryngology examination of The Tamil Nadu Dr. M.G.R Medical University to be held in April 2016.

Dr Rajiv Michael

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Professor and Head of Unit – ENT 1

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Role of human papilloma virus in the etiology of primary malignant sino-nasal tumors.
Dr. Miria Mathews, PG registrar, Oto-Rhino-Laryngology and head and neck Surgery, Dr. Rajiv Michael, Oto-Rhino-Laryngology And Head And Neck Surgery - I, Dr. Priya Abraham, Clinical virology, Dr. Anand Job, ENT-1, Dr. John Mathew, ENT, Dr. Rupa Vedantam, ENT, Mr. R. Manikandan, Clinical Virology.

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Dear Dr. Miria Mathews,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

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The Committees reviewed the following documents:

1. IRB application format
2. Curriculum Vitae' Drs. Miria Mathews, Rajiv Michael, Priya Abraham, Anand Job, John Mathew, Rupa Vedantam, Mr. R Manikandan.
3. Consent form (English, Hindi & Bengali)
4. Information sheet (English, Hindi & Bengali)
5. No of documents 1- 4

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Dr. Chandra Singh	MS, MCH, DMB	Professor, Urology, CMCH.	Internal, Clinician
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We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 80,000/- INR (Rupees Eighty Thousand only) for 2 years. (A sum of Rs 40,000/- will be released for I st installment subsequent installment of 40,000/- each will be released at the end of the first year following the receipt of the interim progress report.)

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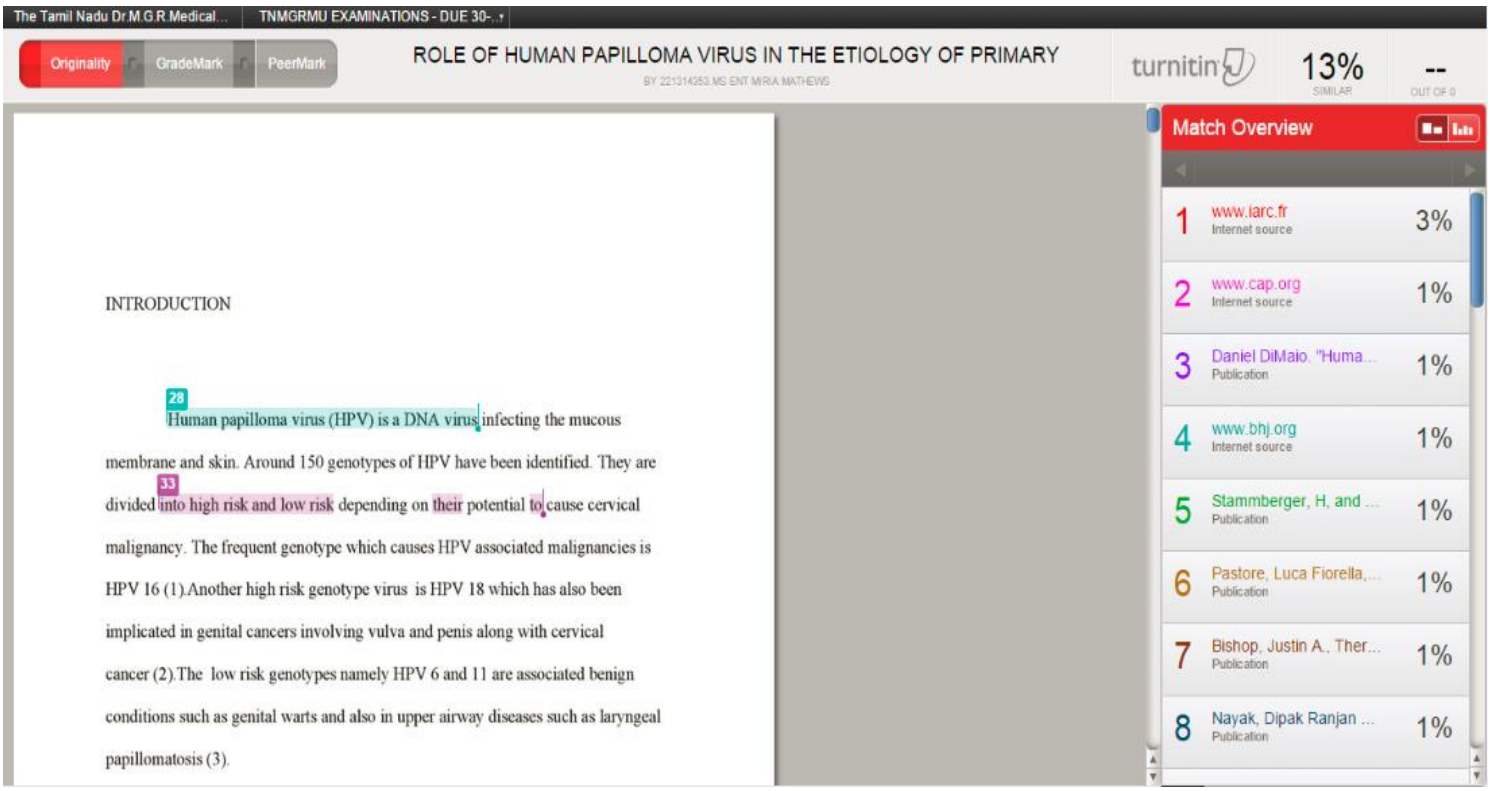

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ROLE OF HPV IN THE ETIOLOGY OF PRIMARY MALIGNANT SINONASAL TUMORS

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CONTENTS

INTRODUCTION

Human papilloma virus (HPV) is a DNA virus infecting the mucous membrane and skin. Around 150 genotypes of HPV have been identified. They are divided into high risk and low risk depending on their potential to cause cervical malignancy. The frequent genotype which causes HPV associated malignancies is HPV 16 (1).Another high risk genotype virus is HPV 18 which has also been implicated in genital cancers involving vulva and penis along with cervical cancer(2).The low risk genotypes namely HPV 6 and 11 are associated benign conditions such as genital warts and also in upper airway diseases such as laryngeal papillomatosis (3).

Just like the squamo-columnar junction seen in the cervix, there are similar sites in the upper aerodigestive tract where two different epithelia are seen. These areas are namely limen vestibule, tonsillar pillar, nasopharyngeal surface soft palate, epiglottis, ventricle, carina and lower end of oesophagus. These areas of upper aerodigestive tract are predisposed to HPV infection similar to cervix(4).HPV transmission mainly happen horizontally through sexual contact. However, newer theories suggest spread through vertical transmission from mother to the child and to a lesser extent horizontally by autoinoculation.

One of the recent advances in head and neck oncology was in the area of oropharyngeal cancers with the discovery of HPV associated malignancies. Prevalence of HPV in oral mucosa of normal adults is as low as 1-2% and is

mostly low risk genotypes (5). However high risk genotypes 16 and 18 were seen in oropharyngeal cancers, mostly squamous cell carcinoma. HPV infection has been proven to predispose to various benign and malignant conditions of the oral cavity and is an emerging risk factor in young patients with no history of any addictions. Studies made an interesting finding that presence of high HPV titres in oropharyngeal malignancy was associated with improved treatment outcomes and better disease free 5 year survival rates. Extensive research on modulating treatment for HPV associated oropharyngeal malignancies are being carried out. Clinical trials to see the role of treatment de-intensification in such patients are underway(6).

Nasal and paranasal sinus malignancies constitute only less than 1 % of the all malignancies and around 3% of upper airway malignancies(7).Out of these, squamous cell carcinoma is the histological type frequently seen followed by adenoid cystic carcinoma which is also the most common salivary type of sinonasal malignancy. Maxillary sinus is the common site to get involved. Exposure to wood dust, smoking and heavy metals has already been implicated as etiological agents for sinonasal malignancies(8).

Association of HPV with oropharyngeal cancers has led to many studies on the prevalence of HPV in different areas of the upper aerodigestive tract and its role in carcinogenesis at these sites. In a study done by Hasegawa M et al in patients with chronic sinusitis, 7% were found to be HPV positive and low risk genotypes were detected in the HPV positive cases (9).Role of HPV in benign sinonasal papilloma especially inverted papilloma is well

established (10). It is already known that inverted papilloma is prone to malignant transformation (5-15%) and that has high recurrence rates despite adequate surgical clearance(11). A review study has shown prevalence of HPV in malignant sinonasal tumors ranges from 20% to 30% (12). HPV genotypes 16 and 18were detected in these cases which are the high risk genotypes associated with cervical malignancy. Similarly malignancies of other subsites such as larynx and nasopharynx also showed presence of high risk HPV(13)(14). Though HPV positivity in oropharyngeal malignancy have shown to have better clinical outcome and survival rates, our knowledge on the behaviour of HPV associated non oropharyngeal head and neck malignancies is very limited.

Data regarding sinonasal tumors in India is very few probably due to rarity of such cases. Since it is proven that HPV positive oropharyngeal cancers have better prognosis, extrapolating it to sinonasal tumours requires further research .This study attempts to find the association of HPV in malignant sinonasal tumors in patients attending ENT OPD in a tertiary level referral hospital in India through a case control study design.

AIM AND OBJECTIVES

AIM

To investigate the role of HPV in primary malignant sinonasal tumors

OBJECTIVES

- PRIMARY OBJECTIVE:

To find out the association of HPV and primary malignant sinonasal tumors.

- SECONDARY OBJECTIVES:

1. To find out the demographics of patients with malignant sinonasal tumors attending ENT OPD in a tertiary care hospital.

2. To find out various risk factors associated with malignant sinonasal tumors attending ENT OPD in a tertiary care hospital.

REVIEW OF LITERATURE

Nasal cavity and paranasal sinuses occupy a comparatively small anatomical space, but they are the site of origin of some of the most complex, diverse group of tumours in the entire human body which include neoplasms derived from any structure in the sinonasal tract such as from mucosal epithelium, seromucinous glands, soft tissues, bone, cartilage, neural/neuroectodermal tissue, haematolymphoid cells and the odontogenic apparatus. Many of the tumours are similar to those found elsewhere in the body but a few, such as the olfactory neuroblastoma, are unique to this site. Yet these malignancies comprise of just 1% of all cancers and less than 3% of upper digestive tract malignancies which makes it a rare tumor to encounter(15).

Human papilloma virus is a small DNA virus which has been implicated in carcinogenesis, common area being cervix. The high risk varieties have been isolated in cervical malignancies and have been proven to predispose the patient to cervical cancer. Studies were done in upper aerodigestive tract which showed presence of HPV in oropharyngeal, laryngeal, nasopharyngeal, oesophageal cancers. Recently intense research in oropharyngeal malignancies has revealed the presence of high risk subtypes mainly associated with squamous cell carcinoma. Studies also showed that these HPV positive oropharyngeal tumors are more sensitive to treatment

especially radiotherapy and have less chance of field cancerization which give better survival rates and decreased rate of recurrence .

Sinonasal malignancies are predominantly squamous cell carcinoma. Exposure to wood dust and heavy metals are implicated in the etiology of sinonasal malignancy. Presence of high risk HPV in different sites of aerodigestive tract malignancies led to studies on the association of HPV with sinonasal malignancies. Recent studies reveal an overall prevalence of around 20%(16). A study done in Barcelona showed that HPV positive sinonasal tumors had a better 5 year survival rate compared to HPV negative sinonasal malignancies(17).

In India, unlike the western countries, head and neck malignancies can be still attributed with tobacco smoking, pan chewing and alcohol consumption as these are rampant in the population. Sexual habits are also quite different from the western population as the indigenous culture is conservative .However these is a small subset of patients which is no risk factors who develop these malignancies. For this group of patients, further research on other etiological factors for such malignancies such as HPV are warranted. As shown in HPV associated oropharyngeal cancers, the implications of HPV association with sinonasal malignancies can gives us a better perspective on management and prognosis in such cases. Indian data on HPV associated sinonasal malignancies are few. This study focuses on finding out the association of HPV with primary sinonasal malignancies in a tertiary care hospital in India.

EMBRYOLOGY OF NASAL CAVITY AND PARANASAL SINUSES

Embryology of face, neck, nasal cavity and paranasal sinuses are closely interlinked and takes places together in a short duration of time. After the development of the branchial arches which happens around the 4th week of intrauterine life, the primitive gut is formed.

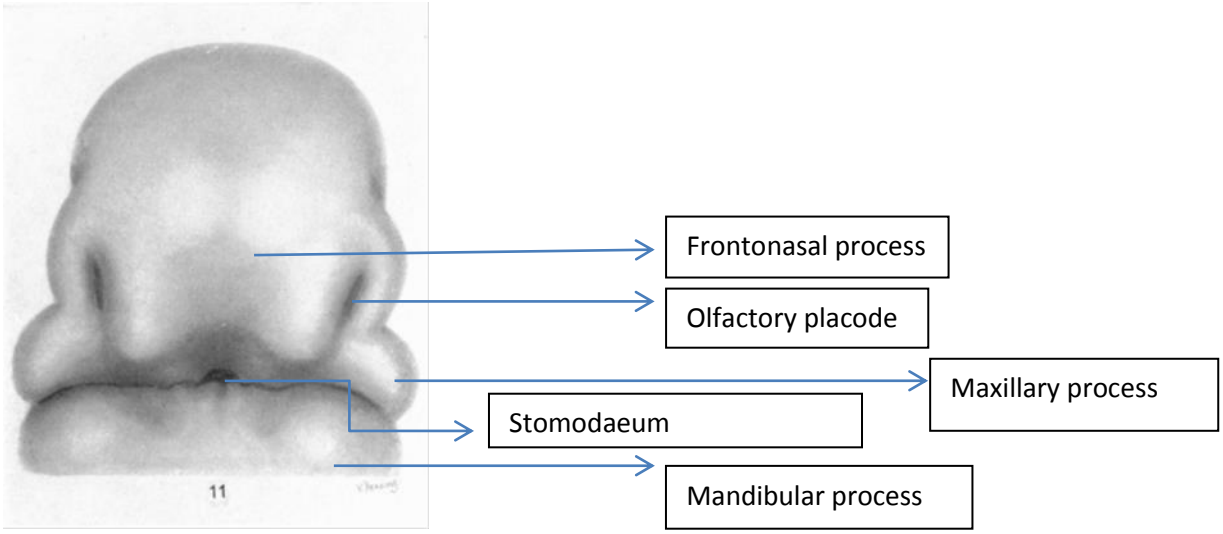

Figure 1: Figure showing the development of face (18).

Stomodaeum is an opening in the middle of the identifiable head and face of the embryo. It is bounded bilaterally by the maxillary and mandibular prominences which are derived from the first arch. Superiorly, the frontonasal process and inferiorly the mandibular arch bound the stomodaeum. From the frontonasal process develops the olfactory placodes which are thickening of ectoderm around primitive mouth which later form nasal cavity. They form olfactory pits which divide the proliferating mesoderm of the frontonasal process into medial and lateral nasal process. The maxillary process fuses with

medial nasal process to form septum and with the lateral nasal process to form the nasomaxillary groove (15).

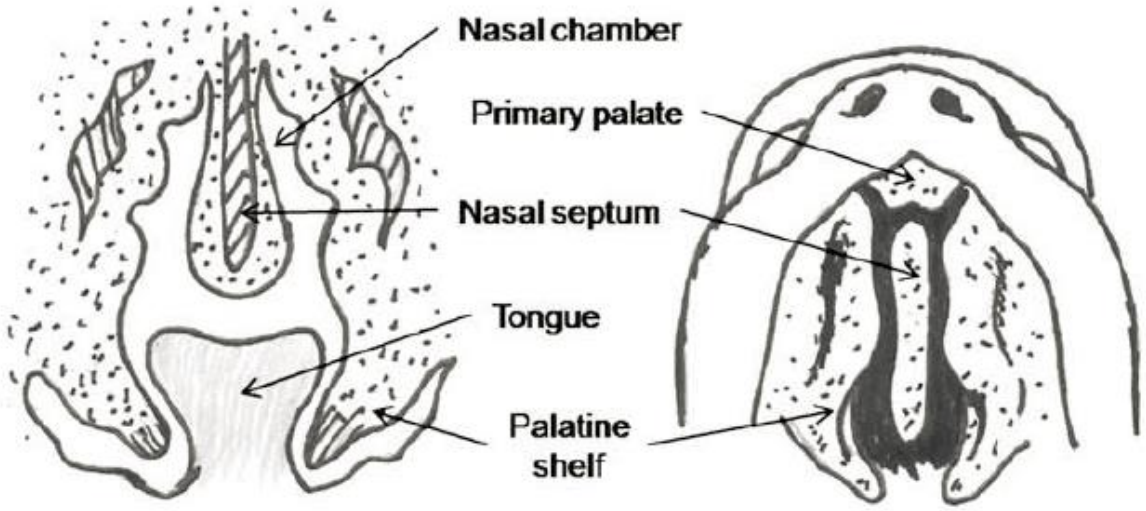

Figure 2: Development of the nasal cavity and palate (19).

The oronasal membrane separates the primitive stomodaeum from the nasal cavity. The two palatal processes of maxilla fuse in the midline to form floor of nose which separates nasal cavity from mouth (16). The nasal cavities open posteriorly via the choana into the nasopharynx. The primitive nasal septum is entirely cartilaginous. The superior part ossifies to form the perpendicular plate of ethmoid and postero-inferiorly, vomer leaving behind an antero-inferior cartilaginous part.

Development of lateral wall of nose starts by 12 weeks of gestation as three medially directed projections from the lateral wall of the nose, called the preturbinates. The anterior most projection forms the agar nasi cells and uncinate process. The inferior projection, also called as the maxilloturbinate projection later forms the inferior turbinate and the maxillary sinus. The third projection, also called the ethmoidoturbinate which is the superior most projection forms the ethmoidal air cells, middle turbinate and superior turbinate with their drainage channels. Between these projections, laterally directed diverticula develop from the primitive choana which later forms the meati.

The paranasal sinuses develop from varying number of ossification centres. The embryonic infundibulum develops form the laterally invaginating middle meatus. Frontal sinus develops from the direct continuation of this infundibulum into frontal recess as a small sac within the inner and outer table of the frontal bone till secondary pneumatisation after 2 years of age. It can also be formed when anterior ethmoidal air cells migrates into the frontal bone. The first sinus to appear is the maxillary sinus around 8 weeks of gestation. It starts as a shallow out pouch from the ethmoid infundibulum into the maxilla. It attains maximum size by 18 yrs of age with an approximate volume of $15cm^2$. The anterior ethmoid sinus and posterior ethmoid develops from invagination of lateral nasal wall into middle meatus and superior meatus respectively. Sphenoid sinus develops from the invagination into sphenoethmoidal recess. The last sinus to complete development is frontal sinus which completes by 8 years of age.

ANATOMY OF NASAL CAVITY AND PARANASAL SINUSES

The nasal cavity is divided into two by the septum in the midline. It extends from external nares to choana posteriorly continuing to form nasopharynx. Vertically, it extends from the palate to the cribriform plate, being broader at its base than superiorly where it narrows to the olfactory cleft. Vestibule is the passage connecting external nares to nasal fossa or nasal cavity proper, posteriorly bound by limen nasi. It is lined by skin containing hair, sebaceous cyst and sweat glands. Nasal cavity proper is lined by ciliated columnar respiratory epithelium with a small area of olfactory epithelium superiorly adjacent to the cribriform plate. Respiratory epithelium is composed of ciliated and nonciliated pseudo stratified columnar cells, goblet cells and basal pluripotential stem cells.

The external framework of the nose is formed by a bony part comprising of the nasal bones with the frontal process of maxilla and a cartilaginous part made up of upper lateral nasal cartilage and lower lateral cartilages which are also called as the alar cartilages along with the nasal septum. This area is supplied by the branches of both external carotid artery through the facial artery with its branches such as the superior labial artery, angular artery, lateral nasal artery, columellar artery and the artery to nasal alae and from the internal carotid artery through the a branch of ophthalmic artery called as dorsal nasal artery.

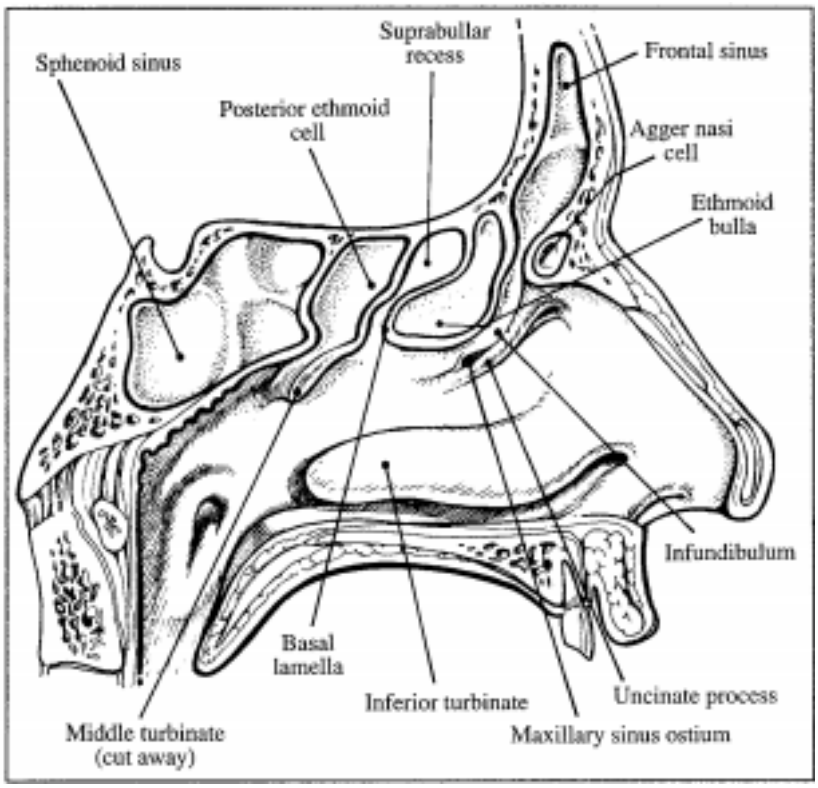

Figure 3: Sagittal section through the ethmoid sinus showing the structures of lateral wall of nose (20).

The lateral nasal wall contains the paranasal sinuses ostia plus three or four turbinates commonly called as superior, middle and inferior turbinates. These turbinates are delicate scroll-like projections of bone and vascular soft tissue. They attach to the lateral nasal wall anteriorly with a posterior free edge. The turbinates are covered with thick mucous membrane and contains venous plexuses. They cover areas called superior, middle and inferior meati which has the opening of different paranasal sinuses. The inferior meatus contain the opening of nasolacrimal duct which connects the lacrimal sac with nose. The middle meatus contains opening of the maxillary sinus and anterior ethmoidal sinus. The frontal sinus opens into the infundibular portion of the middle

meatus through frontal recess into the anterior most part of the middle meatus. The posterior ethmoidal air cells along with the sphenoid sinus open into the sphenoethmoidal recess lying posterior to superior turbinate.

The olfactory recess is an area at the roof of the nose which is bound laterally by the superior turbinate and adjacent lateral nasal wall, and medially by the nasal septum. This region is lined by the olfactory mucosa (OM) which has a yellowish appearance. This mucosa contains bipolar olfactory nerve fibres that cross through the cribriform plate with terminal axons extending into the free surface of the epithelium, where they expand into protrusions bearing cilia (olfactory cilia). Bowman's glands or olfactory glands are seen within the lamina propria. They are similar to serous minor salivary glands. Pseudo stratified columnar ciliated epithelium with interspersed goblet cells lines the nasal cavity and paranasal sinuses. It is also called as Schneiderian mucosa. It is interesting to note that the lamina propria of the epithelium within the paranasal sinuses is loose and well vascularized especially in the maxillary antrum, with seromucinous glands, and can easily become polypoidal as a result of oedema. The septum is lined by relatively thin, ciliated respiratory mucosa, may regularly undergo squamous metaplasia.

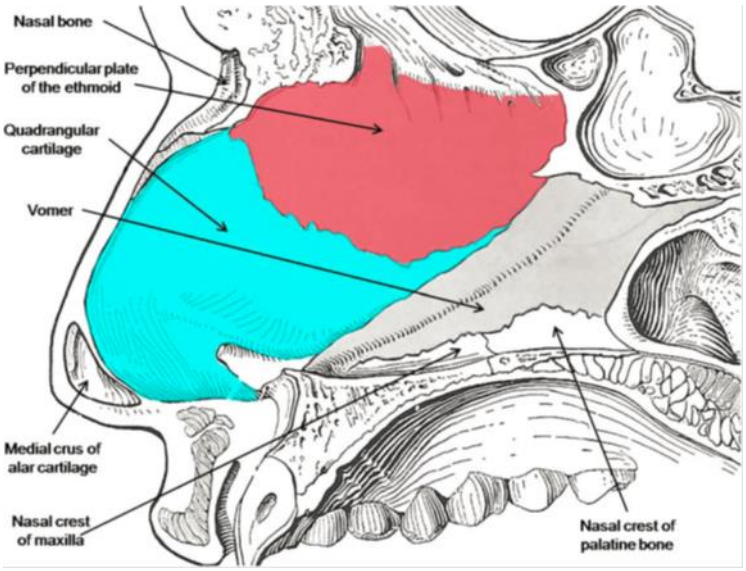

Figure 4: Diagrammatic sagittal view of nasal septum(19).

The nasal septum comprises of 7 parts which can again be divided into bony, cartilaginous and membranous part. The cartilaginous part is formed by the quadrangular cartilage or the septal cartilage. The membranous part is columella. The bony part is formed by the vomer posteroinferiorly, perpendicular plate of ethmoid posterosuperiorly, maxillary crest inferiorly and the anterior nasal spine anterosuperiorly.

There is presence of squamocolumnar junctions in the upper airway namely - limen vestibule (internal nasal valve – junction of vestibule and nasal cavity proper), inferior surface of true cord, ventricles – upper and lower margin, nasopharyngeal surface of soft palate and epiglottis. These sites are prone to HPV infection and thus have a greater chance to develop benign and malignant tumors.

PHYSIOLOGY OF NOSE AND PARANASAL SINUSES

The nose plays an important role in the cleansing and conditioning of inspired air contributes in altering the quality of speech and also is the organ of smell. The inspired air is first filtered by the vibrissae in the vestibule where particulate matter is trapped. The air is then humidified with the help of mucus blanket formed from the secretions of the serous and mucous glands present in the respiratory epithelium. All the paranasal sinuses are lined by ciliated columnar epithelium with goblet cells, which is in continuous with that of nasal cavity. The submucosa contains numerous serous and mucous secreting glands. Stroma may have few infiltrates of lymphocytes, neutrophils, eosinophils, mast cells etc. The temperature of the inspired air is brought to the level of the body temperature by way of heat exchange. The physiological phenomenon where each side of the nose alternates through phases of congestion and decongestion is called nasal cycle.

Functions of Paranasal sinuses include:

1) Air-conditioning of inspired air

2) Impart resonance to the voice

3) Absorb shock applied to the head

4) Secrete mucus to keep nasal chambers moist

5) Provide thermal insulation for the brain

6) Contribute to facial growth

7) Lighten the skull bone

8) Regulation of humidity and temperature of inspired air

The uncinate process has a role in directing the inspired air away from the sinuses, thus protecting them. It probably also directs the expired air into the infundibulum and the maxillary ostium. Inspired air carries allergens and bacteria whereas the expired air is more sterile and allergen free because it is "pre-treated" by the respiratory epithelium. Thus, the sinuses are normally ventilated by a more sterile and allergen free air. Moreover, an important function of the paranasal sinuses is that they preserve the mucociliary activity by providing middle meatus with continual supply of fresh, uncontaminated mucus.

Some believe that the sinuses play a role in conditioning of the inspired air, pressure dampening, heat insulation and voice resonance. Others however, opines that the sinuses may have no function at all and may merely be vestigial structures assuming a significant role when diseased.

ETIOPATHOLOGY OF SINONASAL MALIGNANCIES

Paranasal sinus malignancies remain rare comprising less than 3 % of all head and cancers worldwide (21) . In western population, the incidence is around 1 % and in eastern population around 3 per 100,000 people. A significant majority of tumors occur at an older age (50 to 60 years of age). Although it appears that twice as many men are affected as women, this may be secondary to environmental or occupational exposure. Higher rates are recorded in Japan and certain parts of China and India. Of the entire sinonasal tumour, 60% originate in the maxillary sinus, 20-30% in the nasal cavity, 10-

15% in the ethmoid sinus and just 1% in the sphenoid and frontal sinuses. When considering the paranasal sinuses alone, maxillary sinus tumors comprises of 77% of malignant tumors, 22% in the ethmoid sinus and 1% in the sphenoid and frontal(22). Tumors that arise from the frontal and sphenoid sinuses are rare, yet their involvement through tumor extension is highly suggestive of advanced disease and poor prognosis.

Squamous cell carcinomas (SCC) are the commonest histological type seen(23).The second most common adenoid cystic carcinoma which is an salivary type of malignant sinonasal carcinoma. When SCC remains the most frequent histology in adults, the most common paediatric sinonasal malignancy is rhabdomyosarcoma.

Occupational exposure to wood dust especially the dust of hard woods such as beech and oak, is the main known risk factor for sinonasal cancer(24),(25). The increase in risk (in the order of 5-50 folds) is strongest for adenocarcinomas and in particular for cancers originating from the paranasal sinuses. The effect is present after 40 or more years since first exposure and was also seen it also persists after cessation of exposure. It was also seen that among workers in nickel and chromium manufacture there was an increased risk of developing sinonasal malignancy. Among other suspected occupational carcinogens are formaldehyde, dichloroethyl sulfide and di-isopropyl sulfate. A comparatively weak (relative risks in the range 2-5) but consistent association has been shown between smoking tobacco and sinonasal cancer especially in

squamous cell carcinoma. Exposure to Thorotrast which is a radioactive contrast agent represents an additional risk factor.

With strong evidence of presence of active high risk HPV in oropharyngeal malignancies, research in sinonasal malignancies are also suggesting HPV in etiology of these malignancies. Around 20% of sinonasal malignancies had high risk HPV DNA according to western literature. However studies in India are few to reveal any association.

The sinonasal malignancies are classified broadly into epithelial and non-epithelial types. The most commonly seen are epithelial subtype of which squamous cell carcinoma is the commonest. Other epithelial sinonasal malignancies are adenoid cystic carcinoma and adenocarcinoma. The non - epithelial carcinomas seen are lymphomas which include the NK (natural killer) and T cell types also called as lethal midline granuloma, olfactory neuroblastoma and mucosal melanoma. There are 44 different entities of sinonasal malignancies as classified by World Health Organisation (WHO).

Sinonasal malignancies can be classified histologically by WHO as:

EPITHELIAL TUMORS

- Squamous cell carcinoma
- Sinonasal undifferentiated carcinoma
- Salivary type carcinoma
- Adenocarcinoma
- Neuroendocrine tumors

SOFT TISSUE TUMORS

- Fibrosarcoma
- Leiomyosarcoma
- Rhabdomyosarcoma
- Angiosarcoma
- Malignant peripheral nerve sheath tumors

BONE AND CARTILAGE TUMORS

- Chondrosarcoma
- Fibrosarcoma
- Chordoma
- Osteosarcoma

HAEMATOLYMPHOID MALIGNANCIES

- Lymphoma
- NK cell / T cell lymphoma
- B cell lymphoma
- Extramedullary plasmacytoma
- Langerhans cell histiocytosis

NEUROECTODERMAL TUMORS

- Ewing's sarcoma
- Olfactory neuroblastoma
- Mucosal malignant melanoma
- Primary neuroectodermal tumor
- Melanotic neuroectodermal tumor of infancy

GERM CELL TUMORS

- Teratoma with malignant transformation
- Sinonasal teratosarcocarcinoma

SECONDARY TUMORS

COMMON TYPES OF SINONASAL MALIGNANCIES

Squamous cell carcinoma (SCC)

The most common of the sinonasal malignancies (40% to 50% incidence), SCC arises from the respiratory epithelium and has been broadly classified into keratinising and non-keratinising. It is a rare tumor and is more common in adults which a male preponderance. It is seen in the elderly age group. Evidence supports that tobacco smoking and snuffing is a major risk factor, much as it is for other aerodigestive tract sites(26). Other risk factors linked are aflatoxin, chromium, nickel, and arsenic among others(27). A viral etiology is also associated with sinonasal SCC which is human papilloma virus. Low risk subtypes 6 and 11 are associated with inverted papilloma, of which approximately 10% later transforms to squamous cell malignancy at a later date(28). SCCs tend to recur more quickly than other sinonasal subtypes with mean recurrence of 2 to 3 years(28). The incidence of regional neck metastasis is relatively higher by around 20% compared to other variants(23).

Adenocarcinoma

Adenocarcinoma makes up between 13% to 19% of all paranasal sinus malignancies(29). They have glandular architecture implying that they arise from the surface epithelium or the seromucous glands of the sinonasal tract. Adenocarcinomas are divided into:

1. Salivary type adenocarcinoma

The salivary variant is very rare constituting to around 10% of sinonasal adenocarcinoma(29).The most common type is adenoid cystic carcinoma(ACC). It mostly involves maxillary sinus and nasal cavity. They are often classified histologically into tubular, cribriform, or solid growth pattern. The solid ACCs are the most aggressive. Unlike SCC, recurrence takes years to manifest. Other types are acinic cell carcinoma, mucoepidermoid carcinoma, epithelial-myoepithelial carcinoma, basal cell adenocarcinoma, salivary duct carcinoma, polymorphous low-grade adenocarcinoma and carcinoma ex-pleomorphic adenoma. Since they are locally aggressive tumors with perineural invasion and chance of distant metastasis, their long term prognosis is not good(29).

2. Non salivary type adenocarcinoma.

It is divided into intestinal and non-intestinal types. The nonintestinal adenocarcinomas have a relatively good prognosis. However intestinal-type adenocarcinomas are locally aggressive with a high rate of spread to neck lymph nodes. Histologically they appear similar to colorectal adenocarcinoma.

The 5-year overall survival has been reported to be approximately 50%(29).It commonly involves ethmoid sinus and maxillary sinus(30). Among the known occupational hazards associated with paranasal sinus malignancies, the most common is with wood dust, which gives a 900-fold increased risk in developing adenocarcinoma, specifically the intestinal type(24). As short as 5 years of exposure can place workers at risk for malignancy till to about 40 years from the time of exposure(31). To a lesser degree, leather-related dust exposure also appears to be associated with adenocarcinoma(32).

Sinonasal undifferentiated neoplasms

Sinonasal undifferentiated neoplasms (SNUCs) are aggressive, high-grade malignancies with a distinct pathologic feature showing no clear squamous or glandular differentiation(33). The cells of origin thus remain unclear but are proposed to be arising from schneiderian epithelium or nasal ectoderm. Immunohistochemistry for SNUCs is nonspecific, lacking reactivity for neuroendocrine markers, but it is useful to exclude similar entities such as olfactory neuroblastoma, with which SNUCs were originally classified(33). The clinical presentation is often rapid growth and extensive disease, and more than 80% of patients presenting as advanced non resectable disease(34). Combined modality of treatment includes surgery which is usually cranio-facial resection, radiation, and chemotherapy is recommended, though the appropriate order of treatment (neoadjuvant vs. postoperative chemo radiation) remains unclear(34). Survival is reported in months(35).Nodal disease has been reported at 26% to 27%, with a 5-year overall survival is 22% to 43% with a

high (36). 65% of patients can develop distant metastases and therefore has a high chance for recurrence(36).

Rhabdomyosarcoma

Rhabdomyosarcomas are the most common paranasal sinus malignancies in paediatric age group. Orbit is the most common subsite overall. Rhabdomyosarcomas are derived from primitive mesenchymal tissue. On histopathological examination, it shows myogenic differentiation and on histology, is among the tumors with small round blue cells. Rhabdomyosarcoma is divided into four categories based on histology(37):

1) Embryonal

2) Alveolar

3) Anaplastic

4) Undifferentiated

The embryonal type is the most common variant with an incidence of 55% to 65%(38). It typically affects infants and younger children. It is classified into botryoid and spindle cell subtypes, generally considered to have the most good prognosis(39). The second common variant, the alveolar type (20% to 30% incidence) occurs more often in teens(38). It has a potentially poorer prognosis, and usually requires more intensive multimodality treatment(39). The other two types namely the anaplastic type previously termed pleomorphic rhabdomyosarcoma and undifferentiated largely affects

adults and both of these types has poor prognoses because of their rapid growth and high rate of distant spread(37). In the head and neck, protocols advocate neoadjuvant chemotherapy followed by surgical resection, because recurrence can be high despite aggressive resection(38). Overall, 5-year overall survival is high, especially for orbital rhabdomyosarcoma, at 95%; for parameningeal sites, it is 74%(39).However prognosis largely depends on the histology.

Osteosarcoma and Chondrosarcoma

Head and neck osteosarcoma accounts for less than 10% of all osteosarcomas and less than 1% of all head and neck tumors which makes it a rare entity(40). It is commonly seen in the fourth decade, however has a wide range with equal gender distribution with commonly involved subsites being maxilla and mandible(41). The different histological subtypes are chondroblastic, osteoblastic, fibroblastic and telangiectatic. Generally all head and neck osteosarcomas are high grade and require surgical resection with adjuvant radiation(40). The role of chemotherapy is ill defined, but may benefit patients with poor prognosis. Recurrence with head and neck osteosarcomas are very rare and the overall cure rate is good with 60% to 70%(41).A small subset of these patients had prior history of radiation exposure. A genetic link between retinoblastoma and osteosarcoma on the 13q 14 chromosome makes patients with retinoblastoma predisposed to develop osteosarcoma post treatment, with an increased risk post radiotherapy(42).

Chondrosarcoma of head and neck constitute to about less than 0.1% of all head and neck malignancies(43). It involves mainly the axial skeleton and is very rarely found in head and neck. The regions involved are paranasal sinuses, temporal bone and larynx. The mainstay of management is surgical resection with adjuvant radiotherapy. The overall survival rate is good with around 70%(44).

Lymphoma

Lymphoma is the malignant neoplasm of the lymphocytes. It is classified into Hodgkin's lymphoma and Non-Hodgkin's lymphoma. It contributes to around 5-11% of all head and neck malignancies(45). It is either be B cell type or T cell line. Head and neck is the second common site for extra nodal lymphoma, following gastrointestinal tract(46). It commonly involves the Waldeyer's ring which involves tonsils, base of tongue and nasopharynx or can present as cervical lymphadenopathy. Other head and neck subsites are oral cavity, paranasal sinuses, nasal cavity, thyroid gland, salivary glands, and larynx, parapharyngeal and infratemporal spaces. The common variant seen is B cell type Non- Hodgkin's lymphoma(47). In nasal cavity, NK/T cell type is commoner. An association with Epstein Barr virus has been proposed with lymphomas(37). Computed tomography of head and neck, chest, abdomen and pelvis with concurrent positron emission tomography and bone marrow biopsy is the mainstay for staging(47). The main treatment modality is chemotherapy followed by field radiotherapy. Localized lymphomas have a good outcome

with treatment (5 yr survival 83%)(48). Nasal NK/T cell lymphomas are more aggressive with higher relapses and thereby carries a worse prognosis(45)

Olfactory neuroblastoma

Olfactory neuroblastoma also known as Esthesioneuroblastoma (ENB) are tumors of neuroectodermal origin derived from olfactory epithelium. They make up less than 5% of paranasal sinus malignancies(37).Unlike other tumors of sinonasal tract, this tumor is highly specific to nasal cavity and requires unique management. It has a bimodal age distribution (at the second and sixth decade) with no gender predilection(49). Patients normally presents with unilateral nasal obstruction with epistaxis with history of anosmia. On imaging, the characteristic finding is a dumb bell shaped mass across the cribriform plate(49). Histologically, they are characterized by a lobular appearance with neuroblasts and neurofibrils embedded among highly vascular fibrous stroma. The Kadish staging system is the most widely accepted to predict disease-free survival(37). It has following categories:

Group A: Tumors are limited to the nasal cavity

Group B: Tumors extend only to the paranasal sinus

Group C: Tumors extend beyond the nasal cavity and sinuses

Group D (in Modified Kadish system): Presence of cervical lymphadenopathy or distant metastasis

50% of these tumors are diagnosed as Group C tumors and has a good prognosis (5 year survival rate of 50% to 70%)(37). Treatment if surgical can be endoscopic if the tumor is limited or craniofacial approach for extensive tumors with post-operative radiotherapy as they are typically radiosensitive(50). Palliation with chemotherapy is advised for advanced non resectable tumors and in cases with distant metastasis. There is controversy about the utility of elective neck dissections or elective neck irradiation as these tumors eventually develop cervical neck metastases in 20% to 25% of the patient(50). However, no consensus has been made on this matter. Lungs and bones are the common sites for distant metastasis.

Mucosal melanomas

Sinonasal tract is the most frequent sites for mucosal melanomas in the head and neck(51). Mucosal melanomas comprise less than 1% of all melanomas and are less pigmented than cutaneous lesions(52). They are positive for S-100, human melanoma black 45, and melanin A just like cutaneous lesions. Mucosal melanomas are extremely aggressive. Surgical resection remains the standard of care(52). Post-operative radiotherapy helps in controlling local disease(53). Majority of patients ultimately develop distant metastasis. The most common sites of metastasis are lung, liver, and bone.The5-year overall survival has been reported to be between 25% and 42%(54).

TNM CLASSIFICATION OF SINONASAL MALIGNANCIES

(Classification by American Joint Committee on Cancer (AJCC) 2014)

(For epithelial tumors)

Primary tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

Maxillary sinus

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

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

T3 Tumor invades any of the following: bone of posterior wall of maxillary sinus, subcutaneous tissue, floor or medial wall of orbit, pterigoid fossa and ethmoid sinuses.

T4a Moderately advanced local disease

Tumor invades anterior orbital contents, skin of cheek, pterigoid plates,

infratemporal fossa, cribriform plate, frontal or sphenoid sinuses.

T4b Very advanced disease

Tumor invades any of the following:

Orbital apex

Dura

Brain

Middle cranial fossa

Involvement of cranial nerves other than maxillary division of trigeminal nerve

Nasopharynx

Clivus

Nasal cavity and ethmoid sinus

T1 Tumor restricted to any one subsite +/- bone invasion

T2 Tumor invading two subsites in a single region or extending to involve an adjacent region within naso-ethmoidal complex with or without bony invasion

T3 Tumor extends to invade the medial wall or floor 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

Pterigoid plates

Frontal or sphenoid sinus

T4b Very advanced disease

Tumor invading any of the following:

Orbital apex

Dura

Brain

Middle cranial fossa

Cranial nerves other than maxillary division of trigeminal nerve

Nasopharynx

Clivus

Regional lymph nodes (N)

Nx Regional lymph nodes cannot be assessed

N0 No regional lymph node involvement

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

N2a Metastasis in single ipsilateral lymph node, more than 3 cm but less than 6cm in the greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes none more than 6 cm in the greatest dimension

N2c Metastasis in bilateral or contralateral lymph node none more than 6 cm in the greatest dimension

N3 Metastasis to any lymph node but more than or equal to 6 cm in the greatest dimension

Distant metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

Staging

Stage 0	Tis	N0	M0
Stage 1	T1	N0	M0
Stage 2	T2	N0	M0
Stage 3	T3 T1 T2 T3	N0 N1 N1 N1	M0 M0 M0 M0
Stage 4	T4a T1 T2 T3 T4a T4a	N0 N2 N2 N2 N1 N2	M0 M0 M0 M0 M0 M0
Stage 5	T4b Any T	Any N N3	M0 M0
Stage 6	Any T	Any N	M1

Histologic Grade (G)

Gx	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

PROGNOSIS AND PROGNOSTIC FACTORS OF SINONASAL MALIGNANCIES

Collectively, 5-year survival for all paranasal sinus malignancies is approximately 50%(37). Neck metastasis occurs in only 3% to 20% of patients, whereas distant metastasis occurs in 17% to 25% of patients(28). Malignancies such as squamous cell carcinoma (SCC), sinonasal undifferentiated carcinoma (SNUC) and mucosal melanoma are known to be clinically more aggressive compared with esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma, and adenoid cystic carcinoma. SCC remains the most frequent histology in adults, whereas the most common paediatric sinonasal malignancy is rhabdomyosarcoma. Metastases from other primary cancers do present in the paranasal sinuses: the most commonly cited include those from breast, kidney, and prostate sites(55).

HUMAN PAPILLOMA VIRUS

Human papilloma viruses (HPV) are small, non-enveloped, circular double-stranded DNA viruses which belong to papillomaviridae family that infect the epithelium. They are obligatory intranuclear viruses. There are 120 types that have been identified till date based on the different genetic sequence of L1 which is the outer capsid protein. They infect the basal epithelium through mucosal injury, at the squamocolumnar junctions or on metaplastic epithelium. Most commonly HPV infests the skin to cause warts and mucosal epithelium by at least 40 subtypes to cause infections of varying risks. They

have been classified according to their association with cervical cancer, which is the most common tumor caused by these viruses into:

1) Low-risk or non-oncogenic types - types 6 and 11, can cause benign conditions such as genital warts and papilloma of larynx.
2) High-risk, or oncogenic types - types 16 and 18, acting as precursor to anogenital and oropharyngeal cancers

HPV genome is functionally classified into 3 parts:

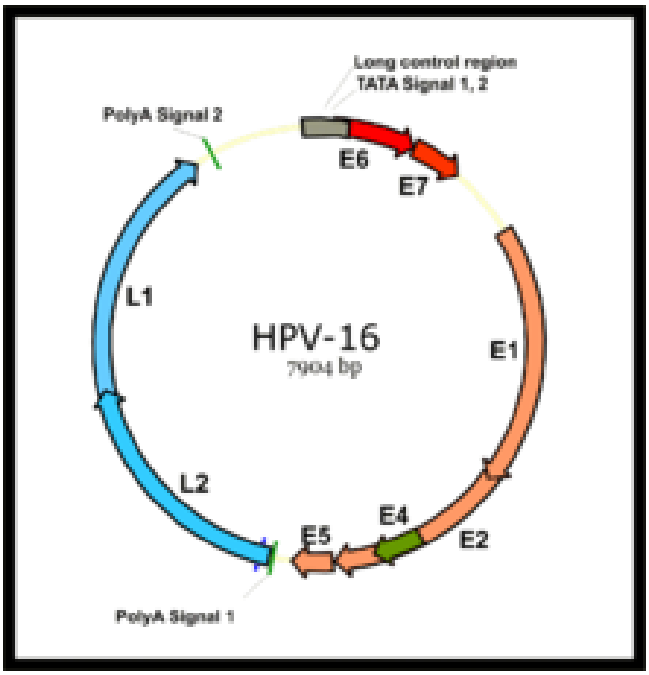

Figure 5: Genomic organisation of HPV 16.

1) Upper regulatory region

It is the non-coding region of the genome which contains 400 – 1000 base pairs. It regulates DNA replication as it controls the open reading frame transcription through the p97 core promoter and silencer sequences. It is also called long control region (LCR).

2) Region for early transcriptional genes

It consists of E1, E2, E4, E5, E6 and E7 open reading frame protein coding sequences which are involved in viral replication. E1 and E2 are pivotal in viral transcription and replication through the various activators and repressor proteins which they code. Maturation and release of virus particles are controlled by E4. E6 encodes for proteins that down regulate p53 gene and E7, for the retinoblastoma gene which is the tumor suppressor gene. Thus E6 and E7 are called viral oncogenes. They are called 'E' as they are expressed early in the life cycle and as mentioned above are vital in neoplastic transformation of the host cell by altering its metabolism(56).

3) Region for late transcriptional genes

These open reading frame sequences namely L1 and L2 code for the structural proteins of viral capsid. HPV is divided into subtypes depending on genetic sequences for L1.

INFECTIONS ASSOCIATED WITH HPV

HPV is attributed to a wide variety of disease such as benign conditions of cervix, skin and oral cavity namely verruca vulgaris, focal epithelial hyperplasia, squamous cell papilloma and condyloma acuminatum to malignancies of anogenital tract, oral cavity and head and neck. It is commonly transmitted by sexual contact and involvement of oral cavity by autoinoculation or by maternal transmission. HPV type 6 and 11were identified in papillomas and condylomas while types 2 and 4 with oral verruca. In the immune compromised, HPV associated infections shows atypical morphology and also multiple subtypes can be isolated. Though HPV infection is quite common in the sexually active groups, it is persistent infection of the virus which causes benign and malignant conditions. These benign conditions can spontaneously regress or can persist to lead on to recurrent infections and even malignant conditions. Few common HPV associated benign conditions are explained below:

Squamous cell papilloma

It is one of the most common benign HPV associated condition. It can affect anogenital tract, skin, oral cavity and even the respiratory tract, commonly seen in larynx. Grossly, it has small finger like projections which made it appear cauliflower like. Laryngeal papillomatosis, a common benign

neoplasm of the larynx is divided into juvenile and adult onset types. Though this condition is infamous for its recurrence, malignant transformation is hardly seen. As in other benign conditions, HPV 6 and 11 subtypes are seen. However HPV 6 is seen to be more aggressive. Maternal and orogenital spread by autoinoculation are common mode of transmission in children. The presentation can vary from change in voice to difficulty in breathing with stridor. Management included securing the airway in case of acute breathing difficulty followed by surgical debridement. Adjuvant therapy with antivirals, anti-reflux drugs, retinoids and immunomodulators are tried with varied benefits. Though the condition might spontaneously resolve, it commonly recurs with the patient needing surgical debridement periodically.

Condyloma acuminatum

Also called venereal wart, it is commonly seen in anogenital tract. Presence of such lesions in oral cavity was reported as early as 1901 when a prostitute developed this lesion in the tongue(57). As in all other HPV associated infections, spread can occur through autoinoculation and maternal transmission. Gingiva, cheeks, lips, hard palate and the site of traumatic event or contact on non-keratinized tissues are the common oral sites involved. Involvement of oral cavity can be seen without anogenital lesions also. It appears as small pedunculated or sessile epithelial proliferations with smaller satellite lesions around (58). Clinically they appear similar to papillomas and warts. It is diagnosed mainly based on histopathological findings.

Verruca vulgaris

They can occur anywhere on the skin, anogenital tract and oral cavity. It appears as small, plane topped, slightly elevated, filiform and non-tender growths. These lesions can also be seen in respiratory tract though very rarely(59). Infections with Epstein-Barr virus (EBV),Cytomegalovirus, Herpes virus and immunodeficiency have also been investigated as possible reasons for this disease(60).

Focal epithelial hyperplasia

Clinically seen as single or multiple mucosal papules commonly found in oral cavity, these lesions are benign. It is more common among females and in lower socioeconomic groups(61). Biopsy is the key to diagnosis. HPV subtypes 13 and 32 are attributed to this condition(61).

MALIGNANCIES ASSOCIATED WITH HPV

The association of HPV with various cancers of urogenital tract and aero digestive tract is an area under extensive research. Unlike most cancers, HPV associated malignancies have been to seen to have a better treatment outcome. This is possible because HPV-associated cancers express HPV viral genes even in advanced stages of disease and down regulation of these viral oncogene expressions can prevent the growth or survival of cancer cells. This

finding gives us the possibility that even late stage cancers can be cured by HPV-targeted strategies which includes medicines which can interfere with the expression or action of viral proteins and therapeutic vaccines that help body to destroy cells which are expressing these proteins(62). So this subset of cancer is of special importance since the aim of treatment is not just prolonging life, but for complete cure.

HPV AND CERVICAL CANCER

Harold Zur Hausen was the first to discover the association between HPV and cervical cancer for which he was awarded Nobel Prize in 2008. Cervical cancer ranks second among the cancers affecting women world over. It is estimated that half of sexual active women has had HPV infection at some point in their life so that 80% of the women are exposed to HPV at least once by age of 50 years. At any given point, 10% of the women have active HPV infection, 4% have cytogenetical abnormalities and1% with benign condition such as genital warts (63). HPV infection is quite common and can spontaneously resolve. After initial infection, overcoming the host immune resistance with possible integration of HPV DNA into the host genome with accumulation of additional mutations within the infected host cell are important steps to persistence of infection which is the first step towards neoplastic changes(64). Unlike other urogenital infections, HPV infection does not have any immediate clinical symptoms such as itching or vaginal discharge. It has been seen that only a small percentage of women with HPV infections develop any serious clinical manifestations. In a large, 10 year cohort study which

enrolled around 20,000 women, only 7% was diagnosed with carcinoma in situ during the course of study(65). It may take years after initial infection for the development of any manifestations clinically. However multiple sexual partners, initiation of sexual activity at any younger age, smoking, immune compromised state and co- infection with Chlamydia increases the risk of developing cancer with HPV infections(66),(67),(64). Around 99.7 % of all cervical cancers are associated with HPV infection (56). It is the sexual active women below the age of 25 years who are largely affected. More than 50% of all cervical cancers are linked with HPV 16(68).Other subtypes seen are 18, 31and 45.Screening for cervical cancer and its diagnosis is made based on Papaincolaou testing (Pap smear) and HPV DNA testing. As of now, there are no effective measures to prevent HPV infection nor are there any good methods for preventing the clinical consequences of HPV infection. Management is mostly symptomatic .However prophylactic HPV vaccines are expected to decrease the burden of HPV associated diseases. These vaccines are not therapeutic. There are 2 types of vaccines that are marketed namely the quadravalent vaccine called Gardasil which gives protection against HPV types – 16,18, 6,11 and the bivalent vaccine called Cervarix , against HPV types – 16 and 18(69). It can be given in girls young as 9 years. It followed by a second dose at the age of 26. These vaccines contain HPV L1 self-assembling particles which trigger off strong neutralizing antibody like action against HPV infection. The antibodies that are produced help the host cells by blocking the virions to enter the epithelial host cells. Young males can also take the

vaccination to prevent genital warts. There are no clinical trials published to find its efficacy in vaginal, vulvar, anal or oral cancers.

HPV AND OROPHARYNGEAL CANCER

Histological similarities in cervical and oral mucosa led on to investigate the role of HPV in oral malignant tumors .One of the first site in head and neck found to have associated with HPV was the oropharynx namely base of tongue and the tonsils. These areas act as viral reservoirs increasing the chance of accessing the basal epithelial layers which is the first step in carcinogenesis. In 1983, the first article was published suggesting an association which showed HPV sequences in verrucous carcinoma in larynx by Southern blot hybridization(70). Recent studies have suggested that HPV infection is an independent risk factor for oral squamous cell cancer (OSCC) (28) (29). Oral cancer which was previously seen commonly in middle aged and elderly now shows an increasing trend among the young. Smoking and alcohol intake as risk factors which could explain only 75% of the cases. HPV associated oral malignancy might explain the change in the recent trends. Clinical evidence also shows that HPV associated carcinoma behave differently. Unlike tobacco associated malignancies which are common in males, these are seen equally in males and females. It affects the young and mostly in patients with no risk factors for developing the cancer. The mode of transmission is by sexual contact. As in other malignancies associated with

HPV, types 16 and 18 are seen commonly and are histologically poorly differentiated, non-keratinising squamous cell carcinoma(71).HPV associated oral malignancies often have increased chances of nodal metastasis with comparatively smaller primary tumor(72). HPV positivity is a good prognostic factor for squamous cell carcinoma of oropharynx(73). Mere HPV positivity do not classify oral malignancy to be associated with HPV, instead presence of biologically active protein such as high-risk E6/E7 mRNA can classify tumor as truly HPV associated(62). p16 expression status by immunohistochemistry can act as good marker for biologically relevant high-risk HPV infection and therefore, prove useful in the classifying OSCC. These tumors have better prognosis since they are associated with increased radiation sensitivity and absence of field cancerization and hence decreased rate of disease progression and local spread(74)(6). Survival rates are better when compared with non HPV associated malignancies. De-escalating present treatment regimens and tailoring them to HPV positive cancers have improved morbidity and mortality(75). Clinical trials are underway to investigate on the role of immunotherapy in virus associated head and neck cancers targeting HPV E6 and E7 oncoproteins. Role of vaccination is limited as its role is prophylactic.

HPV AND SINONASAL TUMORS

HPV and sinonasal malignancies

Sinonasal tract is a rare site for development of carcinoma accounting for 3% of tumors in the upper aerodigestive tract. However there are a wide

variety of cancers that can origin from this area(76). 65% of all sinonasal malignancies are squamous cell carcinomas. Other types are adenocarcinoma, olfactory neuroblastoma, sinonasal undifferentiated carcinoma and adenoid-cystic type. The etiology of sinonasal carcinoma is poorly understood. Exposure to wood dust , heavy metals such as nickel are associated with a sub type namely adenocarcinoma- intestinal variant(77)(78). Though smoking and alcohol are independent risk factors for malignancies of aerodigestive tract, its role as a causative factor in sinonasal malignancies is uncertain(79). Some studies have suggested the synergistic effect of both smoking and alcohol in causing neoplasm of sinonasal tract especially squamous cell carcinoma(80). Thus poor understanding of the etiological factors makes our efforts of understanding and treating the cancer quite challenging. These cancers are seen more in males than females in 3:1 ratio which is characteristically seen in squamous cell carcinomas ,the most common type(81).

The role of HPV in head and neck carcinogenesis is gaining more recognition. It is seen to be associated with oropharyngeal malignancies especially in tumors arising from tonsils and base of tongue. It is the various studies done on oropharyngeal HPV related carcinomas that have led to greater insights on carcinogenesis and helped in developing new ways for HPV detection. It is the seen that these malignancies have a characteristic histological feature and immunophenotype(82). They are typically non-keratinising and have basal cell features(83). Immunophenotypically, it is associated with increased expression of p16 with decreased p53 and high

Ki76 labelling index(84).Though highly sensitive PCR- based assays are able to detect HPV DNA in various benign and malignant sinonasal tumors, it does not differentiate between incidental presence of the virus from cancer causing HPV. Thus association of HPV with any tumor is not confirmed with mere detection of viral DNA, but also co-relating with the immunophenotype features (81).Detection of HPV E6/7 mRNA transcripts and down regulation of host regulatory pathways such as p53 and retinoblastoma pathway are various targets for HPV detection. Viral inactivation of retinoblastoma protein results in over expression of p16. Hence detection of HPV DNA by in situ hybridization along with over expression of p16 is a convincing evidence for biologically active HPV(85). Various studies done on association of HPV with sinonasal malignancies shows results from 0 – 100%.However most of the studies suggest a strong relation of high risk HPV types in sinonasal malignancy, though the causation is not that strong as oropharyngeal carcinomas where biologically active HPV was detected in 80% of tumors(86).Studies have also proven that HPV positive neoplasms are associated with better prognosis. By tumor type, squamous cell carcinoma is commonly associated with HPV. As in oropharyngeal carcinoma, the histological type seen are non-keratinising and basaloid type(87). These non-keratinising squamous cell carcinomas in sinonasal tracts are also known as Schneiderian carcinoma, transitional cell carcinoma or cylindrical cell carcinoma. The mode of infection is unclear in sinonasal malignancies, unlike in oropharyngeal cancers where it is commonly transmitted sexually, though

autoinoculation and maternal transmission has also been suggested. Studies have noted improved clinical outcome in patients with HPV associated sinonasal malignancies(88). But due to lack of uniformity in tumor types and numbers, most studies were unable to fully appreciate the impact of HPV positivity.

HPV and Inverted Papilloma

Inverted papilloma, also known as Schneiderian papilloma, sinonasal papilloma or transitional papilloma is benign, locally aggressive, well differentiated tumors of respiratory epithelium. The name was coined by Ringertz from the characteristic finding of inverting epithelium into the underlying stoma on histological examination. It was first described in 1854 by Ward. These tumors are known for high recurrence rate after surgery and are associated with malignant transformation. It has been seen that 2–56% can develop synchronous primary malignancy and malignant transformation in 5–15% of lesions,(11),(89). With an incidence of 2 in 1 lakh per year , it comprises of 4% of all nasal tumors(90).It is seen thrice more commonly in males and affects the middle aged group. Clinically the tumor usually presents as unilateral nasal obstruction or with epistaxis. Examination reveals polyps arising from commonly the lateral wall of the nose. It can also be seen coming from nasal septum and nasopharynx. Histopathological examination confirms the diagnosis. Computed tomography of the paranasal sinuses shows bone remodelling. Though a benign tumor, it is treated promptly as it behaves aggressively and can harbour carcinoma. The main modality of treatment is

surgical excision(90). Recurrence rates vary from 0% to 78%(89).It depends majorly on the thoroughness of removal. HPV has been implicated in the etiology of inverted papilloma especially in tumors with dysplastic changes and recurrence(83). It has been shown that the neighbouring cells of normal nasal mucosa around inverted papilloma contain HPV DNA(89). Various studies have seen that viral integration of HPV into inverted papilloma can bring about transformation to carcinoma(91).

TREATMENT IMPLICATIONS OF HPV ASSOCIATED MALIGNANCIES

As discussed before, various studies have shown that HPV associated head and neck malignancies especially in oropharynx have shown better prognosis. These tumors responds better to radiation and the absence of field cancerization makes it less locally advanced. Thus de-escalation of treatment regimen for HPV positive malignancy is already underway. With advances in immunotherapy, different options for treating such cancers are also being studied. However, role of HPV vaccine is limited in these tumors.

HPV ASSOCIATED MALIGNANCIES IN INDIA

Head and neck cancers are ranked as the fifth common malignancy in the Southeast region(92). In the Western countries, most of the head and neck malignancies can be attributed to various proven risk factors especially smoking. Studies had shown that tobacco consumption in India is increasing at a rate of 2% per year(93). The patients present with advanced disease and are

still mostly in the middle aged to elderly age group unlike the Western statistics where the trend is tilting towards the younger age group (94). Though prevalence of HPV in all the subsites of head and neck is around 15-67%, prevalence of HPV is less compared to the data from the Western countries(92). However, there are still a small percentage of patients with head and neck malignancies with no associated risk factors, where HPV can be a possible etiology. However studies regarding the prevalence of HPV in non oropharyngeal sites including sinonasal tract are few.

In summary, this study draws attention to the sinonasal tract as a subsite of the HPV associated head and neck cancers. The identification of HPV-related sinonasal carcinomas sets the stage for future studies to determine whether HPV-positivity gives distinct biological and clinical characteristics providing new opportunities for the development of targeted therapies for this patient population as with HPV related carcinoma in other sub sites namely oropharynx.

MATERIAL AND METHODOLOGY

The purpose of this study is to find the association between human papilloma virus and primary malignant sinonasal tumors.

Study design: Case control study

Period of study: 2 years

Setting:

The study was conducted in the ENT department – the outpatient and inpatient services at Christian Medical College, Vellore from December 2013 to July 2015.

Patients eligible for the study were evaluated in the ENT outpatient department. They were divided into cases and controls based on the diagnosis. It was explained to them regarding the study in detail, procedure and tests involved. They were handed information sheet with contact number in case of any clarifications. Once patient was admitted for definitive surgery, informed consent was taken from patients who were enrolled in the study. Tissue was taken for the study during the surgery. The tissues are then transferred into special containers and transported to the virology lab maintaining cold chain where the tissues are stored for HPV DNA analysis.

Inclusion criteria:

All patients coming to Department of ENT with diagnosis of primary malignant sinonasal tumors, inflammatory polyps and chronic sinusitis.

Exclusion criteria:

Patients diagnosed with benign sinonasal tumors or other head and neck malignancies.

Sample size calculation:

Literature study has shown HPV prevalence of 28% in malignant sinonasal carcinoma and upto 7% in patients with chronic sinusitis and normal individuals.

The sample size was calculated using the software nMaster 2.0. With an expected proportion of 7% among controls and among cases 28%, with 80% power and 5% alpha error, the minimum required sample for the comparison of the two proportions in 50 in each group.

Expected odds' ratio : 5

Po (Exposure in controls) : 7%

P1 (Po x OR)/Po (OR-1) +1: 28%

p (P1 +Po)/2: 17.5

q (100-p): 82.5

Z α = 1.96 (type 1 error of 0.05)

Z β = 0.84 (type 2 error of 0.2)

Sample size calculation: 2pq (Z α +Z β)/ (P1-Po) 2 = 50

So total sample required for the study is 100.

Methodology:

Patients presenting in ENT OPD with complaints such as nasal obstruction, epistaxis, facial pain, cheek swelling or allergic symptoms were evaluated by diagnostic rigid nasal endoscopy after history and examination to rule out sinonasal polyps or sinonasal growth. Biopsy was done if a suspicious nasal or palatal mass was present as an outpatient procedure. Patients with diagnosis of sinonasal polyposis were followed up in OPD and were explained in detail regarding the study and the information sheet was given for further clarification. Patient diagnosed with sinonasal malignancies on biopsy, were screened for eligibility and those satisfying the inclusion criteria were interviewed for detailed work up and were explained regarding the study. Those enrolled in the study were reviewed in the ward once they were planned for definitive surgery-functional endoscopic sinus surgery (in case of inflammatory polyps or chronic sinusitis) or appropriate surgery (as in malignant sinonasal tumors) under general anaesthesia. Informed consent was taken. During the surgery, tissue was taken from the lesion (polyps /malignancy).

Sample collection:

The tissue obtained from enrolled cases and controls was transferred to containers containing special medium – called virus transporting medium (VTM).Viral transporting medium is a balanced isotonic solution at physiological pH. It can maintain the virus in a viable state as it contains foetal

calf serum and antibiotics. These containers are then transported in ice containers maintaining cold chain to the virology lab. In the lab, the sample is then shifted to a 1.5ml eppendorf tube and stored at -80 degree Celsius until further testing in the freezer.

DNA extraction protocol:

The kit used is called DNeasy tissue kit (Qiagen GmgH, Hilden, Germany). Using the principle of column separation, DNA is extracted. Foremost, tissues are cut into 25 gram pieces and are digested by ATL buffer and Proteinase K at 56 degree Celsius. Once digested, an equal amount of lysis buffer which is called as AL buffer and ethanol is added. The DNA precipitated is then washed twice with buffers AW1 and AW2. It then eluted with elution buffer. The extract containing DNA is stored at -20 degree Celsius.

HPV DNA detection:

The extracted DNA undergoes PCR with a known positive control and beta globulin as internal control. HPV detection was be done by THE PGMY primer system. The PGMY primer PCR system amplifies the L1 region of the HPV genome resulting in a 450 base pair amplicon. Along with this, an internal control histocompatibility leukocyte antigen (HLA) , beta globulin is amplified producing an 230 base pair amplicon confirming that DNA is extracted in sufficient amounts and that there are no inhibitors in the sample. The presence or absence of target bands (450bp), the sample can be interpreted

as positive or negative. Beta globulin positivity is essential for analysis of sample.

Sequencing:

If detected positive, the amplified PCR products are purified by Millipore filtration and sequenced using an ABI prism big bye terminator cycle sequencing ready reaction kit. The sequences obtained are compared with GenBank HPV sequences. The HPV positive samples are sequenced to know the HPV genotype.

Statistical analysis:

The data of all the patients were collected systematically with the software EPIDATA version 3.1 Statistical analysis was performed using statistical software SPSS (version 13.0). Chi square test was used to find association.

RESULTS

A total of 90 patients were enrolled in the study according to the eligibility criteria of which 50 were controls and 40were cases. Tissue from all the selected patients was sent for HPV DNA analysis according to the strict precautions for tissue transfer to the laboratory. Controls were patients with diagnosis of sinonasal polyposis or chronic sinusitis and cases were patients diagnosed with primary sinonasal malignancy.

DEMOGRAPHIC PROFILE

1. GENDER DISTRIBUTION

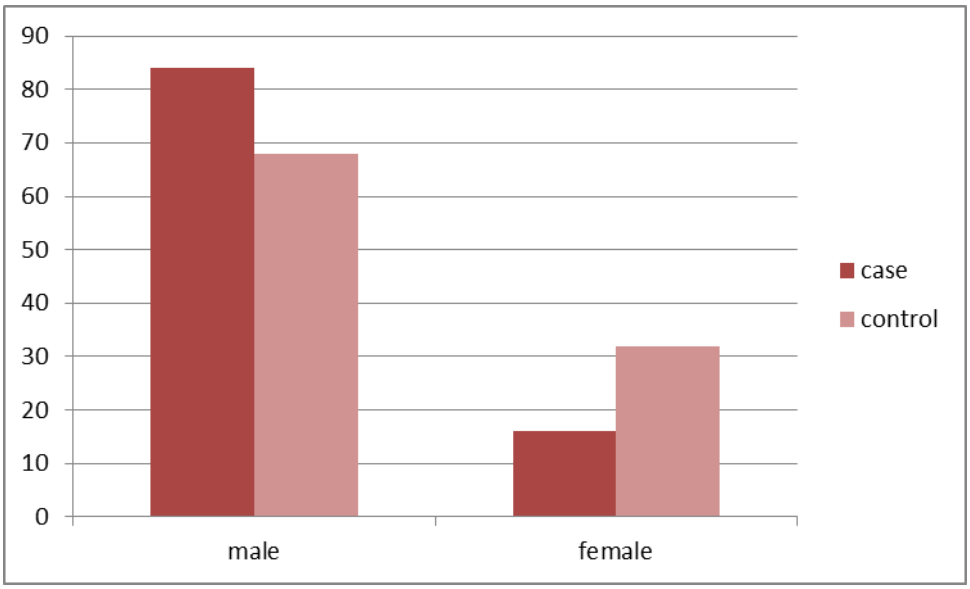

Figure 6: Gender distribution of the patients

In the case arm, the male to female ratio was 5:1 which was found statistically significant ($p < 0.05$). However in the control arm it was 2:1(p-0.9).

2. AGE DISTRIBUTION

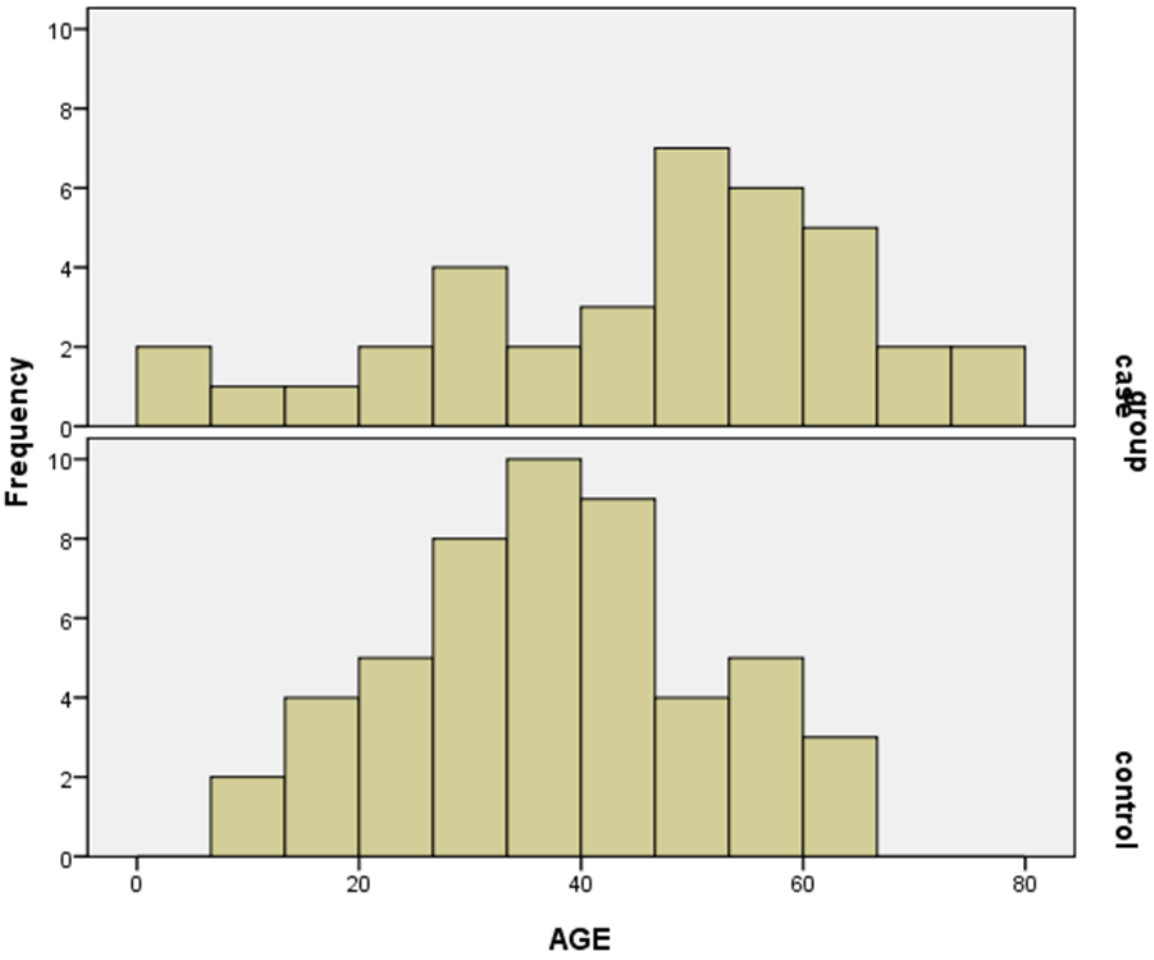

Figure 7: Age distribution among the patients.

Maximum number of controls fell within in the age group of 20-40 years. However the patients in the case arm had a wide distribution of age with majority of patients within 50-60 age groups. The oldest patient was 73 years old and the youngest patient, a 3 year old with a mean of 48 years (SD 19). On statistically analysis, it was found to be significant that sinonasal malignancies were seen in middle to elderly age group whereas sinonasal polyposis and chronic sinusitis was more seen in younger age groups (p-0.02).

3. AREA OF RESIDENCE

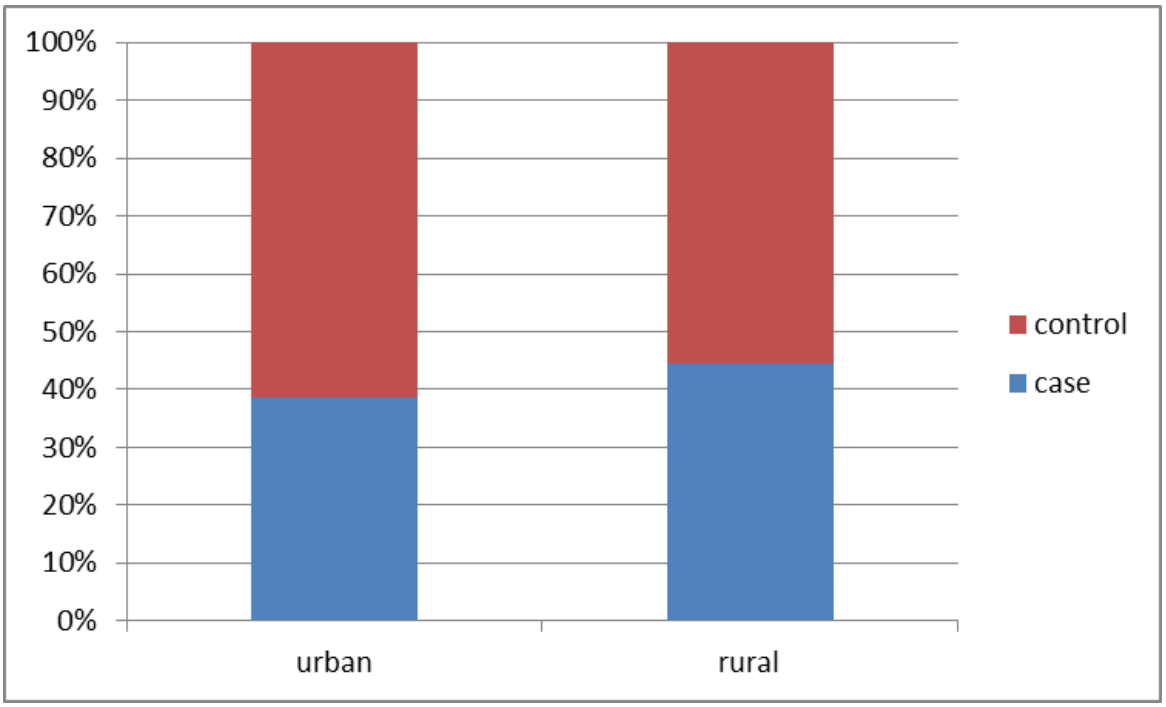

Figure 8: Area of residence of patients.

The proportions of patients coming from rural and urban region were comparable in both control and case arm. It however did not show any statistical significance on analysis (p-0.29)

4. CLINICAL PRESENTATION

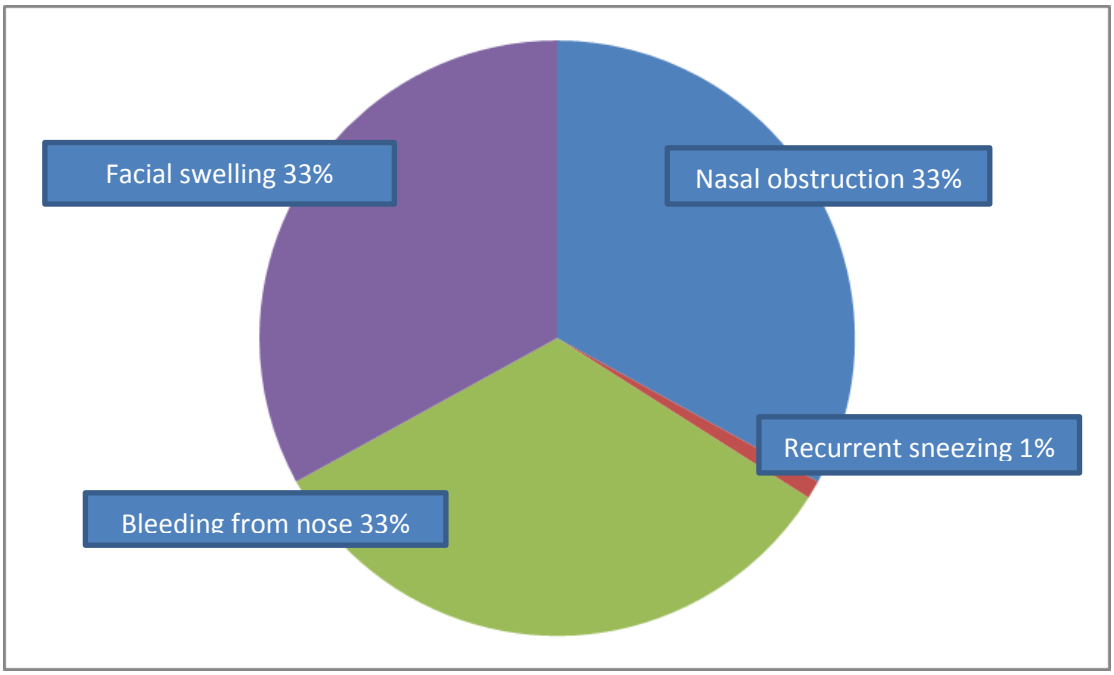

Figure 9: Distribution of various clinical presentations in patients with sinonasal malignancies

In the case arm, the common clinical presentations were nasal obstruction, bleeding from nose and facial swelling.

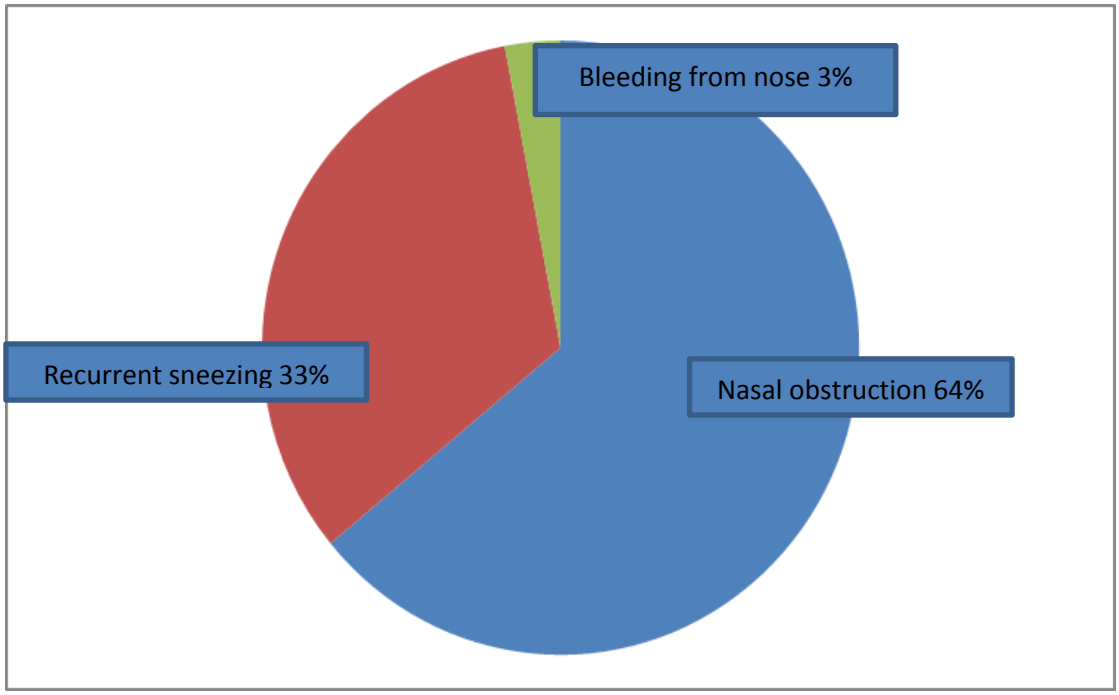

Figure 10: Distribution of various clinical presentations in patients with sinonasal polyposis and chronic sinusitis.

In the control arm, patients commonly presented with history of nasal obstruction or recurrent sneezing with a small percentage of patients with history of bleeding from nose. Symptoms like facial swelling were not seen in cases of chronic sinusitis or sinonasal polyposis. On statistical analysis, co-relation of symptoms such as epistaxis and facial swelling with sinonasal malignancy was found to be statistically significant ($p < 0.05$) suggesting that presence of these nasal symptoms point towards malignancy.

5. DURATION OF SYMPTOMS

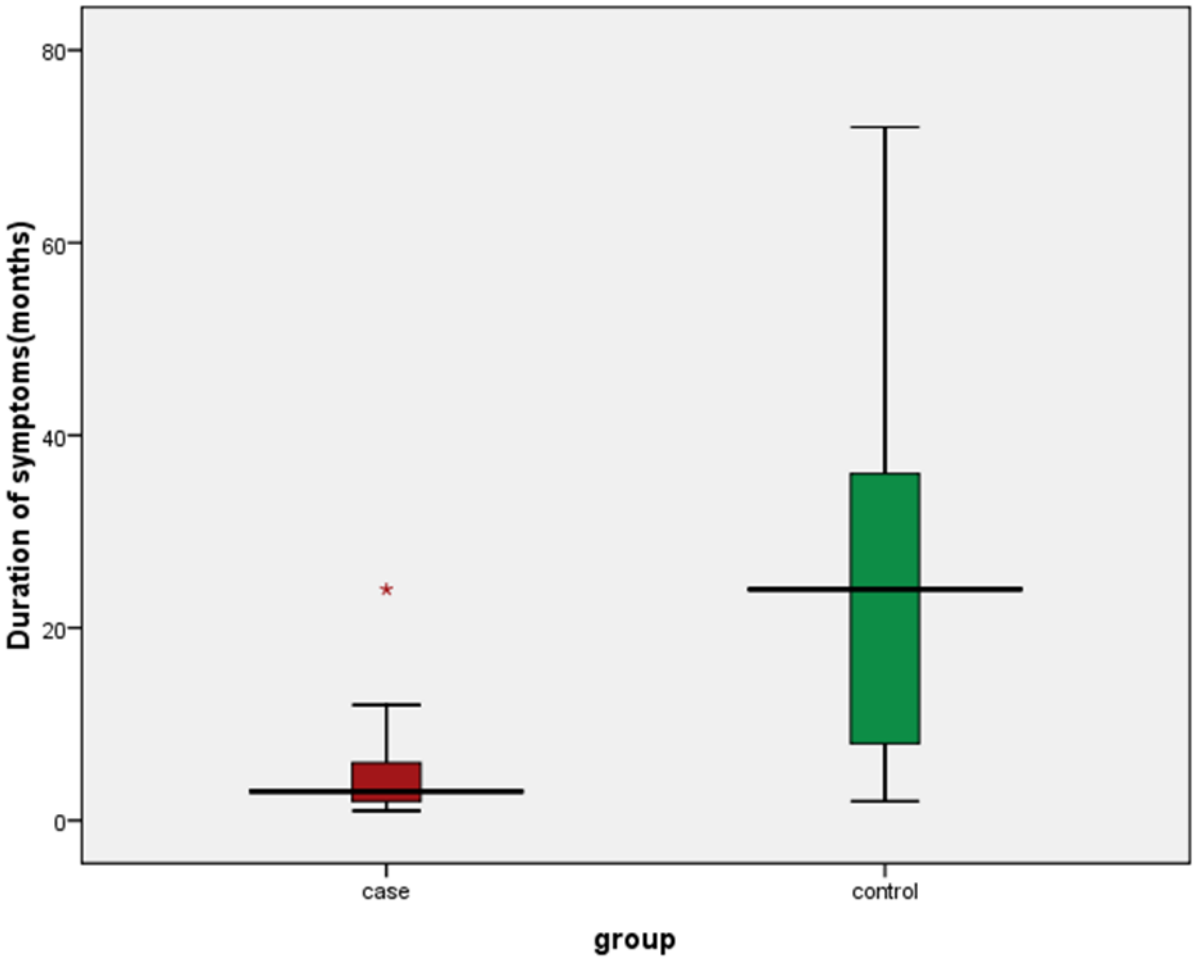

Figure 11: Duration of symptoms in case and control arm

The median duration was seen as 3 months (IQR=2-6) for cases and for controls 24 months (IQR=8-42), ($p<0.001$-MannWhitney U test). In case arm, patients had a shorter duration of symptoms with rapid progression of disease. However in control arm, the presenting symptoms were for a broader duration of symptoms with a minimum duration of 8 months to a maximum duration of 4 years.

RISK FACTORS

1. ADDICTION HISTORY (Smoking/Alcohol/Snuff)

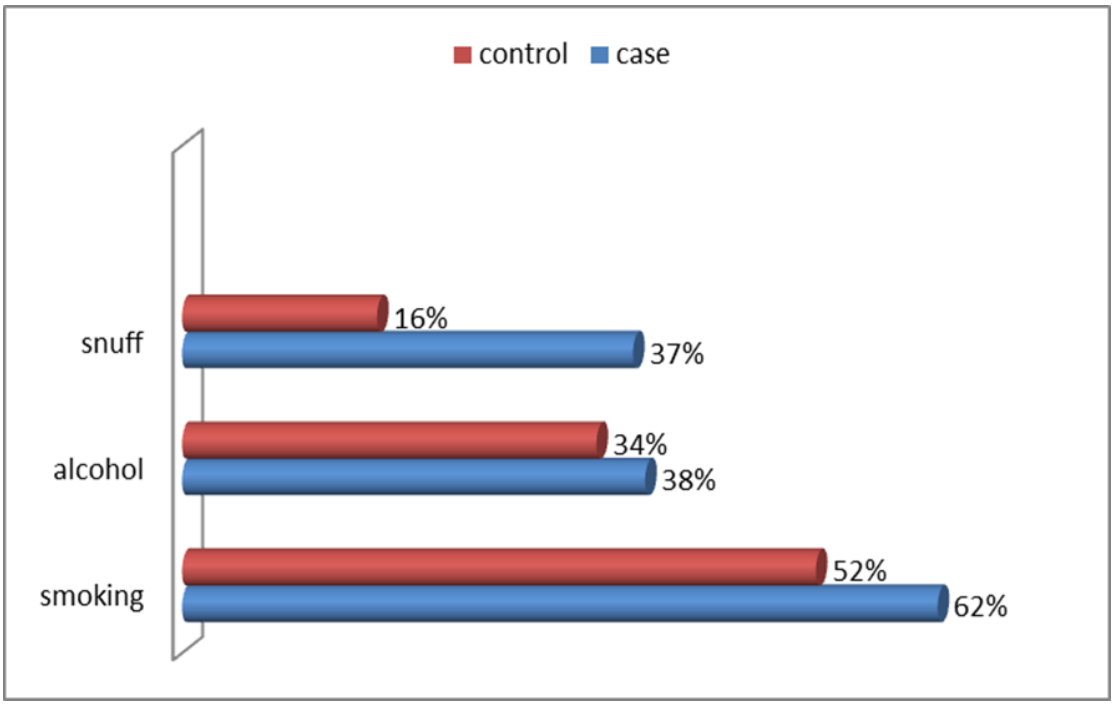

Figure 12: Pattern of addictions in the study groups.

A large proportion of patients had some form of substance abuse or another. Most commonly seen was tobacco and alcohol use. The data on habituation to smoking was comparable between case and control arm however; there was increased percentage of smokers in the case arm. The percentage of patients with history of snuffing was significantly higher in the case arm. These addictions were separately analysed with statistical tools to

find out the association of these addictions (smoking, habituation to alcohol and snuffing) with primary sinonasal malignancies. On analysis, habituation to alcohol was not identified as a risk factor to develop sinonasal malignancies. However the other two factors were evaluated for the same. With a possibility of alcohol as a confounding factor, smoking and snuffing were analysed for disease causation by logistic univariate regression and following results were obtained.

Table 1: Table showing the association of smoking with sinonasal malignancies

history of smoking	case	control	OR (95% CI)	p value
present	26(65%)	24(48%)	1.52(0.64 -3.60)	0.346
absent	14(35%)	26(52%)	1.00	

On analysis, smoking was found to be a risk factor. Data showed a 1.5 increased risk in patients who smoke to develop sinonasal malignancies. However on statistical evaluation, it was not seen significant (p-0.346)

Table 2: Table showing the association of snuffing with sinonasal malignancies

snuffing	case	control	OD(95% CI)	p value
present	15(38%)	8(16%)	3.196(1.17-8.74)	0.024
absent	25(62%)	42(84%)	1.00	

Snuffing was also identified as a risk factor for sinonasal malignancies with 3 times more risk. This finding on statistical analysis was found to be significant ($p<0.05$).

4 cases among the case arm gave history of multiple sexual partners unlike the control arm which had none. However this data was not found to have any statistical significance.

2. OTHER RISK FACTORS

Other risk factors asked for were:

- Spouses with oropharyngeal or genital malignancies
- Radiation exposure
- Family history of sinonasal malignancy
- Occupational hazards such as exposure to wood dust and working with chemicals

There were no patients in case or control arm with the above mentioned risk factors.

3. NO RISK FACTORS

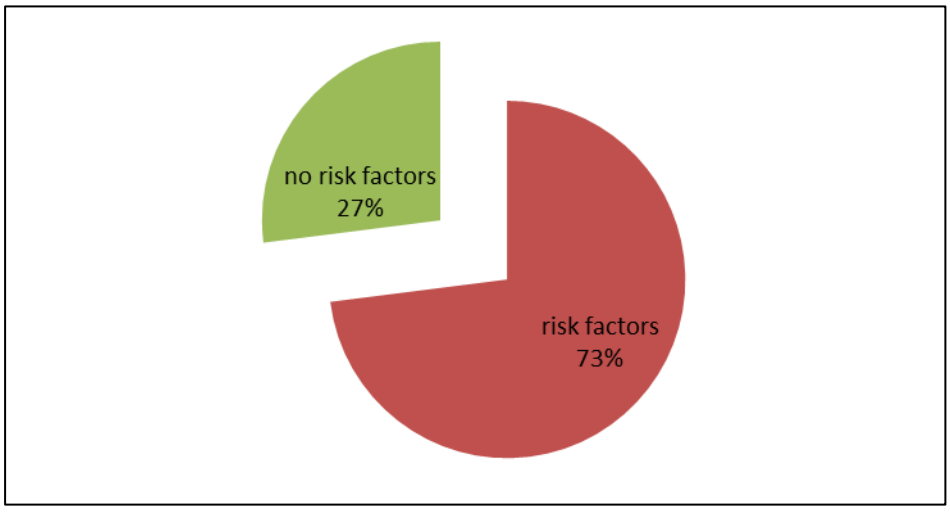

Figure 13: Figure showing the percentage distribution of patients in case arm with and without risk factors

It was interesting to note that in the case arm around 27% (9 cases) of the patients did not give any history of any risk factor exposure which was asked for. It is important to evaluate for any other etiological factors such as HPV in this small proportion of people.

DISEASE PROFILE

1. Pattern of distribution histologically (classified as per WHO classification)

Table 3: Table showing the overall distribution of different sinonasal malignancies classified histologically in the study.

Histological subtypes	No of cases	Percentage
Epithelial tumors	24	60%
Haematolymphoid tumors	5	13%
Bone and cartilage tumors	4	10%
Neuroectodermal tumors	4	10%
Soft tissue tumors	3	7%
Total no of cases	40	100%

As shown in the table, the most common histological subtype of sinonasal malignancies seen in the study population were epithelial tumors, followed by haematolymphoid tumors. Squamous cell carcinoma was the common histological type seen (15 cases).

2. Pattern of distribution according to age

Table 4: Table showing distribution of sinonasal malignancies with age.

Age groups	No of patients (%)	Common histological subtype
< 20 years	4(10%)	Haematolymphoid tumors
20-39 years	8(21%)	Epithelial tumors
40 – 59 years	19 (43%)	Epithelial tumors
>60 years	9(24%)	Epithelial tumors

The pattern of distribution clearly shows that the disease burden falls in the middle age group, following by the elderly. In the younger age group, the tumors diagnosed were predominantly haematolymphoid type.

3. Others

    - The most common sites in the sinonasal region involved with sinonasal malignancy were nasal cavity (18cases) and maxillary sinus (18 cases).
    - Most of the patients with sinonasal malignancies from rural areas presented with advanced disease with the most common presentation being facial swelling. However patients from urban areas presented early with common presentation of epistaxis or nasal obstruction.

Following results were noted for sinonasal squamous cell carcinoma:

- Common age group involved was 40-60 age group
- Common site of involvement was maxillary sinus
- It was seen more in males

HPV DNA POSITIVITY

HPV DNA was not found in the samples from the case or control arm.

DISCUSSION

Sinonasal malignancies are rare and constitute about 3% of all head and neck malignancies(7). Like any other head and neck malignancy, they are associated with significant morbidity. Cancers of nasal cavity usually have subtle symptoms because of which they present only at an advanced stage. Similarly in cancers of paranasal sinuses, tumor being confined to the cavities of the sinuses remains asymptomatic till they extend to surrounding structures. A clear understanding of the demographic profile, etiological agents and risk factors is clinically imperative to diagnose these cases early. Because of the rarity and variety of malignancies seen in this area, it is challenging for a clinician to diagnose and plan on management.

Demographic profile:

In the present study, a total of 40 cases of sinonasal malignancies were enrolled. Most of the patients were within the age group 40 – 60 years. The mean age was 48 years (SD -19) with a range from 3 years to 73 years. Studies have shown that sinonasal malignancies are seen commonly in the middle aged to elderly age group (50 – 70 years).In a study done in West Africa, the mean age was 50 years with a range from 3-69 years(95). A study done by Khademi et al on 71 patients with sinonasal malignancies over a period of 8 years also showed a mean age of 55 years with age ranging from 5 to 60 years(23). Though the age group commonly affected with these malignancies are middle aged to elderly, it should also be noted that it can be

seen in any age groups even at extremes of age unlike benign conditions such as chronic sinusitis or sinonasal polyps where the major age group involved are the young (20-40 years).

Of the 40 cases recruited for the study, there were 33 (84%) males and 7 (16%) females. This data clearly points out a male predominance in these malignancies which is almost 5 times. This was found to be statistically significant ($p<0.05$).Data worldwide reveals similar findings(96). This finding can be explained with increased percentage of addictions and also the work pattern in male gender which can predispose to malignancy. Especially in Indian population, data shows that there are more male smokers, alcoholics and drug addicts compared to females(93).

In the study, 25 patients from the case arm were from rural parts of the country which is around 68%. In an epidemiological survey done on sinonasal malignancies in Iran, it was seen that 73 % of the patients with sinonasal tumors were from the urban parts of the country(96). Various studies have shown that sinonasal malignancy is an occupational hazard for people working in textile industry mainly for adenocarcinoma and adenoid cystic carcinoma(97).In a study done by Comba et al, workers in wood industry and leather industry were also predisposed to malignancies of sinonasal tract due to exposure to carcinogenic organic dust(78). Farming also carries with it a small increased risk of 7% due to the inhalant carcinogens seen in fertilizers(31).It was postulated that as these industries are located in the cities, the prevalence

of sinonasal malignancies was seen more in the urban population. However in our study, there was an observed increased prevalence among rural population. This can be explained as approximately 70% of Indian population live in the villages with farming as the major occupation because of which rural patients tend to predominate in our study(98).

Disease profile:

The most common malignancy seen in the sinonasal tract is squamous cell carcinoma (18). Literature search shows incidence from 35% to 70% worldwide(99).The epithelium of the sinonasal tract over the vestibule is lined by stratified squamous epithelium and the nasal cavity proper with pseudo stratified columnar respiratory epithelium with an area of squamo-columnar junction, at the limen vestibule. This area is especially predisposed to HPV infection(4). In our study, out of the 40 cases that were recruited, 15 (40%) were cases of squamous cell carcinoma. The other common malignancies seen were lymphoma (8%), olfactory neuroblastoma (8%), osteosarcoma (5%), adenocarcinoma (5%), adenoid cystic carcinoma (5%) and sinonasal undifferentiated tumors (5%). However studies show that the second common histological type is adenocarcinoma(100). It should be remembered that there is a wide variety of sinonasal malignancies as any structure in the nasal cavity such as cartilage, bone, olfactory cleft and mucosal epithelium can become the primary site of tumor.

In our study, 45% of the cases of the sinonasal malignancy had the primary site of origin as nasal cavity and 45 % from maxillary sinus. Other studies have shown that the most common site involved is the maxillary sinus which is around 80%, followed by the nasal cavity and ethmoid air cells(96),(99). Isolated sphenoid sinus and frontal sinus malignancies are rare(101). Most of the malignancies present at an advanced stage and it is difficult to find tumors which are confined to one subsite on presentation. There is no biological reason to explain such a pattern of distribution. However theories propose that it corresponds with relative sizes of the sinuses, the surface area of exposure to aerosols and the number of cells exposed to the carcinogen. Further studies are warranted to further understand this trend.

Sinonasal malignancies present initially with very subtle complaints such as nasal obstruction, rhinorrhoea, headache which can mimic common benign conditions such as allergic rhinitis, sinonasal polyposis or chronic sinusitis. These symptoms might improve with symptomatic management. These reasons delay referral from general health practioner to an ENT surgeon. So most of the cases present at an advanced stage. However symptoms like recurrent epistaxis and facial swelling with loose tooth prompt patients to report to healthcare personnel who can refer patients to an otolaryngologist. If sinonasal malignancy is not suspected, the diagnosis can be missed initially. In our study, the frequent presentations were facial swelling (33%), nasal obstruction (33%) and recurrent epistaxis (33%). Duration of symptoms was 2 to 6 months unlike benign conditions. In the control arm, the common

presentations were nasal obstruction (64%) and recurrent sneezing (33%).The duration of symptoms ranged from 6 months to 6 years. Though the clinical symptomatology was similar in the case and control arms, the complaints in patients with sinonasal malignancies were of short duration. On statistical analysis, co- relation of symptoms such as epistaxis and facial swelling with sinonasal malignancy was found to be statistically significant ($p < 0.05$) suggesting that presence of these nasal symptoms point towards malignancy. The symptom of facial swelling was found to be a good predictor of malignancy ($p < 0.05$).

Risk factors:

In our study, there were a total of 26 smokers in the case arm. On statistical analysis, it was seen that smokers are a higher risk to develop sinonasal malignancies (OR -1.5, p-0.2).Extensive research has been done worldwide regarding effect of smoking on different airway malignancies. Studies show increased risk for developing of sinonasal malignancy with smoking especially squamous cell carcinoma.(102).A study done in Ontario showed that with decreasing trends in smoking over a span of years, the population burden of sinonasal carcinomas especially squamous cell carcinoma had come down(102). However it was also noted that over all prevalence of adenocarcinoma did not show similar trend probably as it is caused mainly through occupational exposure to wood, leather and heavy metals such as nickel and chromium salts and fumes. A case control study also proposed that

recent users of tobacco were at a higher risk to develop malignancy compared to the long term user. It also suggested that tobacco smoking is associated with squamous cell carcinoma(79).

Though the number of studies are few, they suggest an association of snuff usage with sinonasal cancers especially in maxillary sinus tumors(103). A study done among the Bantu tribe in Africa showed that increased prevalence of sinonasal malignancy in the population may be due to nasal snuff usage which is a custom and a social practice for the Bantu tribe(104).It was later found that snuff contained large quantities of nickel and chromium which would have been responsible for carcinogenesis. Another study done is Britain showed increased risk of developing sinonasal malignancy with nasal snuff use (105).In our study, we found that use of nasal snuff was relatively commoner in males. Statistical analysis revealed that usage of nasal snuff increases the risk of developing sinonasal carcinoma by three times (OR – 3, p-<0.05).

Literature search showed varying association of habituation of alcohol with sinonasal malignancies. Though it can be associated with malignancies in the other subsites of the upper aerodigestive tract, the mechanism by which it can cause sinonasal malignancy remain unclear. A study done in nasopharyngeal cancers suggested a probable association with alcohol(106). Brinton et al found that alcohol had a very little impact on any histological type of sinonasal malignancy and also that it does not modify the association of these tumors with smoking(105). A study done by Strader et al, interestingly found a significant association of alcohol with sinonasal malignancy(107).

However in our study, on statistical evaluation it was seen that there is no added risk or association of alcohol in the etiology of sinonasal malignancy (OR-<1).

In a study done by Kumaraswamy et al, HPV associated head and neck squamous cell carcinoma was seen in younger with high risk sexual behaviours such as multiple sexual partners, early age of sexual intercourse and unnatural sexual habits(108).Though these tumors were poorly differentiated, they were found to have better prognosis(85).In our study, of the total number of the cases of sinonasal malignancy that were enrolled, 34 (86%) were married whereas 6 (14%) were unmarried. Sexual practices determine the mode of HPV transmission. Patients were not forthcoming with sexual history because of their conservative cultural, religious and ethnic background. Despite these limitations, in our study there were 4 patients in the case arm with history of multiple sexual partners unlike the control arm where there were none. However these 4 cases did not show HPV positivity. Further studies are warranted especially in HPV positive cases to analyse this trend.

Other risk factors such as exposure to wood dust and leather were not present in the study groups. Studies have found that people working in the wood and leather industries are predisposed for tumors of sinonasal tract(24). The common histological subtype of sinonasal malignancy associated with these risk factors is adenocarcinoma(22).Exposure to chemical such as nickel and chromium are prone to develop sinonasal malignancies especially squamous cell carcinoma (22). These substances are proven carcinogens. These

when inhaled, comes in contact with the mucosa of the nasal tract and paranasal sinuses which can trigger carcinogenesis..

HPV has been implicated in the etiology of head and neck carcinoma especially in squamous cell carcinoma. It is particularly significant in patients with no known risk factors such as smoking, tobacco chewing or habituation to alcohol(1). Studies in oropharyngeal malignancies have shown that 80% of these malignancies were positive for high risk HPV such as HPV 16 and 18(88). This discovery has led to improved knowledge on HPV tumorigenesis and development of different tests not only to detect trace amounts of viral DNA, but also to detect biologically active HPV DNA. These HPV associated oropharyngeal malignancies were seen to have better treatment outcome and improved 5 year survival rates. However Indian studies gives inconsistent data on prevalence of HPV in oropharyngeal malignancies(109).The interest in studying the association of HPV in sinonasal malignancies was due to HPV positive benign conditions such as inverted papilloma in the early 80s(110).In a study done by Bishop et al on sinonasal malignancy, 21% of sinonasal malignancies were found to have HPV which was biologically active(88). They also found that they were all squamous cell type histologically and was not seen in all the variants. It was localized to non-keratinising and basaloid squamous cell carcinoma. Similar finding was also noted in oropharyngeal malignancy(87). A study done by Alos et al, HPV associated sinonasal malignancies were seen to better outcome with less rates of recurrence. They opined that these HPV associated malignancies have less chance of field

cancerization and better response to radiotherapy which can explain the improved survival rates(17).

Prevalence of HPV in India for cervical malignancies is reported as 80%. Data on anogenital cancers is very limited. Recent studies in oral cavity malignancy gives varied results from 4% to 70% which an average of 30%(109) as oppose to western studies show prevalence of 80%. One study on laryngeal cancers showed presence of HPV in 30% of cases(13).Data to suggest strong co-relation is very few. In comparison with western data, the prevalence of HPV in India is comparatively less(94). However in a small subsite of head and neck malignancies in younger age group with no risk factors, further studies are warranted to evaluate other etiological factors such as HPV. HPV DNA was not detected in our study of 40 patients with primary sinonasal malignancy.

There were a few limitations to the study. Sinonasal malignancies are rare tumors. Our study was a two year time bound study. Due to the limitation of time we could attain not a larger sample size. However the data on the attained sample size gives us background information regarding the topic of interest. Because of the conservative cultural, religious and ethnic background in our subcontinent, it was difficult to obtain a detailed sexual history. We would suggest a longer study with a larger sample size to study the association between HPV and sinonasal malignancy.

CONCLUSION

The role of HPV in head and neck malignancies is an area of immense interest. Research in oropharyngeal malignancies has shown a significant association with high risk HPV genotypes especially HPV subtype 16. It was also seen that these HPV associated malignancies had better treatment outcome and survival rates which is postulated to be because of the decreased chance of field cancerization and better radiation sensitivity in these tumors. Research is underway to study similar associations in other subsites of head and neck namely nasopharynx, larynx, sinonasal tract and lower end of oesophagus. They are of special interest due to the presence of squamo-columnar junctions at these sites which are predisposed to HPV infection(4).

We studied a total of 90 cases in a case control study design to find the association of HPV and sinonasal malignancy. There were 50 cases in the control arm which were either diagnosed case of sinonasal polyposis or chronic sinusitis and 40 cases in case arm which were histopathologically proved cases of primary sinonasal malignancy. Squamous cell carcinoma (40%) was the common histological subtype of sinonasal malignancy seen in the study. Maxillary sinus (45%) and the nasal cavity (45%) were the frequent subsites involved. Common symptoms at presentation were nasal obstruction (33%), epistaxis (33%) and facial swelling (33%).On statistical analysis, co- relation of symptoms such as epistaxis and facial swelling with sinonasal malignancy was found to be statistically significant ($p < 0.05$) suggesting that presence of these

nasal symptoms point towards malignancy. The symptom of facial swelling alone was found to be a good predictor of sinonasal malignancy ($p < 0.05$). The patients in the case arm had a wide distribution of age with majority of patients within 50-60 age groups. The oldest patient was 73 years old and the youngest patient, a 3 year old with a mean of 48 years (SD 19). On statistically analysis, it was found to be significant that more sinonasal malignancies were seen in the middle to elderly age group unlike the benign diseases (chronic sinusitis, sinonasal polyposis), which affected the younger age groups (p-0.02).Our study revealed a strong association of smoking (OR – 1.5, p-0.2)and snuff usage(OR-3, $p<0.05$) with sinonasal malignancies. This reinforces similar correlation found in published literature. The association between alcohol intake and sinonasal malignancy was not found to be significant. Early diagnosis of sinonasal malignancy is difficult due to the subtle symptoms with which they present and because of similarity in presentation to benign sinonasal conditions such as sinonasal polyposis, allergic rhinitis and chronic sinusitis. These symptoms should be viewed with caution especially in elderly patients with risk factors who present with a short duration of history and rapid progression of disease.

Studies investigating the role of HPV in sinonasal malignancies are less world-wide because of the rarity of these tumors. Few review articles show that HPV prevalence in sinonasal malignancy is around 21% specifically in squamous cell carcinoma(88),(110). However to the best of our knowledge there is no published data on association of HPV with sinonasal malignancy

from the subcontinent. Our hypothesis was that presence of squamo-columnar junction in the sinonasal tract can predispose the area to high risk HPV infection which can trigger carcinogenesis. WHO recommended method for HPV DNA detection was used. In our study, unlike published literature, we were not able to detect HPV DNA in 40 cases of primary sinonasal malignancy. There is also no HPV positive case in the control arm. The reasons for lack of HPV positivity in cases of sinonasal malignancy in our study could be a lower viral load and a smaller sample size. The demographic profile, risk factors and the disease profile is very different in India from the West from where most of the literature is available. Sexual practices determine the mode of HPV transmission. It should also be noted sexual practices are different than that of West because of the conservative society especially in the rural population. So in comparison with western data, the prevalence of HPV in India is comparatively less(72).

Though smoking and snuff usage are very common in Indian population and can be the risk factors which predisposes to malignancies, there is a small subset of patients with no risk factors who develop cancer. In our study, 27% of patients with sinonasal malignancies did not have any exposure of any known risk factors. It becomes relevant to closely follow up these patients to monitor the treatment outcome and survival rate. It is in this subset of patients, other etiological factors such as HPV should be investigated. If an association is found, these patients should be followed up for treatment outcomes and survival. HPV-associated cancers express HPV viral genes even

in advanced stages of disease and down regulation of these viral oncogene expressions can prevent the growth or survival of cancer cells(62). This finding gives us the possibility that even late stage cancers can be cured by HPV-targeted strategies which includes medicines which can interfere with the expression or action of viral proteins and therapeutic vaccines that help body to destroy cells which are expressing these proteins . So this subset of cancer is of special importance since the aim of treatment is not just prolonging life, but for complete cure. Our study investigated the association of HPV with sinonasal malignancy. In our study of 40 cases of primary sinonasal malignancy, HPV DNA was not detected in any of the cases. We would suggest a study over a longer period of time with a larger sample size looking specifically at squamous cell carcinoma to further investigate this association.

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ANNEXURES

WRITTEN INFORMED CONSENT FORM (FOR CASES)

Date:

Study title: Role of HPV (Human papilloma virus) in causing cancers of nose, nasal cavity and paranasal sinus

It has been explained to me by the investigator in the language that I understand that this study is being carried to find out whether HPV can cause cancers of nose, nasal cavity and paranasal sinuses. I have been told that it involves taking a piece of tissue from the nose or paranasal sinuses for PCR analysis (to detect presence of HPV) during the nasal surgery which I will be undergoing for my condition which is done routinely for patients with my disease (clinically diagnosed cancer of nasal cavity and paranasal sinuses).It has also been told that there is no additional risk in the study. It has been explained to me that I am free to withdraw from the study any time I want and will not in any way compromise the treatment, the ENT department is giving me. I understand that my identity and participation will not be revealed in any information released to third parties.

Subjects' Name

Date of Birth/ Age:

i) I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions

ii) I understand my participation is purely voluntary and that I can withdraw from the study anytime, without any reason, without my medical care being affected.

iii) I understand that my identity will not be revealed in any information.

iv) I agree to take part in the above study.

Signature of subject Date

Name of the subject

Signature of the investigator Date

Name of the investigator

Signature of the witness Date

Name of the witness

PATIENT INFORMATION SHEET (for cases)

Date:

Study title: Role of HPV (Human papilloma virus) in causing cancers of nose, nasal cavity and paranasal sinus

The following information is provided to inform you about this study and your participation in it. Please read the information carefully and you are free to ask any questions regarding the study and the information given. The participation in this study is purely voluntary and you are free to withdraw from the study anytime.

Purpose of the study

Human papilloma virus is proven to cause cancers of cervix (part of female genital tract) and oral cavity. Studies have shown that HPV associated oral cancers respond better to treatment and hence has good prognosis. This study is designed to find out the whether HPV infection of nasal cavity and paranasal sinuses can predispose to cause cancer of the same. It will thus help in studying the cause of nasal and paranasal cancers. The results of the study will help us in planning treatment for HPV associated cancers of nasal cavity and paranasal sinuses and also to find out if these are associated with better clinical outcome.

Method to be followed

During the nasal surgery which planned for the condition, a part of tissue is taken for biopsy under general anesthesia after taking written valid consent. This is done routinely for all patients with a similar diagnosis. During the process of taking tissue for biopsy, some extra tissue will be taken for this study. Tissue will be sent for a test called PCR analysis. PCR analysis is a special diagnostic test done to detect the presence of HPV in the tissue.

Confidentiality

The participation in the study will remain confidential and shall be known only to the investigators.

Withdrawal from the study

Participation in this study is purely voluntary and you can withdraw from the study anytime without any reason. It will not compromise your treatment in any way. There won't be any other risks involved in this study and you need not pay any extra money for the test.

Benefits from this study

The results of this study will help in finding out whether HPV infection is associated with cancers of nasal cavity and paranasal sinuses. This in turn will help in planning treatment and later to identify whether such cases are associated with better prognosis.

For any queries, kindly contact (personal mobile number and department address was given)

WRITTEN INFORMED CONSENT FORM (FOR CONTROLS)

Date:

Study title: Role of HPV (Human papilloma virus) in causing cancers of nose, nasal cavity and paranasal sinus

It has been explained to me by the investigator in the language that I understand that this study is being carried to find out whether HPV can cause cancers of nose, nasal cavity and paranasal sinuses. I have been told that it involves taking a piece of tissue from the nose or paranasal sinuses for PCR analysis (to detect presence of HPV) during the nasal surgery which I will be undergoing for my condition which is done routinely for patients with my disease (chronic sinusitis /inflammatory polyps).It has been explained to me that even though I am not having the disease condition (that is cancer of nasal cavity or paranasal sinuses), my participation in this study will help in the treatment of s those having cancer of nasal cavity and paranasal sinuses . It has also been told that there is no additional risk in the study. It has been explained to me that I am free to withdraw from the study any time I want and will not in any way compromise the treatment, the ENT department is giving me. I understand that my identity and participation will not be revealed in any information released to third parties.

Subjects' Name

Date of Birth/ Age:

i) I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions

ii) I understand my participation is purely voluntary and that I can withdraw from the study anytime, without any reason, without my medical care being affected.

iii) I understand that my identity will not be revealed in any information.

iv) I agree to take part in the above study.

Signature of subject Date

Name of the subject

Signature of the investigator Date

Name of the investigator

Signature of the witness Date

Name of the witness

PATIENT INFORMATION SHEET (for controls)

Date:

Study title: Role of HPV (Human papilloma virus) in causing cancers of nose, nasal cavity and paranasal sinus

The following information is provided to inform you about this study and your participation in it. Please read the information carefully and you are free to ask any questions regarding the study and the information given. The participation in this study is purely voluntary and you are free to withdraw from the study anytime.

Purpose of the study

Human papilloma virus is proven to cause cancers of cervix (part of female genital tract) and oral cavity. Studies have shown that HPV associated oral cancers respond better to treatment and hence has good prognosis. This study is designed to find out the whether HPV infection of nasal cavity and paranasal sinuses can predispose to cause cancer of the same. It will thus help in studying the cause of nasal and paranasal cancers. The results of the study will help us in planning treatment for HPV associated cancers of nasal cavity and paranasal sinuses and also to find out if these are associated with better clinical outcome. Even though you are not having the disease condition (that is cancer of nasal cavity or paranasal sinuses), your participation in this study will help those having cancer of nasal cavity and paranasal sinuses.

Method to be followed

During the nasal surgery which is planned for the condition, a part of tissue is taken for biopsy under general anesthesia after taking written valid consent. This is done routinely for all patients with a similar diagnosis. During the process of taking tissue for biopsy, some extra tissue will be taken for this study. Tissue will be sent for a test called PCR analysis. PCR analysis is a special diagnostic test done to detect the presence of HPV in the tissue.

Confidentiality

The participation in the study will remain confidential and shall be known only to the investigators.

Withdrawal from the study

Participation in this study is purely voluntary and you can withdraw from the study anytime without any reason. It will not compromise your treatment in any way. There won't be any other risks involved in this study and you need not pay any extra money for the test.

Benefits from this study

The results of this study will help in finding out whether HPV infection is associated with cancers of nasal cavity and paranasal sinuses. This in turn will help in planning treatment and later to identify whether such cases are associated with better prognosis.

For any queries, kindly contact (personal mobile number and department address was given)

CASE RESEARCH PROTOCOL

DATE:

NAME:

HOSPITAL NO:

DEMOGRAPHICS

AGE:

GENDER:

PROFESSION:

AREA OF RESIDENCE: URBAN/RURAL

MARITAL STATUS:

ABOUT THE DISEASE:

CLINICAL PRESENTATION: (NASAL OBSTRUCTION/BLEEDING FROM NOSE/RECURRENT SNEEZING/FACIAL SWELLING)

DURATION OF SYMPTOMS:

RISK FACTORS:

SEXUAL HISTORY: (MULTIPLE SEXUAL PARTNERS)

SPOUSE DIAGNOSED WITH GENITAL CANCERS/OROPHARYNGEAL CANCERS:

SMOKING:

ALCOHOL:

SNUFFING:

ANY PRIOR NOSE SURGERIES:

HISTORY OF PREVIOUS RADIATION TO HEAD AND NECK:

FAMILY HISTORY:

DIAGNOSIS:

DATA SHEET

id	name	hno	diag	site	age	sex	resi	marry	smok	alco	snuf	sexhis	spouse	expose	aller	surg	rad	clini	dura
1	saravanan	160494f	sinonasal polyposis		37	1	2	1	1	0	0	0	0	0	1	0	0	1	8
2	natarajan	915601a	sinonasal polyposis		58	1	2	1	1	0	0	0	0	0	1	0	0	1	24
3	senthil	848061f	sinonasal polyposis		34	1	2	1	1	1	0	0	0	0	1	0	0	1	3
4	nitai	896613f	sinonasal polyposis		32	1	1	1	1	0	0	0	0	0	1	0	0	2	36
5	ramya	024655g	sinonasal polyposis		14	1	1	2	0	0	0	0	0	0	1	0	0	1	60
6	sakina	038354g	chronic sinusitis		31	2	2	1	0	0	0	0	0	0	1	0	0	2	24
7	santhunath	009293g	sinonasal polyposis		40	1	2	1	1	1	0	0	0	0	1	0	0	1	24
8	muthu	023024g	sinonasal polyposis		52	1	2	1	1	1	0	0	0	0	1	0	0	1	6
9	senthila	013264g	chronic sinusitis		58	1	2	1	1	1	0	0	0	0	1	0	0	1	60
10	davy kk	690382f	chronic sinusitis		60	1	1	1	0	0	0	0	0	0	1	0	0	1	6
11	suparna	853380f	sinonasal polyposis		24	2	2	1	0	0	0	0	0	0	1	0	0	1	60
12	swarup	021618g	sinonasal polyposis		44	1	1	1	1	1	1	0	0	0	1	0	0	2	56
13	barani	723963f	sinonasal polyposis		35	1	2	1	1	1	0	0	0	0	1	0	0	2	36
14	anjaly	049078g	chronic sinusitis		24	2	1	1	0	0	0	0	0	0	1	0	0	1	24
15	amal	942479d	sinonasal polyposis		43	1	2	1	1	0	0	0	0	0	1	0	0	1	60
16	bharathi	851078f	chronic sinusitis		38	2	2	1	0	0	0	0	0	0	1	0	0	1	3
17	annamalai	877378f	sinonasal polyposis		44	1	2	1	1	1	1	0	0	0	1	0	0	2	12
18	susanta	851923f	sinonasal polyposis		19	1	1	2	0	0	0	0	0	0	1	0	0		
19	gautam saha	872130f	chronic sinusitis		44	1	2	1	1	1	0	0	0	0	0	1	0	1	6
20	indra narain	537520d	sinonasal polyposis		61	1	1	1	0	0	0	0	0	0	1	0	0	1	6
21	kripa pal	854394f	sinonasal polyp		12	2	2	2	0	0	0	0	0	0	1	0	0	1	8
22	babu	303037d	chronic sinusitis		51	1	2	1	1	1	1	0	0	0	0	0	0	1	24
23	chandrasekhar	002724g	sinonasal polyposis		55	1	2	1	0	0	0	0	0	0	1	0	0	2	2
24	shabnam	024865g	sinonasal polyposis		25	2	1	1	0	0	0	0	0	0	1	0	0	1	24
25	nandini	607615f	sinonasal polyposis		22	2	2	2	0	0	0	0	0	0	1	0	0	2	6
26	saif imroz	712497f	sinonasal polyposis		17	1	1	2	0	0	0	0	0	0	1	0	0	1	24
27	ambika	805307f	sinonasal polyposis		29	2	2	1	0	0	0	0	0	0	1	0	0	1	12
28	anitha	170188d	chronic sinusitis		33	2	2	1	0	0	0	0	0	0	1	0	0	1	72
29	muniraj	811890f	sinonasal polyposis		55	1	2	1	1	1	0	0	0	0	1	0	0	1	24
30	rama devi	507184f	sinonasal polyposis		43	2	2	1	1	0	1	0	0	0	1	0	0	1	24

31	tamilselvan	756865f	sinonasal polyposis		28	1	2	2	1	1	1	0	0	0	1	0	0	1	24
32	rajeshwari	770017f	sinonasal polyposis		23	2	2	2	0	0	0	0	0	0	1	0	0	2	36
33	gorachand jana	884919f	sinonasal polyposis		16	1	1	1	0	0	0	0	0	0	1	0	0	2	3
34	jawed salam	027293g	sinonasal polyposis		49	1	1	1	1	0	0	0	0	0	1	0	0	1	12
35	karthik sarkar	043923g	sinonasal polyposis		43	1	1	1	1	1	0	0	0	0	1	0	0	1	36
36	johnson	193445f	sinonasal polyposis		35	2	2	1	0	0	0	0	0	0	1	0	0	2	36
37	rajeshwari	023517g	sinonasal polyposis		37	2	2	1	0	0	0	0	0	0	1	0	0	1	70
38	alok modani	708142f	sinonasal polyposis		41	1	1	1	1	0	0	0	0	0	1	0	0	2	24
39	chabi rana	813936f	sinonasal polyposis		63	2	1	1	1	0	1	0	0	0	1	0	0	3	6
40	kalyan kundu	168253d	sinonasal polyposis		28	1	2	2	0	1	0	0	0	0	1	0	0	2	12
41	ramavtar harijan	074047f	sinonasal polyposis		43	1	2	1	1	0	0	0	0	0	1	0	0	1	48
42	md nurul islam	853108f	sinonasal polyposis		59	2	2	1	1	1	1	0	0	0	1	0	0	3	7
43	jayaraman	819537f	sinonasal polyposis		38	1	2	1	1	1	1	0	0	0	1	0	0	1	60
44	jolly mathew	701075c	chronic sinusitis		35	2	1	1	0	0	0	0	0	0	1	0	0	2	12
45	tuna kumar	023169g	chronic sinusitis		35	1	2	1	1	0	0	0	0	0	1	0	0	2	24
46	lokeshwaran	059157f	sinonasal polyposis		8	1	1	2	0	0	0	0	0	0	1	0	0	2	12
47	sukumar shaw	036059g	chronic sinusitis		38	1	1	1	0	1	0	0	0	0	1	0	0	1	60
48	krishnapas	851078f	sinonasal polyposis		50	1	2	1	0	1	0	0	0	0	1	0	0	1	24
49	tarakanth	895861f	chronic sinusitis		33	1	1	1	1	0	0	0	0	0	1	0	0	1	60
50	tapan	034487g	chronic sinusitis		33	1	1	1	1	0	0	0	0	0	1	0	0	2	48
51	mani	166066g	SCC non keratinising	2	63	1	2	1	1	1	1			0	0	0	0	3	8
52	ashutosh	852538f	SCC well differentiated	2	50	1	2	1	1	1	1		0	0	0	0	0	1	3
53	ramesh	190243g	SCC poorly differentiated	1	49	1	1	1	1	1	0	0	0	0	0	0	0	1	4
54	anil nandi	139555g	SCC poorly differentiated	2	65	1	2	1	1	1	0	0	0	0	0	0	0	1	2
55	narayan mahato	143404f	SCC poorly differentiated	2	65	1	1	1	1	1	0	0	0	0	0	0	0	3	1
56	samendra	089999g	undifferentiated carcinoma	1	64	1	2	1	1	1	1	0	0	0	0	0	0	1	6

57	nagaraj	884534f	SCC poorly differentiated	2	54	1	2	1	1	1	0	0	0	0	0	0	0	1	1
58	kusum devi	809564f	SCC well differentiated	2	49	2	2	1	1	0	1	0	0	0	0	0	0	5	3
59	md iqbal	021925g	SCC poorly differentiated	1	57	1	2	1	1	0	1	0	0	0	0	0	0	1	2
60	mohalminual	041888g	undifferentiated carcinoma	1	15	1	2	2	0	0	0	0	0	0	0	0	0	3	2
61	ganesh ramani	802371d	SCC moderately differentiated	2	42	1	2	1	1	1	1	0	0	0	0	0	0	3	1
62	swapan saha	806379f	SCC moderately differentiated	2	38	1	2	1	1	1	1	1	0	0	0	0	0	5	6
63	abani kumar	767959f	SCC moderately differentiated	1	74	1	2	1	1	1	1	0	0	0	0	0	0	1	6
64	sunday	818419f	SCC moderately differentiated	2	71	1	1	1	1	1	1	1	0	0	0	0	0	5	6
65	mahaboob basha	787295f	SCC poorly differentiated	2	30	1	2	1	1	0	0	0	0	0	0	0	0	5	1
66	md samad	845243f	SCC well differentiated	2	53	1	2	1	1	0	1	0	0	0	0	0	0	5	24
67	murshida	860018f	SCC poorly differentiated	1	28	2	2	1	0	0	0	0	0	0	0	0	0	3	4
68	assiya	255592c	olfactory neuroblastoma	4	52	2	2	1	0	0	0	0	0	0	0	0	0	3	2
69	ashok kumar	387948d	olfactory neuroblastoma	4	59	1	2	1	1	0	0	0	0	0	0	0	0	3	6
70	khajer ali laskar	516393d	olfactory neuroblastoma	4	54	1	1	1	0	0	0	0	0	0	0	0	0	3	1
71	lumberlong	099285g	adenoid cystic carcinoma	1	42	1	1	1	1	1	1	0	0	0	0	0	0	1	2
72	jitin kundu	192627g	adenocarcinoma	1	54	1	2	1	1	1	1	0	0	0	0	0	0	5	3
73	sushanta	088834g	osteosarcoma	2	46	1	2	1	1	0	0	0	0	0	0	0	0	5	12
74	ajay das	916357c	osteosarcoma	2	79	1	2	1	0	0	1	0	0	0	0	0	0	1	12
75	induja nair	840467f	chondrosarcoma	1	23	2	2	1	0	0	0	0	0	0	0	0	0	5	3
76	shanmugham	520354g	lymphoma	1	64	1	1	1	1	0	0	0	0	0	0	0	0	3	1
77	kartik jana	025092g	lymphoma	3	6	1	2	2	0	0	0	0	0	0	0	0	0	5	1
78	nawal kishore	680791f	rhabdomyosarcoma	1	28	1	2	2	0	0	0	0	0	0	0	0	0	1	1

79	bimal kumar	790231f	plasma cell neoplasm	1	38	1	1	1	0	1	0	0	0	0	0	0	0	3	3
80	sayantan roy	787976f	osteosarcoma	2	10	1	1	2	0	0	0	0	0	0	0	0	0	5	2
81	md kammal	042961g	mesenchymal tumor	1	48	1	1	1	0	0	0	0	0	0	0	0	0	2	8
82	ananda mohan das	053106g	anaplastic plasmacytoma	1	73	1	1	1	1	0	0	0	0	0	0	0	0	3	4
83	tusu santra	808052f	neuroectodermal tumor	2	2	2	2	2	0	0	0	0	0	0	0	0	0	5	6
84	md ali	068364g	neuroendocrine tumor	1	53	1	2	1	0	0	1	0	0	0	0	0	0	3	9
85	biswajit	937983f	round cell neoplasm	1	24	1	1	1	1	0	0	0	0	0	0	0	0	1	2
86	dona	945276f	pleomorphic sarcoma	1	32	2	1	1	0	0	0	0	0	0	0	0	0	1	3
87	babu	156732g	sarcomatoid carcinoma	2	54	1	2	1	1	0	0	0	0	0	0	0	0	5	2
88	tafsir alam	273828g	adenocarcinoma	2	49	1	1	1	1	1	1	0	0	0	0	0	0	3	5
89	ram	190243g	neuroendocrine tumor	1	49	1	2	1	1	0	0	0	0	0	0	0	0	1	7
90	beulah	259928g	adenoid cystic carcinoma	2	38	2	2	1	0	0	0	0	0	0	0	0	0	3	8