INTRODUCTION:

Common in Chinese. asso with EBV. Histologically undifferentiated / non keratinizing carcinoma types are common.

EPIDEMIOLOGY:

South China has 20% of worlds cases of Nasopharyngeal Ca. (guandong ca)

India its 1 in 1,00,000

Men : Women ➔ 3:1

This Tumour occurs at a much younger age than other cancers

Its incidence starts to rise after the second decade of life and slowly reaches a plateau, for both sexes, after the fifth decade then very gradually drops with increasing age

Bimodal ➔ 15 to 20 yrs and 40 to 50 yrs

It has been suggested that individuals with a certain HLA haplotype may not be able to mount specific cell-mediated immunity to infection caused by EBV.

Consistent deletion on the short arm of chromosomes 3 and 9 have been found on NPC biopsies, supporting the hypothesis of an NPC tumour suppressor gene locus at these sites.

EBV genome was found in NPC cells. The discovery of EBV receptors on human pharyngeal epithelia.

AETIOLOGY

1. EBV
2. Exposure to chemical agents i.e. tobacco, drugs, and plant products.
3. Dietary factors: Ingestion of salted fish (volatile nitrosamines), preserved vegetables, fermented food stuff containing Nitrosamines and nitro precursors
4. Cooking habits: Household smoke and fumes
5. Religious practices: like incense and joss stick smoke
6. Occupation: Exposure to industrial fumes / chemicals, metal smelting, Formaldehyde, wood dust
7. Other causes: Socioeconomic status, Nutritional deficiencies, weaning habits
8. HLA-A, B and DR locus situated on the short arm of chromosome 6
9. If Infection is delayed until adolescence, the clinical syndrome of infectious mononucleosis may result.

**IMMUNOLOGY IN NASOPHARYNGEAL CARCINOMA**

- Cell mediated immunity: is impaired in patients with nasopharyngeal carcinoma
- This can be demonstrated by Mantoux test (in vivo), and Phytohaemagglutinin response of lymphocytes (in vitro)
- It is possible that this defective specific cell mediated immunity to EB virus allows the virus to be reactivated in the salivary glands. **Increased EB virus loads causes increased anti EB virus IgA antibodies**
- EB virus was found in abundance in the lymphoepithelium of the nasopharynx (mainly B Lymphocytes)
- Primary infection of this virus takes place in childhood and is always accompanied by seroconversion.
- EB virus is present in dormant state in small numbers of circulating B cells or in saliva.
- This virus may be reactivated during immunocompromised states.
- Demonstrable humoral immune response in patients with NPC against EB virus determined antigens (VCA viral capsid antigens, Early antigen EA, and nuclear antigen EBNA).

**MARKERS**

- Associated with nasopharyngeal carcinoma include:
  a. IgA and IgG to **Viral Capsid Antigen** (useful IgA/VCA, IgG/VCA)
  b. IgA and IgG to **Early Antigen** (useful IgA/EA, IgG/EA)
  c. Antibody to **Nuclear Antigen**
  d. Antigen dependent cellular cytotoxicity antibodies
- Normal values of these titres are:
  - Anti EB virus VCA / IgG = up to 1 : 160
  - Anti EB virus EA / IgG = up to 1 : 160
  - Anti EBV VCA / IgA = below 1 : 5
  - Anti EBV EA / IgA = below 1: 5
- **The titres of IgA / VCA and IgA / EA are useful clinical indices for follow up of patients after treatment.** The IgA anti-VCA appears to be more **sensitive** but less **specific** than IgA anti-EA.
- Titres may decline to a low level or remain static after successful treatment.
- The **period between detection of raised IgA / VCA and clinical onset of stage I nasopharyngeal carcinoma ranged from 8 - 30 months**

**PROGNOSTIC SEROLOGICAL MARKERS**

- Inversely proportional to mean titres of VCA & EA antibodies
- Good prognosis is indicated by high Antigen Dependent Cellular Cytotoxicity Antibodies
CLINICAL PRESENTATION

- The marked invasive and metastatic properties are responsible for its symptomatology.
- 50% present with upper neck swelling
- 30% present with nasal symptoms blood stained nasal discharge, nasal obstruction, post-nasal drip or even frank epistaxis
- 20% with deafness, tinnitus, Otalgia.
- 20% Headache
- OME and retracted tympanic membrane due to mechanical effects of tumour.
- 75% present with palpable cervical lymphadenopathy
- Cranial nerves 5 and 6 are the most commonly involved
- Cranial nerves 3-6, when affected together, are indicative of Cavernous Sinus Involvement
- Trismus, before radiotherapy, is rare and occurs only with direct infiltration of the pterygoid muscles
- Systemic metastasis at presentation is rare although eventually most NPC patients die of distant failure. The bones and lungs are the most common sites for secondary deposits followed by the liver.
- The tumour arising from nasopharynx may spread in the following directions:
  1. **Anteriorly** to nasal cavity, paranasal sinuses, Pterygopalatine fossa and orbital apex.
  2. **Posteriorly** to the retropharyngeal space and node of Rouviere, destruction of lateral mass of atlas
  3. **Laterally** into the Parapharyngeal space
     a. **Prestyloid compartment** with involvement of mandibular nerve, pterygoid muscles and infiltration of deep lobe of parotid gland.
     b. **Poststyloid compartment** causing vascular compression of carotid sheath, invasion of last four cranial nerves (9,10,11,12) and cervical sympathetic nerves
  4. **Superiorly** through the body of sphenoid and sinus involving the parasellar structures and optic nerve, petrous apex and foramen lacerum
     o Cavernous sinus may be involved along with III, IV, V, and VI.
     o The brain may also be affected by direct spread and not by haematogenous spread
  5. **Inferiorly** into the oral cavity and retrotonsillar regions
  6. Painless cervical lymphadenopathy because of its tendency for early lymphatic spread.
     a. Lateral group of retropharyngeal node of Rouviere is the first echelon node.
     b. The first node to become palpable is the jugulodigastric node / apical node under the sternomastoid muscle.
     c. These are second echelon nodes. Ipsilateral and bilateral nodal involvement are common
  7. Epistaxis : only seen as blood tinged mucous secretion.
  8. Audiological symptoms like tinnitus, otalgia and deafness. Caused by blockage to the nasopharyngeal end of eustachian tube by the Tumour mass
  9. Neurological symptoms like headache, cranial nerve palsy (any cranial nerve can be involved), and **Horner's syndrome**
  10. **Distant metastasis to bone lungs and liver**

HISTOLOGICAL CLASSIFICATION OF NASOPHARYNGEAL CARCINOMA

- Earlier believed to be malignant Lymphoepithelioma
- Now the tumour cells are confirmed to be epithelial in origin, since they stain positive for Cytokeratin.
The lymphocytes that infiltrate the tumour sites are reactive in nature. Analysis shows that these are predominantly T-Lymphocytes and most of these are CD8+. 

**WHO classification**

1. **EARLIER 3 subtypes**
   1. Type I squamous cell carcinoma (keratinizing):
     - well differentiated
     - moderately differentiated
     - poorly differentiated
   2. Type II Nonkeratinizing carcinoma
   3. Type III Undifferentiated carcinoma

McGuire and Suen told type two and three of WHO classification are in continuum.

Coincidentally, the [WHO (1978)](https://www.cancer.gov/types/head-and-neck/epstein-barr-ca) classification was revised in the same year into two grades:

**Grade 1** – Keratinizing squamous cell carcinoma and

**Grade 2** – Nonkeratinizing squamous cell or undifferentiated carcinoma. Mostly Endemic areas

In General – **Grade 1** tumours are less aggressive than grade 2 tumours, however, they are also less radiosensitive.

**Overall**, the prognosis for patients with grade 1 tumours is less favourable when compared stage to stage with patients having grade 2 tumours.

**DIAGNOSIS**

- History, Clinical Examination
- Nasal Endoscopy
- Biopsy
- Serology (IgA anti-VCA titre is high although lacking in specificity, especially at low levels. The IgA anti-EA titre, on the other hand, is less sensitive but its specificity is extremely high. These tests, especially in combination, are useful)
- FNAC
- Immunochemical staining: Stained for Epstein-Barr virus-associated nuclear antigen (EBNA) by specific monoclonal antibodies

**DIFFERENTIAL DIAGNOSIS**

Sinonasal undifferentiated Ca

Amelanotic melanoma

**ROLE OF IMAGING**

- **CT scan** – preferred, to identify the site for biopsy of the submucosal lesion, **help in the staging of the disease**
- **MRI** scanning is useful and the most **accurate method of evaluating primary Tumour**
PET scanning is useful in diagnosis recurrent / residual lesions following RT
Biopsy of the lesion is the definitive confirmatory investigation

**TUMOUR STAGING:**

**Modified Ho's classification:**

- Primary Tumour (T)
  - T1 – Nasopharynx involvement only
  - T2n – Involvement of nasal cavity in addition
  - T2o – Involvement of oropharynx in addition
  - T2p – Involvement of parapharyngeal region
  - T3a – Bony involvement below the skull base including the floor of sphenoid
  - T3b – Involvement of skull base
  - T3c – Cranial nerves involvement
  - T3d – Orbit, laryngopharynx, infratemporal fossa
  - T3p – Parapharyngeal region
- Regional nodes (N)
  - N0 - No nodes
  - N1 - Nodes above skin crease at laryngeal cartilage
  - N2 - Nodes below the skin crease but above the supraclavicular fossa
  - N3 - Supraclavicular nodes
- Metastasis (M)
  - Mo - No distant metastasis
  - M1 - Distant metastasis

**STAGING**

- I (T1, T2n, T2o) No Mo
- IIA (T2, T2n, T2o) N1, N2 Mo
- IIB (T2p, T3, T3p) No Mo
- IIIA (T2p, T3, T3p) N1, N2 Mo
- IIIb (T1, T2n, T2o) N3 Mo
- IVa (T2p, T3, T3p) N3 Mo
- IVb M1 (any T, any N)

**AJCC classification**

- Tx - Primary Tumour cannot be assessed
- T0 - No evidence of primary Tumour
- Tis - Carcinoma in situ
- T1 - Tumour confined to the nasopharynx
- T2 - Tumour extends to soft tissues
  - T2a - Tumour extends to the oropharynx / nasal cavity without Parapharyngeal extension
  - T2b - Tumour with Parapharyngeal extension
- T3 - Tumour involves bony structures / paranasal sinuses
- T4 - Tumour with intracranial extension / involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or **masticator space**

Regional node (N)
Nx - Regional nodes cannot be assessed
No - No nodal metastasis
N1 - **Unilateral** metastasis in lymph nodes 6cms or less in the greatest dimension above the supraclavicular fossa
N2 - Bilateral nodal metastasis 6 cms or less in the greatest dimension above the supraclavicular fossa
N3 - Metastasis in nodes greater than 6 cms
N3a - Extension to supraclavicular fossa

**Staging:**
- Stage 0 - Tis No Mo
- Stage I - T1 No Mo
- Stage IIa - T2a No Mo
- Stage IIb - T1 -2a N1 Mo
- Stage III - T1 - 2b N0,1 Mo
- Stage IVa - T4 Nc 2 Mo
- Stage IVb - Any T N3 Mo
- Stage IVc - Any T Any N M1

**TREATMENT**

Nasopharyngeal carcinoma is a highly radiosensitive Tumour hence **irradiation** is the preferred modality of treatment for primary, local and regional disease. For advanced disease chemotherapy is added. Surgery only for local and regional failures.

- For early disease (stage I-II), conventional radiotherapy alone is adequate
- Megavoltage external radiotherapy is the treatment modality of choice. This is given through two lateral opposing and one anterior fold. Treatment should be delivered without interruption in 5 days per week for 6 weeks delivering a total dose of 60-65 Gy.
- Chemotherapy (CISPLATIN) is believed to act as a radiosensitizer and helps to reduce the chance of distant metastases.
- After primary treatment, patients should be seen at least **two-monthly for the first year and three monthly for the second and third year, six-monthly thereafter**. The response of local disease is best followed up by repeated nasoendoscopy.
- Annual chest radiographs in the first few years after treatment may pick up lung metastases
- Persistent local disease confined to the nasopharynx can be treated with further radiotherapy or by nasopharyngectomy.
- **Stereotactic radiotherapy**, instead of brachytherapy, should be used when the tumour is either too bulky or situated close to critical structures, such as the optic nerve
- Any neck disease that remains, whether persistent or recurrent, thereafter should best be treated by surgical resection
- Role of surgery: is limited to biopsy of the lesion and confirming the diagnosis. If there is nodal metastasis then block neck dissection should be resorted to.
- The **majority of relapses occur in the first three year**
SURGERY

All patients should be restaged beforehand with full metastatic work up to exclude lung, bone and liver metastases. For systemic metastases, PET and whole-body scan is probably the most sensitive single test.

Involvement of the skull base, cranial nerves, vertebral bodies and carotid sheath and its contents are absolute contraindications.

ANTERIOR APPROACHES

1. Lateral rhinotomy
2. Transnasal transmaxillary (A medial or subtotal maxillectomy can be performed to give the exposure needed. The nasopharynx, the ipsilateral sphenethmoidal complex, Pterygopalatine fossa and the medial end of the infratemporal fossa are all within reach)
3. Midfacial degloving (This is essentially a bilateral transnasal, transmaxillary approach. The procedure is carried out through a sublabial incision leaving no visible scar. With both infraorbital nerves safeguarded, the midface is degloved subperiosteally up to the root of the nose. Sufficient access to the nasopharynx is obtained with bilateral medial maxillectomy. The Pterygopalatine fossa and the medial end of the infratemporal fossa on either side can be reached by extending the extent of the maxillectomy)
4. Le Fort I osteotomy
5. Maxillary swing - MC used ➔ Through a Weber-Fergusson-Longmire incision, the entire maxilla is separated from its bony foundations and swung laterally intact with the masseter muscle and the cheek flap. Access to the opposite side is enhanced by removing the posterior part of the nasal septum. After tumour resection has been completed, the maxilla is swung back and fixed to the facial skeleton.

INFERIOR APPROACH

1. Transpalatal (Access to the nasopharynx is gained by raising a palatal mucoperiosteal flap off the hard palate so that the soft palate is separated from its bony portion. The posterior edge (nearly half) of the bony palate is then removed as necessary. The greater palatine neurovascular pedicle needs to be mobilized bilaterally from its bony canal so that all soft tissues of the palate can be retracted downward during the tumour resection.)
2. Mandibular swing (This is essentially a trans cervical, transmandibular, trans palatal approach via a Frazier incision)

LATERAL APPROACH

Access to the nasopharynx and the adjacent areas is made through the infratemporal fossa. This approach is limited by many critical structures including the facial nerve and the carotid sheath. It is used mainly when the tumour extends laterally to the para pharyngeal space.

If a neck node persists in the absence of distant metastases, radical neck dissection should be performed, as the potential benefit is greater than harm

Poor prognostic factors

Old age, male gender, cranial nerve palsy, level and fixity of lymph nodes
The average five-year survival achieved by conventional radiotherapy alone is excellent for early disease: approximately 80-90 percent for stage I and 70-80 percent for stage II

**OTHER TREATMENT MODALITIES**

1. Photodynamic therapy
2. Immunotherapy