Nasopharyngeal Carcinoma

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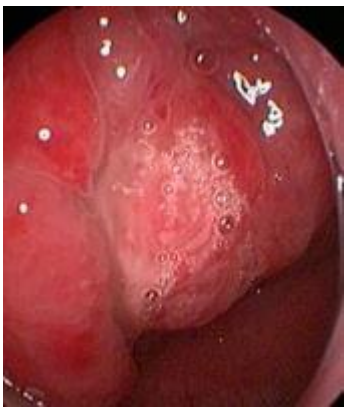

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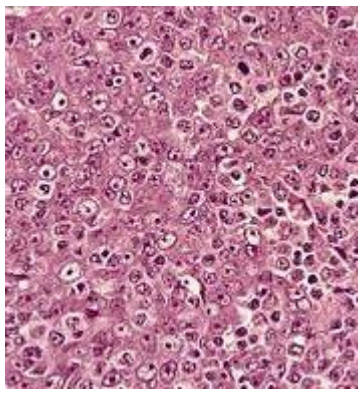
Introduction

Synonyms: NPC, Guangdong tumor

The relatively inaccessible location of the nasopharynx and the wide spectrum of presenting symptoms make early diagnosis difficult. This is also called as an enigmatic tumor



Three subtypes are recognized as per WHO classification:

Type I - Squamous cell carcinoma typically found in adult population

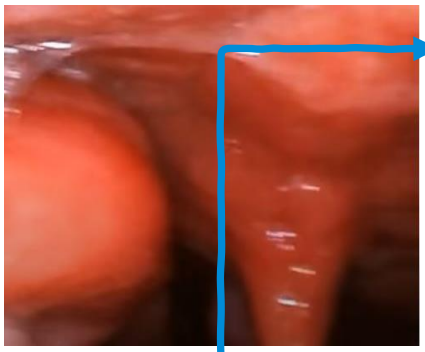
Type II - Non keratinizing carcinoma

Type III - Undifferentiated carcinoma

Most common malignancy involving nasopharynx.
Common among Chinese.
Considered to be an endemic disorder in southern China
Closely associated with Epstein Barr virus infections

Anatomy

It is the superior part of pharynx, with its inferior border defined as the lower level of the soft palate.



Underneath the mucosal layer lies the muscular layer formed by the superior constrictor muscles. At the upper part of the clivus and roof the nasopharynx superior constrictor is absent. The pharyngobasilar fascia forms the outermost layer of the nasopharyngeal wall.

Pharyngobasilar fascia anteriorly attaches to the medial pterygoid plates on both sides.

Nasopharynx lies at the junction of oropharynx and nasal cavity. It is open inferiorly. Its walls are rigid and bony. It is lined by pseudostratified squamous epithelium similar to that of the mucosa of nasal cavity

Boundaries of Nasopharynx

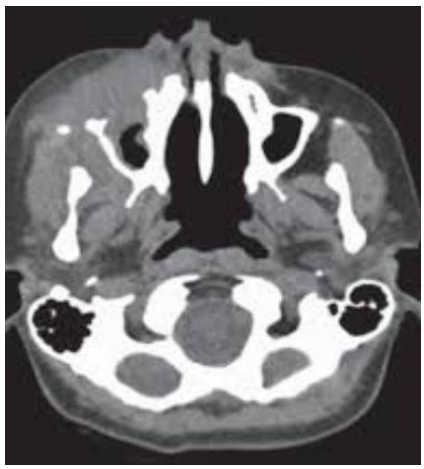
Anterior - Posterior choanae and posterior portion of nasal septum
Floor - Soft palate and part of hard palate
Roof - It is sloping anteroposteriorly. It is formed by basisphenoid and basiocciput. C1 and C2 vetebrae also contribute
Posterior - It communicates with oropharynx. This area is guarded by a ring known as Passavant's ridge
Lateral - The pharyngeal end of eustachean tube is seen here. Around the pharyngeal end of the ET is seen a pad of fat known as the Ostman's fat pad.

Fossa of Rosenmuller is seen above and behind the pharyngeal end of ET. It is about 1.5 cm deep. Its apex is close relationship with the carotid canal, and its base is closely related to the skull base. Foramen lacerum lies medially. Nasopharyngeal carcinoma commonly arises from the fossa of Rosenmuller.

Applied Anatomy

Cancers from the lateral wall can spread to the pterygopalatine fossa via the sphenopalatine foramen. From the pterygopalatine foramen cancer spreads along the foramen rotundum and into the cavernous sinus intracranially producing ophthalmoplegia.
Floor of the sphenoid that forms the anterior part of roof of the nasopharynx is thin and the cancer can easily spread into the sphenoid sinus. From the sphenoid sinus, the cancer can spread into the orbital apex and cause eye symptoms

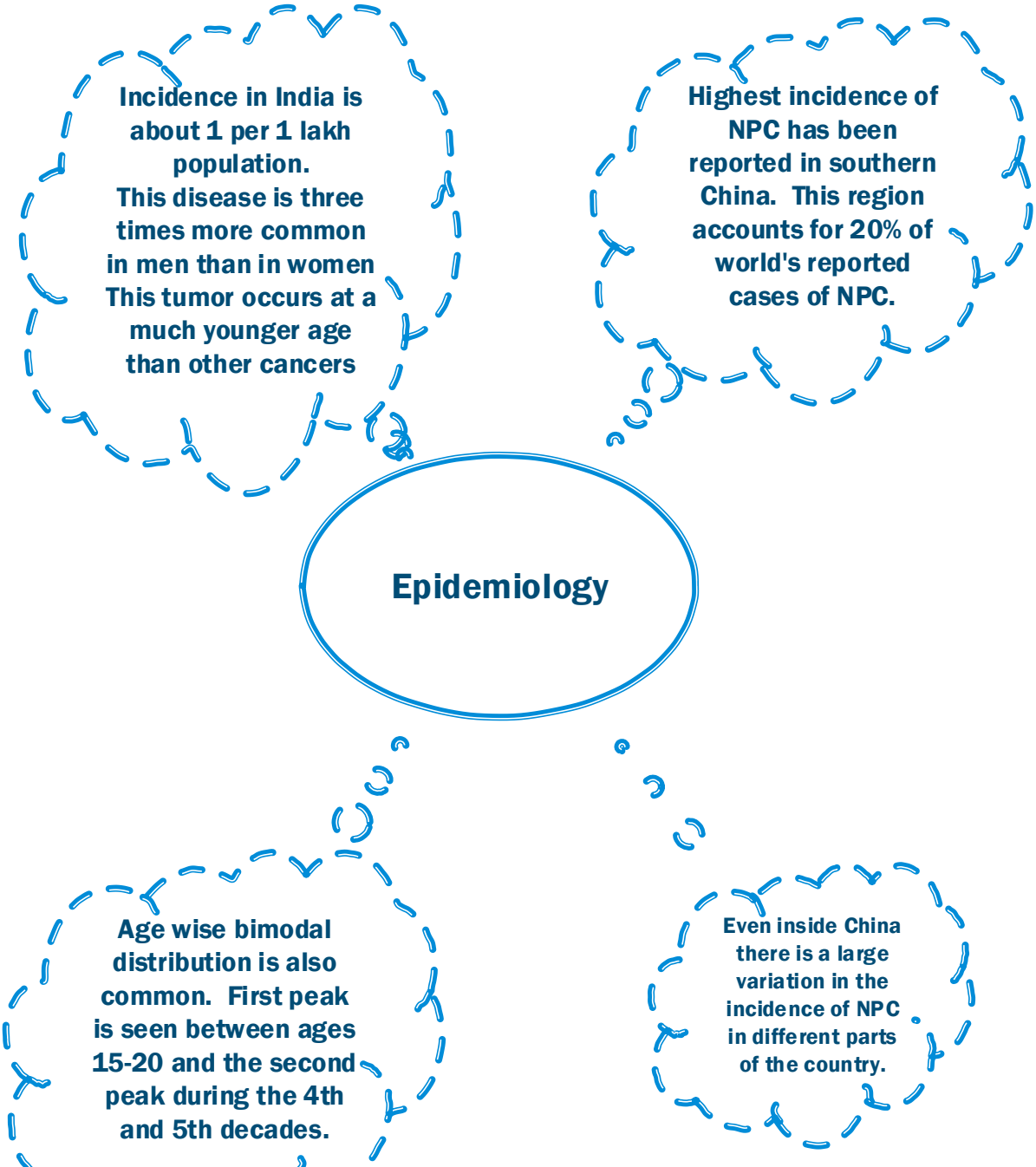
The anterior portion of the lateral wall of nasopharynx is bounded by the pterygoid plates while the posterior portion of the lateral wall is devoid of bone.



There is extensive lymphatic drainage to both sides of the neck from the nasopharynx. The first echelon of lymphatic drainage is the retropharyngeal lymph nodes (nodes of Rouviere). From the retropharyngeal nodes the lymphatic drainage continues to the upper jugular nodes.
Retropharyngeal node closely abuts the carotid sheath. Enlarged retropharyngeal node may partially or completely encase the parapharyngeal portion of internal carotid artery. Cancer can also spread along the carotid sheath superiorly into the foramen lacerum and into the intracranial cavity.

Lateral to the pharyngobasilar fascia are the parapharyngeal spaces with fat pads and muscles of the soft palate (Levator palatini, tensor veli palatini and salpingopharyngeus on both sides). Cancer of nasopharynx readily spreads to the ipsilateral parapharyngeal space.

Epidemiology



Aetiology

Current thinking is that individual HLA subtypes associated with NPC may have impaired immune response to EBV infection and clearance of the virus from the epithelium. The establishment of latent EBV infection in the epithelium of the nasopharynx may lead to pre-malignant changes in the epithelium, later progressing to invasive cancer.

Genes at the 6p21 locus within the HLA region is associated with NPC.

Aetiology

Aetiology

1. EB virus infections have been postulated to be the etiological agent responsible for NPC
2. Exposure to chemical agents (tobacco, drugs, and plant products)
3. Dietary factors: Ingestion of salted fish, 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 industrical fumes / chemicals, metal smelting, Formaldehyde
7. Other causes - Socioeconomic status, nutritional deficiencies
8. Genetic susceptibility: Many HLA haplotypes have been associated with increased incidence of nasopharyngeal carcinoma. The loci involved are the HLA-A, B and DR locus situated on the short arm of chromosome 6.

Pathology

Commonest type of malignancy in the nasopharynx arises from the epithelium. WHO categorized epithelial malignancies in the nasopharynx into three subtypes:
Type I - Well differentiated keratinizing squamous cell carcinoma
Type II - Non keratinizing carcinoma
Type III - Undifferentiated carcinoma

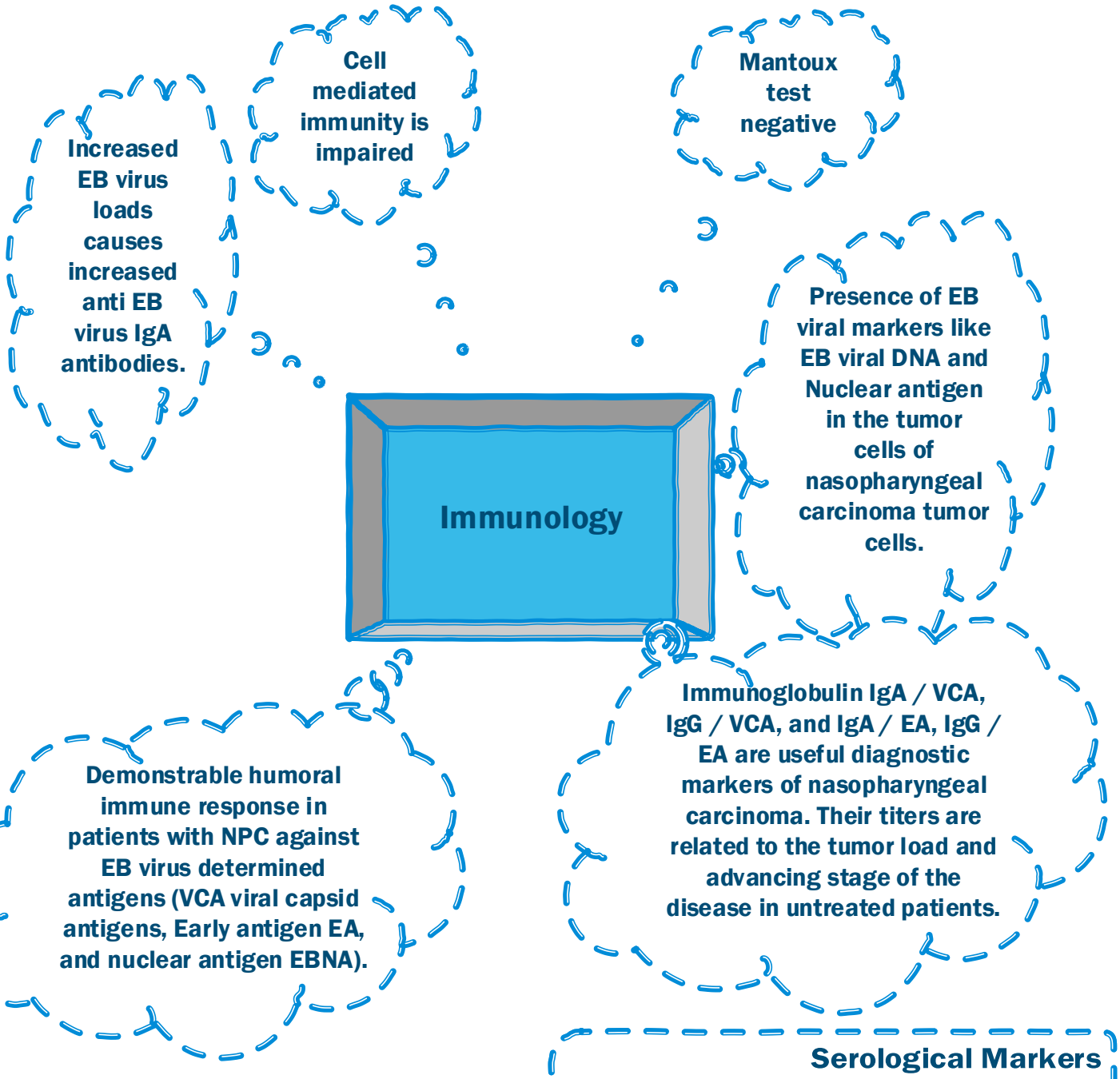
Pathology

Histology of keratinizing squamous cell carcinoma is similar to other well differentiated squamous cell carcinoma in the upper aerodigestive tract. There are some distinctive histologic features in nonkeratinizing carcinoma, which is predominant in high incidence / endemic regions.

WHO classification was modified into two types by combining type 3 and type 2 into one (non keratinizing carcinoma). Non keratinizing type can be further subdivided into differentiated and undifferentiated types

Malignant cells are infiltrated with lymphocytes and plasma cells. These lymphocytes are predominantly T cell and are CD8+ The term lymphoepithelial carcinoma has been coined to describe this feature that is different from other undifferentiated carcinoma of the head and neck region.

Immunology



Serological Markers

a. IgA and IgG to viral capsid antigen

b. IgA and IgG to early antigen

c. Antibody to nuclear antigen

d. Antibody dependent cellular cytotoxicity antibodies

Immunology Contd.

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. 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:

1. Prognosis and survival are inversely proportional to the geometrical mean titres of VCA and EA antibodies.

2. Good prognosis is indicated by high antigen dependent cellular cytotoxicity antibodies

Clinical Features

Early cancers of nasopharynx produce very minimal / trivial symptoms which gets ignored by the patient / and goes undetected by physicians.

Central location of nasopharynx enables multidirectional spread of cancer.

Clinical Presentation

Local signs & symptoms of NPC can be categorized under the following four categories:
Nasal
Otological
Cervical
Neurological

Symptoms can involve many surrounding organs likes ears and eyes producing symptoms that would not immediately point towards the nasopharynx.

Nasal signs & symptoms

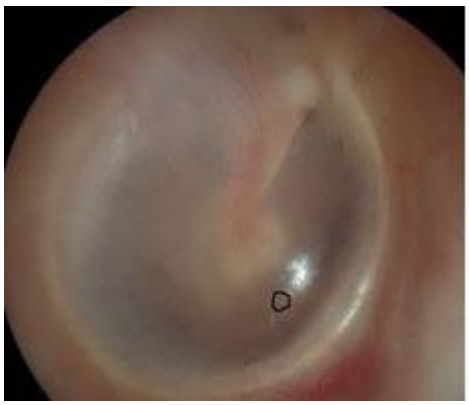
Blood stained nasal discharge / post nasal drip
In large tumors nasal block
Cacosmia / smell of blood if bleeding is from the tumor

Nasopharynx is a difficult area to examine. Post nasal examination using a post nasal mirror could reveal the presence of the tumor, but this is a difficult examination to perform.

Otological signs & symptoms

1. Recent onset ipsilateral hearing loss
2. Muffled sound
3. Tinnitus
4. Sensation of ear block

Nearly 40% of patients with NPC suffer from some form of ear symptom. Majority of otological symptoms are caused due to obstruction of the Eustachean tube secondary to the tumor bulk / invasion.



Otoscopy:

Could reveal the presence of middle ear effusion.

Nasopharynx should always be examined in patients with unexplained persistent middle ear effusion

Neck signs & symptoms

Nearly 70% of patients with NPC have enlarged neck nodes on presentation. Nearly a third of these patients have bilateral enlarged neck nodes.

Enlarging neck mass is the commonest symptom that brings the patient to the doctor.

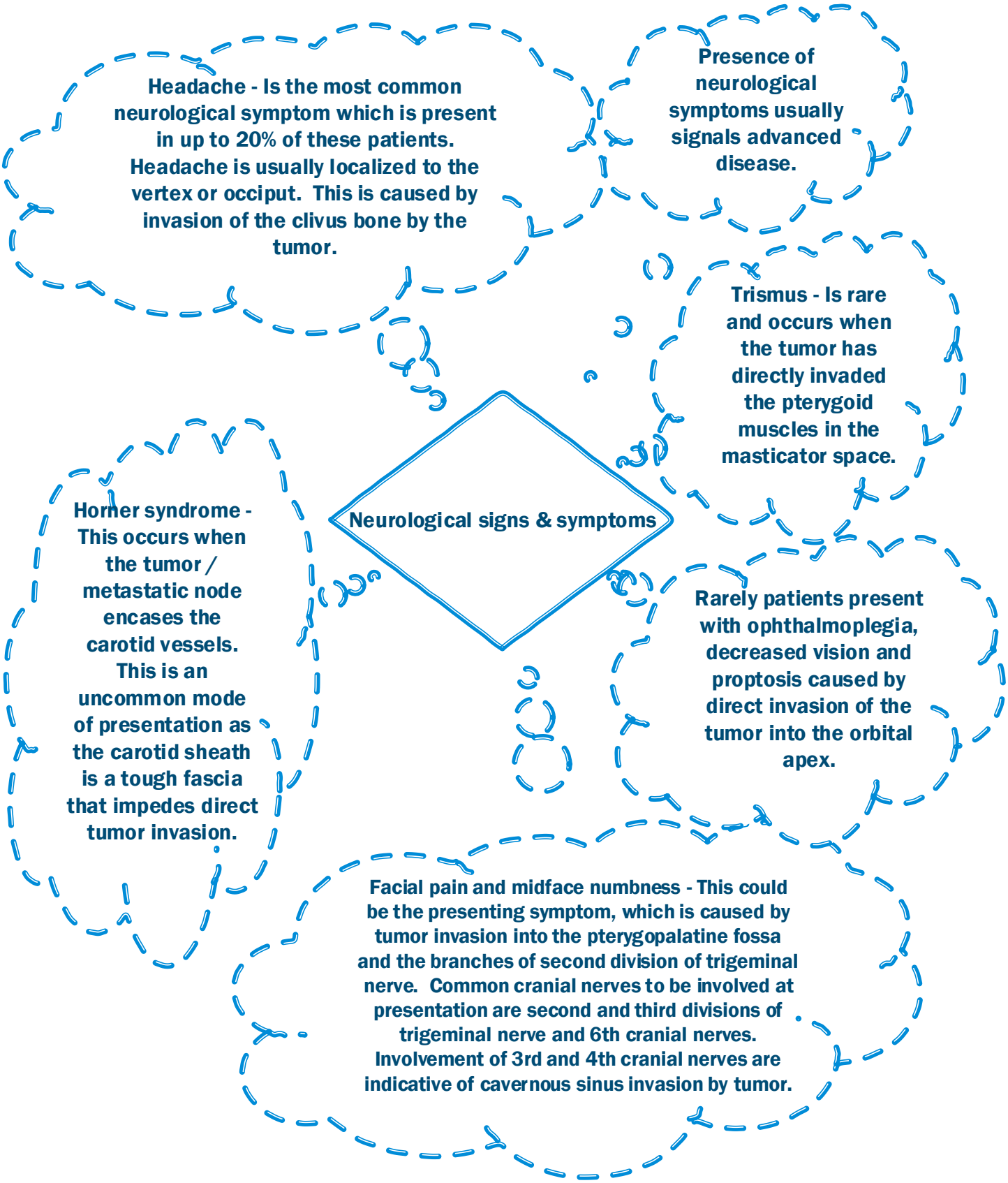
Most frequently involved nodes are level II (upper jugular) and upper level V (apex of posterior triangle).

Lymphatic spread of NPC occurs in an orderly fashion from superior to inferior.

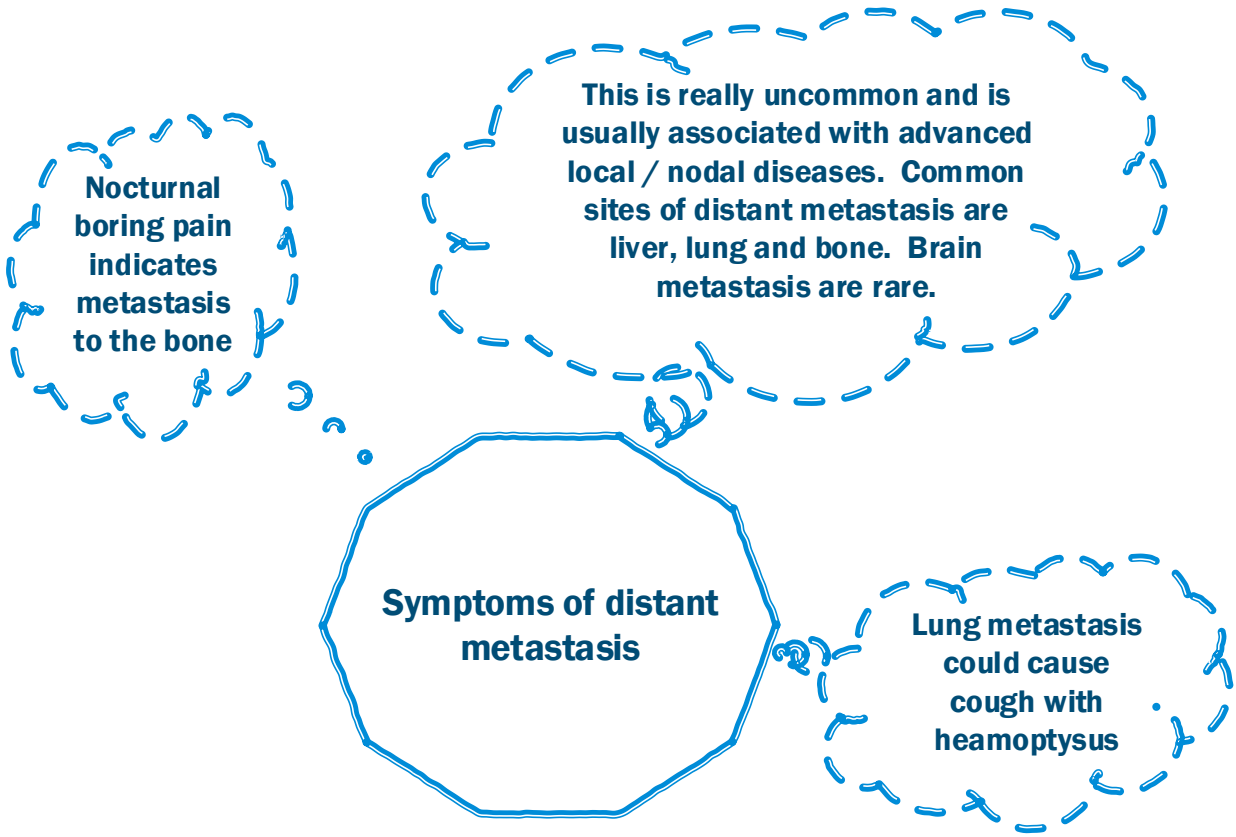
An isolated enlarged supraclavicular node is almost never a lymph node metastasis from NPC.

Occasionally, NPC patients can present with metastatic nodes from unknown primary. In these patients the primary is usually very small and may not be obvious on endoscopic examination. Modern imaging modalities like MRI and PET scan could reveal the presence of small cancer in the nasopharynx.

Neurological symptoms & signs



Symptoms of distant metastasis



One special scenario that could lead to diagnostic confusion is the finding of histologically proven lymphoepithelial carcinoma in a lung nodule, which can be a primary lymphoepithelial carcinoma of lung / distant metastasis from a nasopharyngeal primary. In these patients a PET scan can help in differentiating between lung primary and distant metastasis.

Paraneoplastic syndrome:

About 1% of NPC patients develop dermatomyositis as a para-neoplastic syndrome. About 12% of dermatomyositis patients developed NPC. Dermatomyositis can develop concurrently with NPC.

Diagnosis

A good history, together with a thorough clinical examination including endoscopy of the nasopharynx is the basis for making the diagnosis. In majority of these patients a tumor mass will be found in the nasopharynx and biopsy should be taken without any delay. In about 5% of cases tumor may not be visible in the nasopharynx.

History:

NPC should be considered as a differential diagnosis in patients who present with symptoms and those who live in high risk areas in any of the 4 categories:

Nasal
Otological
Cervical
Neurological

Symptoms include:

Tinnitus
Ear block
Blood stained nasal discharge
Ancestry of the patient

Family history should also be elicited

General Examination

Examination of nasopharynx:

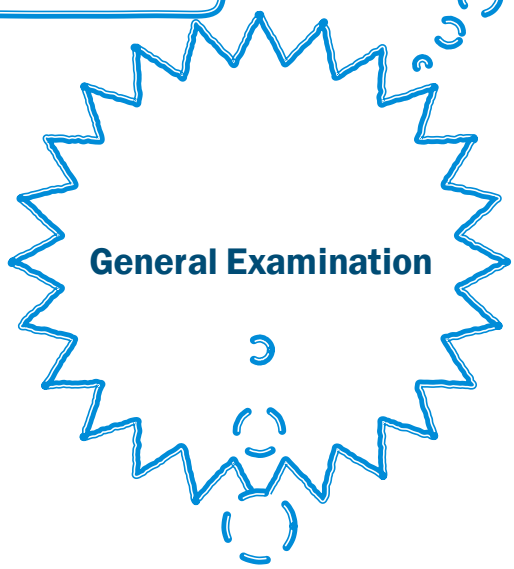
Traditionally nasopharynx is visualized using a post nasal mirror. Now with the advent of nasal endoscope, the same can be used to visualize the nasopharynx. Advantages of nasal endoscopy include:

1. Nasopharynx could be visualized and examined under high resolution

2. The entire examination process can be recorded and documented

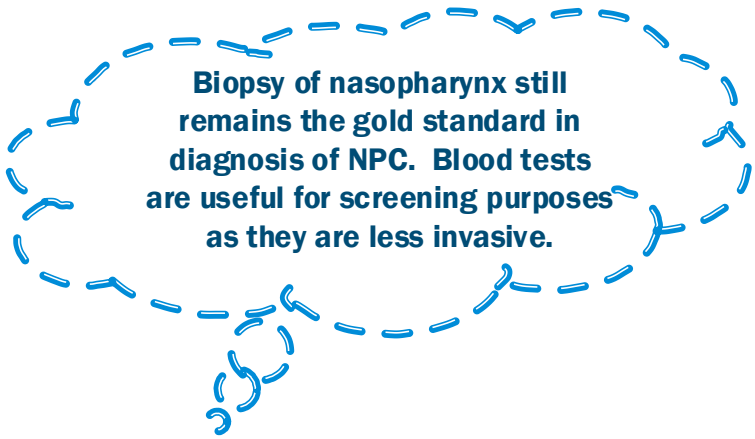
3. Biopsy can also be taken in the same sitting

A full head and neck examination needs to be performed in all these patients. Otitis media with effusion should be looked out for.



Cranial nerve lesions and cervical adenopathy should be examined for. When nodes are palpable, their site and size must be carefully assessed as a part of staging process.

Laboratory Tests



Lab Tests

EBV antibodies serology:

The initial association of EBV infection with NPC was identified when patients with NPC regularly were found to have elevated levels of EBV antibodies in the serum.

IgA antibodies against viral capsid antigen (VCA)

Early antigen (EA)

EBV nuclear antigen 1 (EBNA1) are commonly used as tumor markers to screen for NPC

Elevated Serum EBV IgG titre signifies prior infection by the virus

Elevated serum EBV IgM titre indicates recent infection

It should be stressed that elevated serum EBV IgG and serum EBV IgM are not useful screening tests to rule out NPC as most adults will have been infected by EBV at an earlier age.

EBV IgA VCA is sensitive but not specific for NPC while EBV IgA EA is specific but not sensitive for detecting NPC. Combining both these tests can increase the sensitivity and specificity of the serological tests

EBV serology is not an ideal tumor marker for NPC as the serology has weak correlation with the stage of the disease, it is also unable to reflect the tumor response to therapy and does not show increasing titre in recurrent disease. Despite its deficiency, EBV serology is still widely employed in endemic areas for screening.

EBV DNA Titre

EBV genome is found in all cancer cells of the endemic form of NPC. EBV DNA will be shed into the patient's blood stream during cell turnover. More advanced stage NPC will have a higher tumor load and larger cancer cell turnover. Detection of EBV DNA in plasma could be used as a tumor marker for NPC. Real time PCR can be used in identifying EBV DNA.

Apart from diagnostic and screening purposes, plasma EBV DNA levels can have prognostic impliation. A high level of EBV DNA before treatment correlates with a larger tumor load, and more advanced stage of the cancer. Plasma EBV DNA levels rapidly decrease to undetectable or very low levels within 1-2 weeks after completion of treatment. Persistently elevated plasma EBV DNA levels after treatment may signify persistent loco-regional disease or development of distant metastasis. An initial drop in plasma EBV DNA titre following treatment indicates response to the treatment. Later increase in this value following this drop indicates tumor recurrence / metastasis.

Nasopharyngeal brushing for EBV DNA:

EBV DNA levels can be elevated in other EBV associated diseases. In order to avoid diagnostic difficulties with NPC brushing of the nasopharynx is performed and the cells obtained are sent for EBV DNA detection with qt-PCR. Newer designs of transoral brushing and detection of EBV DNA show promising results.

Cytology:

Smears from FNAC from enlarged neck nodes can differentiate between metastasis from squamous cell carcinoma and undifferentiated carcinoma. Immunohistochemical staining for EBV RNA a definitive diagnosis of NPC with neck node metastasis can be made.

Imaging

Plain radiograph:

Plain radiographs of nasopharynx is neither sensitive nor specific enough for clinical use and has been superseded by other modalities. A plain x-ray chest can be done as initial screening for lung metastasis and general health status. Orthopantomogram is performed by a dentist prior to irradiation

CT:

Initially CT scan was used as a staging modality now it has been replaced by MRI

MRI:

This is the preferred imaging modality for NPC staging because of its superior soft tissue resolution. MRI can better delineate parapharyngeal extension

PET scan:

This is being increasingly used in the management of NPC. PET scan is a functional imaging study and is combined with cross sectional imaging modality like CT scan for anatomical localization. 18FDG is used as an isotope. It gets concentrated in areas of malignancy due to increased glucose metabolism. PET-CT is very useful in assessing residual and recurrent disease after treatment

Ultrasound is useful in the assessment of neck node metastasis.

Staging AJCC

Primary tumour (T)>		Regional lymph nodes (N)	
Tx	Primary tumour cannot be assessed	**N1**	Unilateral metastasis, in cervical lymph node(s), and/or unilateral or bilateral metastasis in retropharyngeal lymph nodes, 6 cm or less, above the caudal border of cricoid carilage
T1	Tumour confined to nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal space involvement	**N2**	Bilateral metastasis in cervical lymph node(s), 6 cm or less above the caudal border of cricoid cartilage
T2	Tumour with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid, and/or prevertebral muscles	**N2**	Metastasis in cervical lymph node(s) greater than 6 cm in dimension and/or extension below the caudal border of cricoid cartilage
T3	Tumour invades bony structures of skull base cervical vertebra, pterygoid structures, and/or paranasal sinuses		
T4	Tumour with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or infiltration beyond the lateral surface of the lateral pterygoid muscle		

Metastatic disease (M)	
M0	No distant metastasis
M1	Distant metastasis present

Stage groups			
I	T1	N0	M0
II	T1 T2	N1 N0, N1	M0 M0
III	T1, T2 T3	N2 N0-, N1, N2	M0 M0
IVA	T4 Any T	N0, N1, N2 N3	M0 M0
IVB	Any T	N3	M0
IV	Compressed previous stage IVB now IVA		

Management

IMRT starts with making an individualized immobilization device, usually a thermoplastic cast for the head and neck for each patient. Then a planning CT is obtained with the patient in cast and in treatment position.

Non-keratinizing subtype of NPC is a radiosensitive tumor and it is the main stay in the treatment of NPC. Introduction of intensity modulated radiotherapy (IMRT) has improved the efficacy of radiotherapy.

Surgery is limited to obtaining biopsy from the lesion. Secondary nodal deposits can also be surgically removed

Chemotherapy has been used in combination with RT in advanced cases

Intensity modulated radiotherapy

Planning CT scan is used for localization of targets and normal tissues. The required dose of radiation to targets and the dose constraints to normal tissues are input into the computer planning system. This will generate optimal radiation plan that concentrates the radiation dose in targets while minimizing the dose to normal tissues.

CTV2 - High risk subclinical diseased is covered by this dose. It includes CTV1 with margin plus areas at risk of microscopic involvement, including the entire nasopharynx, retropharyngeal node regions, skull base, clivus, pterygoid fossae, parapharyngeal space, sphenoid sinus, and the posterior part of nasal cavity / maxillary sinus and pterygopalatine fossa. This requires atleast 60 Gy of radiation dose.

CTV1 - This includes GTV with margin and requires radiation dose of around 70 Gy.

IMRT has "dose painting" capacity that allows different dose levels to different regions to be applied in the same treatment. With IMRT local control rates of over 90% have been reported.

Different treatment targets:

Gross tumour volume (GTV):

Tagets the primary in nasopharynx and for involved neck nodes.

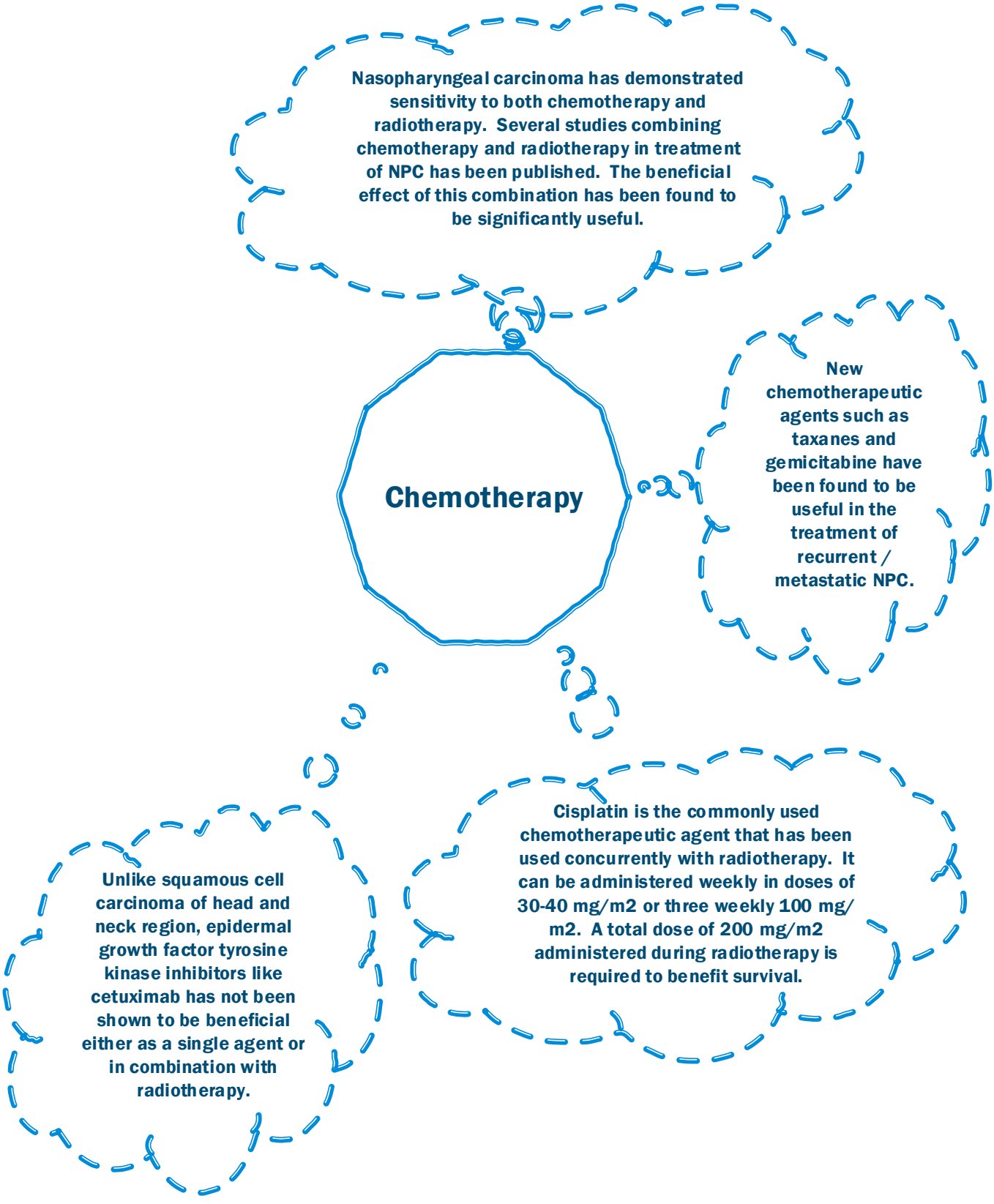
Clinical target volume (CTV):

This includes GTV and radiation covers for subclinical disease spread around nasopharynx andneck.

Planning target volume:

This includes CTV with a margin to allow for possible errors in daily positioning and treatment of patient during radiotherapy

Chemotherapy



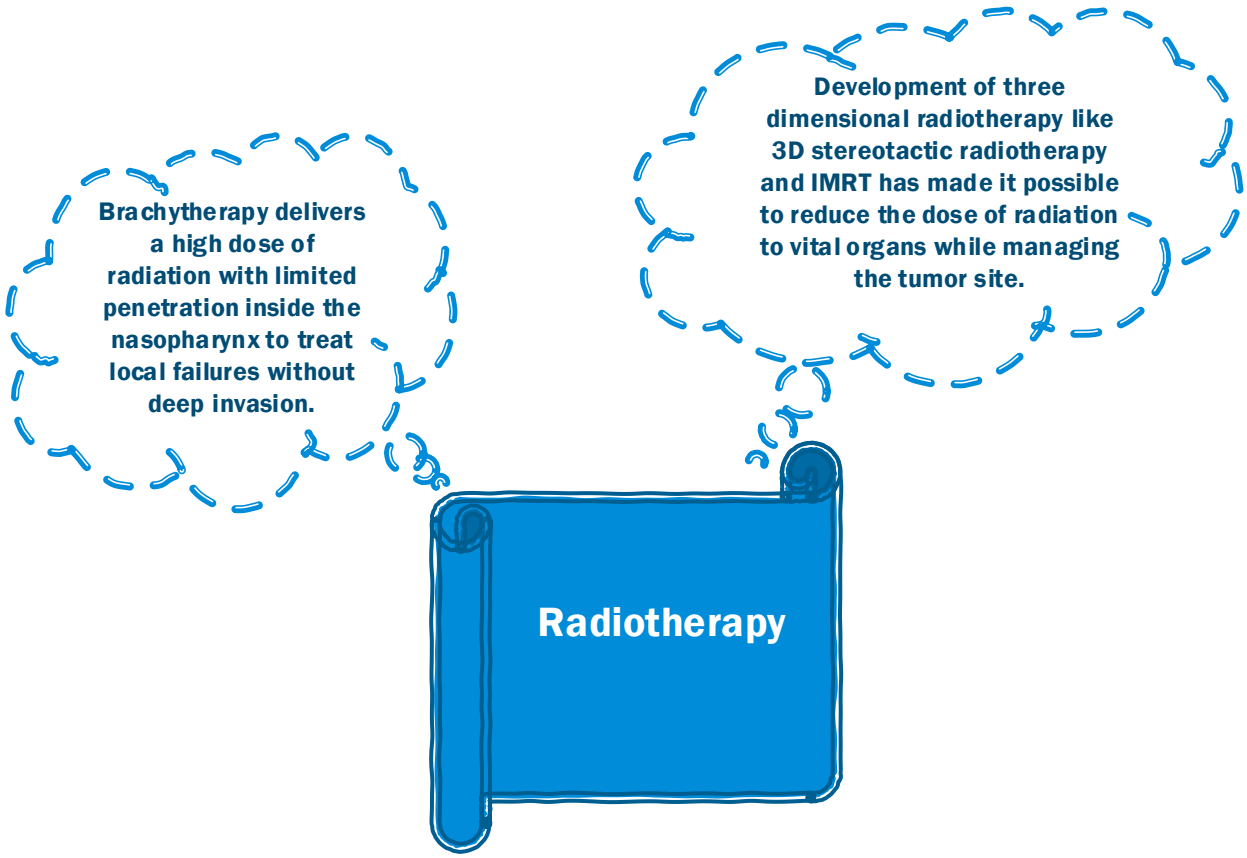
Salvage Treatment

Salvage treatment for NPC is only moderately successful but with significant morbidities. This is because patients with recurrences have already been exposed to the toxicities of previous treatment. The choice of salvage treatment would have to keep in mind the tolerance of normal tissue.

Radiotherapy for local failures:

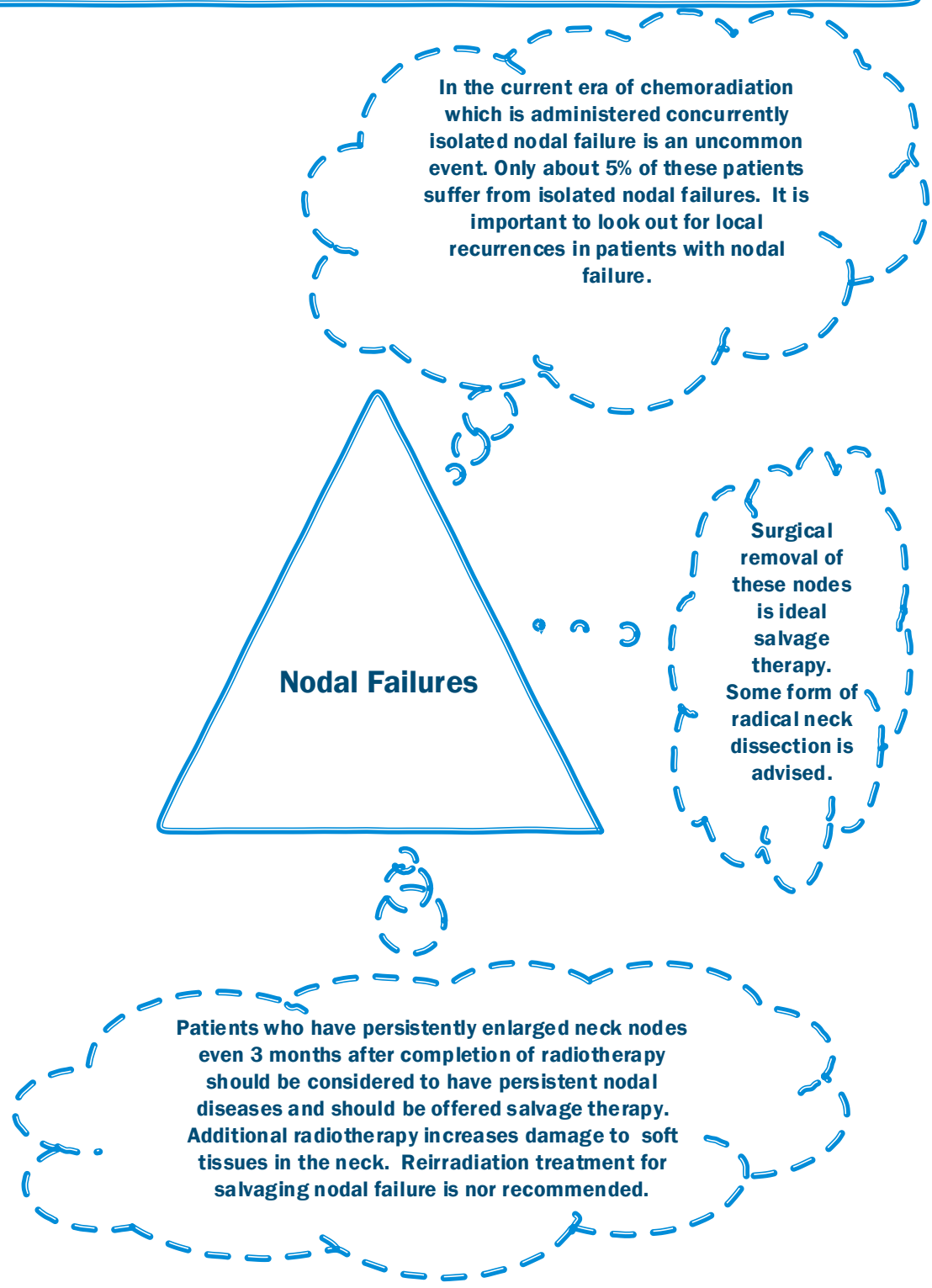
Radiotherapy for local failures can be delivered by external beam / local brachytherapy. Main limiting factor in re-irradiation is the tolerance of vital organs like brainstem, optic chiasma, and temporal lobe to radiation. Traditional two dimensional re-irradiation for for local failure had poor results with a 5 year survival rates of only 8%.

Radiotherapy for local failures



Main sources of radiation used are iridium-192, gold 198. Both these isotopes emit gamma radiation. Brachytherapy delivery needs the use of different techniques. Iridium 198 can be loaded into a tailor made plastic mould fitted into the nasopharynx via the oral cavity under local anesthesia. To deliver gold 198 isotope, the gold grains are implanted to the nasopharynx after the soft palate is split open under general anesthesia. Both these techniques are suitable only for small tumors (less than 2 cm in maximal dimension). 5 year survival rate in this type of therapy ranges between 50-60%.

Radiotherapy for nodal failures



Surgery for local failure

Nasopharynx is a difficult area to access surgically. Majority of these access routes require facial incisions and multiple osteotomies and the need to transgress significant amount of normal tissue to expose nasopharynx. Nasopharyngeal resection (nasopharyngectomy) is reserved only for salvaging radiation failures.

This surgical procedure should be offered only to those patients who can withstand a 5 hour surgery. Tumors that show internal carotid artery encasement / extensive skull base infiltration / intracranial extension are not suitable candidates for salvage surgery.

Approaches used to access nasopharynx:

Transpalatal approach - Inferior approach
Transcervico-mandibulo-palatal approach (inferolateral approach)
Midfacial degloving approach (anterior approach)
Maxillary swing approach (anterolateral approach)
Facial translocation approach (anterolateral approach)
Lateral skull base approach (lateral approach)

Complications of Treatment

Complications of treatment:

Radical radiotherapy for NPC always exposes normal tissue in the vicinity of the tumor to a damaging dose of radiation.

1. Mucositis of the oral cavity, oropharynx and hypopharynx. This can be aggravated severely with concurrent chemotherapy. A majority of these patients would need nasogastric feeding during this phase of treatment.

2. Reduction of salivary gland function causing xerostomia

3. Otitis media with effusion / otitis externa / Persistnet otitis media

4. Osteoradionecrosis of temporal bone

5. Sensorineural hearing loss

6. Olfactory dysfunction

7. Nasal mucosal crusting

8. Sinusitis / foul smelling nasal discharge

9. Radiation induced fibrosis is another late complication causing neck stiffness and trismus

10. Osteoradionecrosis of skull base

11. Hypothalamic pituitary dysfunction

12. Internal carotid artery aneurysm (rare)