Chapter 19: Nasopharynx (the postnasal space)

C. T. Chew

The human nasopharynx is mainly derived from the primitive pharynx. It represents the nasal portion of the pharynx behind the nasal cavity and above the free border of the soft palate. It has also been called the postnasal space and epipharynx, with criticisms as to the proper terminology. The propositions of postnasal space and epipharynx are mere descriptive anatomical concepts. The concept that there is an anterior 'nasal' and posterior 'pharyngeal' component is supported by embryological, morphological and functional considerations (Kanagasuntheram, Wong and Chan, 1969; Leela, Kanagasuntheram and Khoo, 1974).

Morphological and histological studies show that the anterior portion proximal to the tubal orifice resembles the nasal cavity morphologically, while the posterior portion possesses features resembling the oropharynx. The junctional zone is the belt along the tubal orifice where the first and third pharyngeal arches meet.

Innervation studies show that the portion proximal to the tubal orifice is innervated by the maxillary division of the trigeminal (V) nerve, and that posterior to the tubal orifice by the glossopharyngeal (IX) nerve.

Functional studies with contrast and cinefluorography reveal structural differences between the two components. Contractility is observed only in the posterior portion.

Surgical anatomy

The average dimensions of the nasopharynx in the adult are 4 cm high, 4 cm wide and 3 cm in length. The posterior wall is about 8 cm from the pyriform aperture along the floor of the nose.

The anterior wall is formed by the choanal orifice and the posterior margin of the nasal septum.

The floor is formed by the upper surface of the soft palate, which occupies the anterior two-thirds, and by the nasopharyngeal isthmus.

The roof and posterior wall form a continuous sloping surface bounded by the body of the sphenoid, the basiocciput and the first two cervical vertebrae to the level of the soft palate. The upper portion of the posterior wall lies in front of the anterior arch of the atlas with a mass of lymphoid tissue embedded in the mucous membrane (nasopharyngeal tonsil or adenoid). The prevertebral fascia and muscles separate the adenoid from the vertebrae.

The lateral wall is dominated by the pharyngeal orifice of the eustachian tube. Located in the middle of the wall, it is about 1.5 cm equidistant from the roof, posterior wall, choana and the floor. The tubal elevation (torus tubarius), created by the elastic cartilage of the tube, is particularly prominent in its upper and posterior lip. Behind the posterior margin of the torus, between it and the posterior wall, lies the lateral pharyngeal recess or the fossa of
Rosenmüller. Aggregates of lymphoid tissue of variable sizes around the tubal orifice and part of the recess are collectively called the tubal tonsil.

The fossa of Rosenmüller is situated at a corner between the lateral and dorsal walls. Although not obvious in infants, the recess can measure up to 1.5 cm in depth in adults. More often than not it appears as a cleft, trabeculated at times and recedes posterolaterally to an apex near to the edge of the carotid canal opening. It opens into the nasopharynx at a point below the foramen lacerum.

Anatomical relations of the fossa of Rosenmüller are:

- Anteriorly: eustachian tube and levator palatini
- Posteriorly: pharyngeal wall mucosa overlying the pharyngobasilar fascia and retropharyngeal space, containing the lateral-retropharyngeal lymph node of Rouvière
- Medially: nasopharyngeal cavity
- Superiorly: foramen lacerum and floor of carotid canal
- Posterolateral (apex): carotid canal opening and petrous apex posteriorly, foramen ovale and spinosum laterally
- Laterally: tensor palatine and the mandibular nerve, and the prestyloid compartment of the parapharyngeal space. The fossa forms the medial border of the most superior part of the parapharyngeal space.

As the superior constrictor does not reach the base of skull, a lateral gap (sinus of Morgagni) is created. This gap is bridged only by the pharyngobasilar fascia. Through this, the eustachian tube with its two muscles, one on each side, enters the nasopharynx. Along the inferior border of the two muscles the fossa of Rosenmüller is separated from the parapharyngeal space by mucosa and pharyngobasilar fascia. Thus tumours can easily infiltrate and breach this area to spread into the parapharyngeal space.

**Epithelial lining of the nasopharynx**

The nasopharyngeal mucosa is thrown into numerous folds and crypts. The actual surface area is approximately 50 cm² in the adult. During fetal life there is a gradual transition of the respiratory ciliated epithelium to squamous type in the lower and posterior part of the nasopharynx. True squamous metaplasia occurs only in postnatal life and is completed by about 10 years of age. About 60% of the total epithelial surface is lined by stratified squamous epithelium. The mucosa abutting the choanae and immediate nasopharyngeal roof is completely lined by ciliated epithelium. Patches of squamous and ciliated epithelium, intermingling with islets of transitional or intermediate types, cover the rest of the roof and lateral walls. The posterior wall is dominated by squamous epithelium. The nasopharyngeal mucosa differs from the rest of the upper respiratory tract in that the subepithelial connective tissue is rich in lymphoid tissue. It consists of numerous small lymphocytes, plasmacytes, reticular cells and fibroblasts. This 'lymphoepithelium' together with aggregates of lymphoid tissue and the tonsils constitute Waldeyer's ring.
Anatomically, the adenoid tissue is lined by epithelium which is thrown into numerous folds separating the lymphoid follicles. There are also deep crypts similar to those in the palatine tonsil. The lymphoid tissue consists of both T and B lymphocytes, with the latter predominating. The adenoid is poorly developed at birth and is not visible on X-ray in infants under the age of 1 month but is clinically identifiable by the fourth month. It is radiologically demonstrable in only 50% of infants under 6 months, and in all infants by the age of 6 months (Capitanio and Kirkpatrick, 1970). Radiologically, the adenoid appears as a soft tissue shadow mass on the roof and posterior nasopharyngeal wall immediately below the pituitary fossa.

By the age of 2 years, hypertrophy and hyperplasia of the adenoid occurs. Rapid growth occurs from 3 to 5 years with a consequent decrease in the nasopharyngeal airway. After that the adenoid size remains relatively constant while the nasopharynx increases in size (Jeans et al, 1981). Involution of the adenoid occurs after puberty; however, the lymphoid tissue persists into old age.

The adenoid is of clinical importance. Any diminution in size or its absence could indicate an underlying immunodeficiency, for example familial hypogammaglobulinaemia and Wiskott-Aldrich syndrome. The presence of a nasopharyngeal mass in infants under the age of 1 month should raise the suspicion of a tumour such as encephalocele, as the adenoids are not detectable at this age.

Pharyngeal hypophysis

The anterior pituitary gland is formed by a median ectodermal upgrowth from an invagination (Rathke's pouch) of the stomatodeum immediately in front of the buccopharyngeal membrane. This upgrowth migrates cranially through the mesenchymal tissue, which later forms the body of the sphenoid, to rest in the anlage of sella turcica. Its original course is identified by the craniopharyngeal canal. Breaks may occur in the buccopharyngeal stalk to form accessory or aberrant endocrine tissues in the body of the sphenoid (Boyd, 1956). Remnants of the stalk persist in the nasopharyngeal roof to form the pharyngeal hypophysis which is a tiny elongated body of tissue in the mucoperiosteum underlying the posterior vomerosphenoidal articulation. Histologically the pharyngeal hypophysis contains chromophobe cells similar to those in the pituitary. Its functional role is not clear but it has been observed to undergo hypertrophy in women over the age of 50 years (McGrath, 1971). The pharyngeal and ectopic hypophyseal tissue may give rise to chromophobe adenoma in the nasopharynx or sphenoid (without sellar enlargement or involvement).

The pharyngeal bursa

This structure is often confused with Rathke's pouch. When present, it appears as a median sac-like depression in the posterior nasopharyngeal wall just above the upper fibres of the superior constrictor (Dorrance, 1931). It may extend upwards to the tubercle of the occiput. Inflammation of the pharyngeal bursa is known as Thornwaldt's bursitis.
Tumours of the nasopharynx

Many types of tumours, including rare, primitive ones, have been described in the nasopharynx (Table 19.1). Only a few nasopharyngeal tumours, for example hairy polyps, have characteristic macroscopic appearances. Preliminary biopsy is often required for histodiagnosis before starting treatment. The histodiagnosis of some tumours can be difficult. Of all the tumours, carcinoma is the most common. It is unique in its epidemiology and racial predisposition, with distinctive immunogenetics influencing its prognosis and survival.

Table 19.1 WHO classification of tumours of the nasopharynx (Shamugaratnam and Sobin, 1978)

I Epithelial tumours

(a) Benign
   (1) Squamous cell papilloma
   (2) Oxyphilic adenoma (oncocytoma)
   (3) Pleomorphic adenoma
   (4) Others

(b) Malignant
   (1) Nasopharyngeal carcinoma
   (2) Adenocarcinoma
   (3) Adenocystic carcinoma
   (4) Others

II Soft tissue tumours

(a) Benign
   (1) Juvenile angiofibroma
   (2) Neurofibroma
   (3) Neurilemmoma (schwannoma)
   (4) Paraganglioma (chemodectoma)
   (5) Others

(b) Malignant
   (1) Fibrosarcoma
   (2) Rhabdomyosarcoma
   (3) Neurogenic sarcoma
   (4) Others

III Tumours of bone and cartilage

IV Tumours of lymphoid and haematopoietic tissues

Malignant lymphomata
V Miscellaneous tumours

(a) Benign
   (1) Teratoma
       solid
cystic (dermoid cyst)
   (2) Pituitary adenoma
   (3) Meningioma

(b) Malignant
   (1) Malignant melanoma
   (2) Chordoma
   (3) Craniopharyngioma
   (4) Others

VI Secondary tumours

VII Unclassified tumours

VII Tumour-like lesions

   (1) Pseudoepitheliomatous hyperplasia
   (2) Oncocytic metaplasia and hyperplasia
   (3) Cysts
   (4) Angiogranuloma
   (5) Fibromatosis
   (6) Amyloid deposits
   (7) Infective granuloma
   (8) Benign lymphoid hyperplasia
   (9) Lethal midline granuloma (Stewart's)
   (10) Wegener's granulomatosis.

Situated at the skull base with close proximity to the surrounding head and neck spaces, the nasopharynx is a clinical blind spot in many aspects. Tumours arising here may masquerade their symptoms to regions other than the primary site. This has often led to delayed diagnosis and treatment.

It is important to keep in mind that in all painless head and neck lumps, malignancy must be suspected and a primary tumour in the nasopharynx can elude exhaustive investigations, including computerized tomographic study and biopsy. If a nasopharyngeal carcinoma is suspected continued searching is worthwhile, because very often the elusive answer may lie beneath the apparently normal mucosa.

Nasopharyngeal cancer

besides the 'lymphoepithelium', the nasopharyngeal wall also contains glandular and connective tissues surrounded by bones and cartilage of the skull base. A wide variety of
malignant tumours may originate in the nasopharynx from the many types of tissue elements present there (Table 19.2).

Table 19.2 Types of malignant nasopharyngeal tumours

(1) Epithelial
   Nasopharyngeal carcinoma, adenocarcinoma, adenoid cystic carcinoma, others
(2) Lymphoid and haematopoietic
   Malignant lymphoma, Hodgkin's disease, Burkitt's lymphoma, plasmacytoma
(3) Bone and cartilage
   Chondrosarcoma, osteosarcoma
(4) Soft tissue
   Fibrosarcoma, rhabdomyosarcoma, others
(5) Miscellaneous
   Malignant melanoma, chordoma, craniopharyngioma, others.

The relative proportion of cancer types in the nasopharynx varies in different countries. Nasopharyngeal carcinoma is the most common form irrespective of geography and race. It constitutes more than 90% of all nasopharyngeal cancers in most countries. In populations and countries with a high incidence of nasopharyngeal cancer, for example south-east Asia, nasopharyngeal carcinoma predominates over other types of cancer, so much so that the ratio is approximately 99:1 (Shamugaratnam et al, 1979).

Epidemiology of nasopharyngeal cancer

Geography and race

Nasopharyngeal carcinoma has a distinctive epidemiological pattern. Its incidence among the Chinese and other south-east Asians is about 10 to 50 times higher than that of other countries. This cancer is not strictly associated with the Mongoloid race per se, as the northern Chinese, Koreans, and Japanese all have a low incidence.

The highest incidence (age-standardized rate (ASR) of 15-30/100,000 males) occurs in southern China, Hong Kong, south-east-Asian Chinese and emigrant Chinese elsewhere. Moderately elevated incidences (ASR 5-15/100,000 males) are found among other south-east Asian races (Malays, Indonesians, Kuzdans, Thais and Filipinos), Eskimos and some North Africans, Malta, Tunisia, Algeria and the Sudan have much lower incidences than the Asian countries but are still appreciably higher than those in America and Europe. Low incidence (ASR 1 or less per 100,000 males) is present in the rest of the world.

Geographical and migrant variations in Chinese nasopharyngeal carcinoma

Descriptions of neck growths with eventual death were documented in the ancient Chinese medical literature. These descriptions were most probably those of nasopharyngeal carcinoma. In China, remarkable geographical variations in incidence are observed. It is highest in the south and declines towards the north. When and where the southern Chinese emigrate, they retain their high risk of nasopharyngeal carcinoma. Their incidence is appreciably higher than that of the indigenous population. The incidence of nasopharyngeal
carcinoma among Chinese born in the USA is about 20 times higher than that of the Caucasians; but is significantly lower - about one-half - than that of Chinese born in China and those in Singapore. However, in Singapore, there is no significant difference in risk between Chinese born in China and those in Singapore. It is interesting to note that the incidence of nasopharyngeal carcinoma among the Cantonese (Chinese of Guandong origin) in Singapore (age-standardized rate per 100,000 males is 29.4, females 10.8) is very close to that of Hong Kong, where more than 90% of the population are Cantonese.

Racial differences

There is a variation of incidence of nasopharyngeal carcinoma among different ethnic groups in countries with multiracial populations, for example Hawaii and Singapore. In Singapore, the incidence of nasopharyngeal carcinoma is highest among the Chinese, intermediate among Malays and lowest among the Indians. The Indians, basically a low-risk group, have not shown any increase in the incidence of nasopharyngeal cancer despite residing in a country with high incidence. This contrasts with the Eskimos in Alaska who live in a low-risk country but have a high incidence, approximately 15 times that of the general US population (Lanier et al, 1976).

Even among the souther Chinese, there is a marked variation in the incidence of nasopharyngeal cancer among the dialects or specific community groups. The rate of nasopharyngeal carcinoma among the Cantonese is approximately twice that of the other two major groups (Shamugaratnam, 1978).

Sex

Nasopharyngeal carcinoma is more common in males with the age-standardized male:female ratio between 2-3:1.

Age

The plateau age distribution curve

The age-incidence rate curve of nasopharyngeal carcinoma is different from other forms of cancer. It begins to rise at the end of the second decade of life and reaches a peak in the fourth decade, and then stays at a plateau. This contrasts sharply with the other leading epithelial cancers of the lung and oesophagus. The shape of the age distribution curve suggests exposure to carcinogens early in life and/or an interaction of viral or environmental agents with susceptible genes. The absence of a progressive increase in older age suggests reduced exposure or susceptibility with age.

Bimodal age distribution

In Chinese, nasopharyngeal carcinoma is rare below the age of 15 years. However, in certain low-risk populations, a second peak is observed in the age distribution curve. In Tunisia, 15% of patients with nasopharyngeal carcinoma are below the age of 16 years. There is also a high proportion of nasopharyngeal carcinoma in patients below 20 years of age in other low-risk countries such as India (Bombay), Uganda, the Sudan, among US blacks and
in the Kadazans (high-risk group) in east Malaysia. This bimodal distribution suggests the influence of different aetiological factors or variations in host response.

**Environmental factors**

The aetiology of nasopharyngeal carcinoma remains obscure. A susceptible genetic constitution clearly plays a part and some environmental cofactors are equally important. The significance of environmental factors is supported by the following observations:

1. Epidemiological data on geographical clustering in southern China and Chinese emigrant populations

2. The age-incidence rate curve in the high-risk population

3. Time trend: the high risk for the disease among the Chinese in southern China, Hong Kong and Singapore have virtually remained unchanged for the last 50 years. The incidence of the disease in the second and third generation of Chinese born in the USA has declined when compared with that of their forefathers and relations in the East. The difference can be partly attributed to the change in the environment and life-style. On the other hand, the environmental change is not profound in south-east Asia. The Chinese have retained their 'micro-environment' preserving the oriental life-style especially with regard to food and customs. It is therefore likely that any associated environmental risk factor(s) is closely linked to the traditional rather than the modern life-style of the southern Chinese. Besides the Epstein-Barr virus, a variety of inhaled and ingested agents have been proposed as the aetiology (Table 19.4). Some of these propositions are supported by findings from controlled studies and laboratory evidence, but most are inconclusive.

**Table 19.4 Various environmental agents/factors implicated in the aetiology of nasopharyngeal carcinoma**

<table>
<thead>
<tr>
<th>Agent/factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>Raised antibody</td>
</tr>
<tr>
<td>Viral genome in tumour cells</td>
</tr>
<tr>
<td>Chemical tobacco</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Chemical drugs</td>
</tr>
<tr>
<td>Chinese herbal medicine</td>
</tr>
<tr>
<td>Plant products</td>
</tr>
<tr>
<td>Epstein-Barr virus activating properties/cofactors</td>
</tr>
<tr>
<td>Diet</td>
</tr>
<tr>
<td>Salted fish</td>
</tr>
<tr>
<td>Nitrosamines</td>
</tr>
<tr>
<td>Cooking habits</td>
</tr>
<tr>
<td>Household smoke and fumes</td>
</tr>
<tr>
<td>Religious practices</td>
</tr>
<tr>
<td>Incense and joss stick smoke</td>
</tr>
<tr>
<td>Occupation</td>
</tr>
<tr>
<td>Industrial fumes and chemicals</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Socioeconomic status</td>
</tr>
<tr>
<td>Previous otorlaryngological ailments</td>
</tr>
<tr>
<td>Weaning habits</td>
</tr>
<tr>
<td>Nutritional deficiencies</td>
</tr>
<tr>
<td>Metals (arsenic, chromium, nickel).</td>
</tr>
</tbody>
</table>
**Household smoke and cigarette smoking**

Exposure to smoke has long been suggested as a risk factor following observations on indoor cooking in chimney-free homes in southern China. There appears to be no relationship between nasopharyngeal carcinoma and household smoke. The boat-people of south China who cook in the open air have a higher incidence of nasopharyngeal carcinoma, and the women who are more exposed to smoke from firewood used in cooking have a lower risk than men. The geographical distribution of nasopharyngeal carcinoma bears no relationship to the pattern of cigarette consumption or the incidence of lung cancer.

**Occupation**

Exposure to nickel, chromium and radioactive metals has been associated with cancer of the nose and paranasal sinuses but not with nasopharyngeal carcinoma. Inhalation of chemical fumes in certain occupations may explain the occurrence of nasopharyngeal carcinoma in industrialized countries with a low incidence. There is recent evidence to suggest a relationship between chemicals and activation of Epstein-Barr virus. A remarkably high detection rate of nasopharyngeal carcinoma was reported in a chemical factory during an Epstein-Barr virus serological survey in Wuchou City, China (Zeng et al, 1985).

**Ingestants**

Salted fish had been proposed as an important aetiological factor in the southern Chinese population. Ungutted salted marine fish contains an appreciable amount of volatile nitrosamine, principally N-nitrosodimethylamine and N-nitrosodiethylamine. These are known to induce squamous cell carcinoma and adenocarcinoma in the nasal and paranasal cavities in experimental animals (Huang et al, 1978). However, this does not satisfactorily explain the male predominance of nasopharyngeal carcinoma. Previous controlled studies relating the incidence of nasopharyngeal carcinoma to that of consumption of salted fish in California (Henderson et al, 1976) and Malaysia (Armstrong, Kannan Kutty and Armstrong, 1978) did not show any significant correlation, although a recent follow-up report on the same Malaysian study indicated childhood salted fish consumption a risk factor (Armstrong et al, 1983).

**Histopathology**

Nasopharyngeal carcinoma arises from the crypts and squamous or respiratory epithelium lining the wall. It may be preceded by squamous metaplasia. There has been considerable disagreement over the histological classification of nasopharyngeal carcinoma. Terminologies such as lymphoepithelioma, undifferentiated carcinoma, non-keratinizing carcinoma, transitional cell carcinoma and anaplastic carcinoma have been used to describe the poorly differentiated carcinoma that commonly occurs in the nasopharynx. The term 'lymphoepithelioma' is used to describe non-keratinizing and undifferentiated nasopharyngeal carcinoma in which numerous lymphocytes are found among the tumour cells. The lymphoid elements are not neoplastic. According to the WHO Classification (Shamugaratnam and Sobin, 1978), three histological types are recognized on the basis of their light microscopic appearances:
(1) squamous cell carcinoma
   (a) well differentiated
   (b) moderately differentiated
   (c) poorly differentiated
(2) non-keratinizing carcinoma
(3) undifferentiated carcinoma.

**Squamous differentiation**

All histological subtypes of nasopharyngeal carcinoma consistently show ultrastructural and immunohistochemical evidences of squamous differentiation. These include the non-keratinizing and undifferentiated carcinomata with no evidence of squamous differentiation on light microscopy. Therefore they may be considered variants of the squamous carcinoma. The most common subtype seen in high-risk countries is the undifferentiated type.

**Clinical-pathological significance**

*Cervical lymph node metastases*

Nasopharyngeal carcinoma and its metastases often display fairly characteristic cytological and histological features which enable a presumptive diagnosis of their origin to be made. This would then alert an unsuspecting surgeon to search for the primary tumour after excising a lymph node, without prior examination by an otolaryngologist.

**Clinical presentations of nasopharyngeal carcinoma**

*Macroscopic appearances*

Nasopharyngeal carcinoma has no characteristic macroscopic features. The lesion may appear ulcerative and by infiltrative or be a more exuberant polypoid type of tumour. Inflammation of the 'lymphoepithelioma' may mimic tumour appearance. Very early preclinical and infiltrative carcinoma retains a relatively normal mucosal appearance, and the diagnosis is based on histopathology.

*Anatomical sites of origin*

Primary tumour distribution is found in the following order of frequency:

(1) lateral wall
(2) superior-posterior wall
(3) more than one wall
(4) anterior wall and floor.

More than 80% of the tumours are unilateral. The right and left sides are equally affected. Most of the tumours arise from the lateral wall, especially the fossa of Rosenmüller and around the eustachian cushion.
Symptomatology

The marked invasive and metastatic powers of the nasopharyngeal carcinoma are responsible for the symptomatology. From the primary site the tumour may spread in one or more of the following directions:

(1) anteriorly to the nasal cavity and paranasal sinuses, pterygopalatine fossa and apex of orbit

(2) posteriorly to the retropharyngeal space and node of Rouvière, destroying the lateral mass of atlas

(3) laterally into the parapharyngeal space

(a) prestyloid compartment: with involvement of the mandibular nerve, pterygoid muscles and infiltration of the deep lobe of parotid

(b) poststyloid compartment: with vascular compression of the carotid sheath and vessels, and invasion of the last four cranial nerves and cervical sympathetic nerves

(4) superiorly through the sphenoid body and sinus involving the parasellar structures and optic nerve, petrous apex and foramen lacerum, spreading along the carotid canal into the cavernous sinus involving nerves III, IV, V, and VI

(5) inferiorly to the oral cavity and retrotonsillar regions.

Clinical features

Most patients have multiple symptoms which are insidious in onset and are sometimes disregarded by the patients and doctors. The main symptoms are cervical lymphadenopathy (60%), epistaxis and nasorespiratory symptoms (40%), audiological symptoms (tinnitus, otalgia, deafness) (30%), neurological symptoms (headache, cranial nerve palsies) (20%), and metastases which may be local (paranasal sinus, parapharyngeal space, infratemporal fossa, orbit and parotid) or distant (spine, lung and liver).

Cervical lymphadenopathy

Nasopharyngeal carcinoma has a tendency for early lymphatic spread. The lateral retropharyngeal lymph node (of Rouvière) is the first lymphatic filter and is not palpable. The common first palpable node is the jugulodigastric and/or the apical node under the sternomastoid. Contralateral lymph node metastasis is not uncommon.

The parotid gland and lymph nodes can be involved if the parapharyngeal space is breached. Secondary deposits may mimic a primary parotid tumour. Parotidectomy has been erroneously performed as a result.
**Epistaxis and nasorespiratory symptoms**

Epistaxis as primary presenting symptom is unusual; it is more commonly seen in advanced nasopharyngeal carcinoma with or without skull base erosion or postradiation infection. Blood-stained nasal mucus and saliva on hawking are more frequently seen. Erosion into the maxillary antrum mimics sinusitis. The blood-stained rhinorrhoea from nasopharyngeal carcinoma may masquerade as primary maxillary cancer. Complete nasal obstruction is a late presentation; should it occur in the early stage of the disease, it is often due to superimposed infection. Ozaena occurs as a result of tumour necrosis and is typical of advanced nasopharyngeal carcinoma.

**Tinnitus and aural symptoms**

Serous otitis media with tinnitus is not an uncommon presentation of nasopharyngeal carcinoma and the primary tumour may be insignificant in the peritubal region. Adult Chinese patients with unresolving serous otitis media have to be presumed to have nasopharyngeal carcinoma until proven otherwise.

**Neurological palsies**

All the cranial nerves, either singly or in groups, can be affected by nasopharyngeal carcinoma through tumour invasion or compression. The most frequently involved cranial nerves are V, VI, IX and X, accounting for 50% of all palsies (Khor et al, 1975). Nerves IX and X are invariably involved together and are the most common group to be affected. The nerves to the ocular muscles (III, IV and VI) are the next group commonly affected. Isolated single cranial nerve palsy is common with nerves V and VI.

**Pain and headache**

Pain is an ominous symptom in nasopharyngeal carcinoma. Severe pain with headache is the hallmark of terminal disease. It signifies tumour erosion to the skull base and surrounding structures. Sepsis, particularly in sphenoidal sinusitis, also produces severe headache. If accompanied by trismus, the disease is in an advanced stage for the tumour has involved the pterygopalatine fossa and the pterygoid muscles.

Atypical facial pain or unexplained headache in the absence of obvious clinical findings in the nasopharynx may be a presenting symptom of nasopharyngeal carcinoma. The nasopharynx can appear deceptively normal when the carcinoma has in fact spread extensively outwards by submucosal infiltration. In such situations, a computerized tomography (CT) scan of the nasopharynx and base of skull is most helpful in delineating the outlying tumour extension and skull base erosion. The small nasopharyngeal primary may just represent the tip of the 'tumour iceberg'.

**Distant metastases**

The incidence rate of distant metastases is about 30%, of which skeletal metastases account for more than one-half. The thoracolumbar spine is the most common site of involvement followed by the lung and liver. Distant metastases indicate a grave prognosis.
with a median survival of 3 months; 90% of patients die within one year of diagnosis of the first metastasis. In a study of 352 consecutive cases of nasopharyngeal cancer treated with radiotherapy (Khor et al, 1978), 60% of patients who manifested distant metastases had no evidence of recurrent disease in the nasopharynx or cervical nodes. This implies that a significant proportion of patients probably have occult metastases at the time of initial diagnosis.

**Nasopharyngeal examination**

Examination of the nasopharynx can be problematic. Although anatomically the width of the nasopharynx is 4 cm, the ‘functional channel’ is only about 2 cm (Khoo, Chia and Naplon, 1967). Posterior rhinoscopy is also restricted by the pharyngeal reflex, patient cooperation and inability to open the mouth. Furthermore, the mirror may only give an ‘edge-on’ view of the fossa of Rosenmüller due to the latter's posterolateral inclination. Nevertheless, mirror examination is still the quickest way to assess the nasopharynx, sometimes under anaesthesia. In this procedure, the patient is placed in the tonsillectomy position with a Boyle-Davis gag. Two polythene tubes or catheters, inserted naso-orally, retract the soft palate forward. Transoral mirror examination is then performed with a mirror that has been dipped in diluted cetrimide - this effectively demists the mirror. Biopsy is performed via the nose with the help of the mirror view or Yankauer speculum transorally.

Although a transoral nasopharyngoscope provides a panoramic view under magnification, it has not eliminated the limiting factors of posterior rhinoscopy. With the introduction of transnasal fibreoptic nasopharyngoscope, close-up end-on viewing of the nasopharynx has been possible. Any tiny growth which escapes detection with routine mirror examination can be identified. Biopsy can also be performed under direct visual guidance.

**Nasopharyngeal biopsy**

**Methods**

1. transnasal
   - (a) blind
   - (b) posterior mirror rhinoscopy
   - (c) endoscopy
2. transoral
   - (a) Yankauer speculum
   - (b) rigid endoscopy.

**Transnasal blind biopsy**

The slim Hildyard postnasal biopsy forceps is preferred for routine nasopharyngeal biopsy. Specimens from its 3 mm diameter cup are more than adequate for tissue histopathology. In this method, the forceps are inserted along the nasal floor, slightly angulated upwards and laterally to bite at the posterolateral nasopharyngeal wall. It causes little discomfort to the patient. Clinically positive nasopharyngeal carcinomata are often diagnosed at the first biopsy. However, small or anteriorly placed tumours (about 10%) may be missed by this method.
**Flexible fibreoptic nasopharyngoscope**

This is the most useful and versatile endoscope for nasopharyngeal and upper aerodigestive system examination. Before the procedure, the nose is first anaesthetized with 5% cocaine spray (or 4% lignocaine if patient is allergic to cocaine). Two orange sticks (one for each nostril) with cotton pledgets soaked with 5% cocaine are inserted along the floor to the nasopharynx. With this method, anaesthesia of the nasopharynx is often achieved. However, one must be aware of a common pitfall, that is the failure to keep the pledget sticks in the nasopharynx. This may occur as a result of the soft palate propelling the pledget sticks away from the nasopharyngeal wall. This reflex action usually stops once the nasopharynx is anaesthetized. An induction time of 10 minutes is allowed before the endoscopic procedure. The flexible scope is then inserted transnasally. It gives a good view of the nasal floor, the walls of the nasopharynx and the fossa of Rosenmüller. On passing it below the soft palate, pharyngolaryngoscopy can be performed.

**Flexible endoscopic biopsy**

The more recent nasopharyngoscopes are equipped with biopsy forceps (introduced through the suction channel). However, the biopsy specimen is tiny and not always suitable for immunohistological study. An improvised method using an older flexible nasopharyngoscope (Olympus ENF-P) and Hildyard forceps is described.

The flexible nasopharyngoscope is first introduced through the nose contralateral to the nasopharyngeal tumour. Its tip is directed towards the tumour. As the nasopharyngoscope is rather short (total length of scope 45 cm and diameter of insertion tube 4 mm), it can be steadied with one hand once it is in the nasopharynx. The Hildyard biopsy forceps are then inserted along the nasal floor on the side of the tumour into the nasopharynx. In fact, in most cases, it is small enough to be introduced through the same nostrils as the endoscope. The position of the biopsy forceps can be checked by the scope.

The advantages of this method include:

1. Tiny tumours in any quadrant including the difficult fossa of Rosenmüller can be biopsied accurately

2. The usual problem of postbiopsy bleeding obscuring the vision is avoided as the scope is far away from the biopsy site

3. It is also a reliable method to detect and biopsy postradiation tumour recurrence beneath the necrotic scab that may persist long after radiotherapy

4. It obviates the need for diagnostic nasopharyngeal curettage. This latter procedure should be discouraged, as it is almost impossible to curette the lateral nasopharyngeal wall, where most tumours primarily occur.
Stage-classification of nasopharyngeal carcinoma

Few staging systems of head and neck cancers have encountered more controversy than that of nasopharyngeal carcinoma. To date there are no fewer than 10 different classifications.

1952 Geist and Portman
1962 UICC (modified 1974 and 1978)
1965 Chinese classification (Shanghai)
1970 J. H. C. Ho (Hong Kong, modified 1978)
1971 Chen and Fletcher (M. D. Anderson Hospital, Houston)
1975 German work group of clinical oncology (Cologne)
1976 American joint committee (modified 1978)
1977 Kyoto symposium (Japan)
1979 Changsha conference (China)
1981 Guangzhou stage-classification

None has gained general acceptance. Recent classifications are modifications of the older systems. The proposed Guangzhou stage-classification (19891) is one such modification to be evaluated. A synopsis of the stage-classifications in use is given in Appendix 19.1.

Treatment

Radiotherapy

Radiotherapy is the definitive treatment for nasopharyngeal carcinoma and its regional nodal metastases. Complications such as radiation myelitis, brainstem damage, optic atrophy and retinitis are rare. However, mucositis, xerostomia, dental caries and radiation serous otitis media are some of the sequelae of the treatment. Pretreatment dental clearance and treatment of oral sepsis is mandatory. It is a prophylactic measure against postradiation radionecrosis following dental extraction.

Chemotherapy has been used to supplement radiotherapy for advanced cervical nodal metastases as well as to treat visceral metastases. However, the result is disappointing.

Results

Results of treatment vary with the stage of disease and the age of the patient. Comparison of treatment results between different centres is made difficult by the lack of a generally accepted stage-classification. The accepted overall 5-year survival rate is 30-40% with megavoltage radiation therapy.

Role of surgery

Surgery plays a minor role in the treatment of nasopharyngeal carcinoma. It is restricted to obtaining a biopsy and inspection of the nasopharynx, for example palatal fenestration, in selected patients. This procedure is seldom performed nowadays following the
introduction of fibreoptic scopes. Radioresistant nodes may be removed by radical neck dissection.

**Immunology of nasopharyngeal carcinoma**

**General cell-mediated immunity in nasopharyngeal carcinoma patients**

Impaired T-cell functions are found in more than one-half of newly diagnosed and untreated patients with nasopharyngeal carcinoma. This can be demonstrated *in vivo* by the Mantoux test and *in vitro* by the phytohaemagglutinin response of lymphocytes (Chan et al, 1978). Similar impairment is also observed in treated patients who are in remission. Cell-mediated immunity against Epstein-Barr virus is still present in patients with nasopharyngeal cancer as demonstrable by the lymphocyte transformation assay against Epstein-Barr virion antigens, even though as a group they seem to have a lower response than control populations (Chan, Chew and Kunaratnam, 1979). Impaired viral specific T-cell immunity and increased suppressor T-cell activity in patients with nasopharyngeal cancer suggest immunosuppression. Antigen overload has been suggested to be the cause of the immunosuppression.

**Epstein-Barr virus and its association with nasopharyngeal carcinoma**

This is one of the herpes viruses. Its lymphotropic action is restricted to the B lymphocytes which are found in abundance in the 'lymphoepithelium'. Epstein-Barr virus primary infection takes place in childhood and is always accompanied by seroconversion and harbouring of the virus in a dormant state for life. The virus may be reactivated with raised serological titres in immunosuppressive states. Among human cancers, only Burkitt's lymphoma and nasopharyngeal carcinoma are closely associated with Epstein-Barr virus. These two cancers have different seroepidemiological backgrounds. Nasopharyngeal carcinoma is an epithelial tumour and is not related to the endemicity of the Epstein-Barr virus. Decades elapse between primary infection (< 5 years of age in southern Chinese) and the occurrence of nasopharyngeal carcinoma (peak around the fourth decade). Its association with Epstein-Barr virus is supported by:

1. the presence of a humoral immune response, in patients with nasopharyngeal carcinoma against Epstein-Barr virus-determined antigens, including the structural antigens such as the viral capsid antigen (VCA), early antigen (EA) and nuclear antigen (EBNA)

2. the presence of Epstein-Barr viral markers, DNA and nuclear antigen, in nasopharyngeal carcinoma tumour cells (Wolf, Hausen and Becker, 1973). However, Epstein-Barr viral particles have yet to be observed in nasopharyngeal carcinoma cells from biopsy samples.

**Aetiological role of Epstein-Barr virus in nasopharyngeal carcinoma**

More than 90% of patients with nasopharyngeal carcinoma have elevated antibody titres to Epstein-Barr virus-determined antigens compared with controls of the same ethnic group and geographical location. Of the many types of nasopharyngeal carcinoma, only the undifferentiated/poorly differentiated forms consistently express, irrespective of race or geographical location, the Epstein-Barr nuclear antigen which is an indicator of the presence...
of Epstein-Barr virus genome (Desganges et al, 1975; Andersson-Anvert et al, 1977). Moderately to well-differentiated nasopharyngeal carcinomata are devoid of Epstein-Barr virus DNA or nuclear antigen. Like the normal population, this patient group does not have elevated antibody to Epstein-Barr virus antigens. Other aerodigestive tract carcinomata have so far failed to produce Epstein-Barr virus markers with the exception of undifferentiated carcinoma of the nasal fossa (Huang et al, 1978a).

It is not clear at present how the viral DNA becomes associated with the epithelial carcinoma cells or when the epithelial cells are infected by the virus, whether it is before or after the malignant change (passenger virus), or as a result of impaired host immunity. After all, only the B lymphocytes are known to have receptors for Epstein-Barr virus. The aetiological role of the virus in nasopharyngeal carcinoma is still controversial.

**Epstein-Barr serological markers**

In comparison to patients with other head and neck carcinomata, patients with nasopharyngeal carcinoma have a broader spectrum and higher geometric mean titres of a series of Epstein-Barr virus antibodies (Henle et al, 19970). Important Epstein-Barr virus-related antibodies in nasopharyngeal carcinoma are:

(1) IgA and IgG to viral capsid antigen
(2) IgA and IgG to early antigen
(3) antibody to nuclear antigen
(4) antibody-dependent cellular cytotoxicity antibodies.

These are of clinical importance in evaluating a patient with nasopharyngeal carcinoma for the stage of the disease at the time of diagnosis, the effect of and response to therapy, and the clinical course and survival.

Antibodies against viral capsid antigen, early antigen and nuclear antigen are the most useful in clinical practice and their titres correlate well with each other. The IgA response to Epstein-Barr virus antigens in nasopharyngeal carcinoma is unique and characteristic of patients with nasopharyngeal carcinoma. Antibody-dependent cellular cytotoxicity, a process known to be effective in the destruction of viral-infected cells, appears to act on Epstein-barr virus-induced membrane antigens. It is capable of destroying the infected cells. The antibody-dependent cellular cytotoxicity antibodies titre may represent a functional immune response against tumour cells in vivo.

**Seroimmunological index in the diagnosis of nasopharyngeal carcinoma**

Immunoglobulins IgA/VCA, IgG/VCA, and IgA/EA, IgG/EA are useful diagnostic markers of nasopharyngeal carcinoma. Their titres are related to the tumour load, and geometric mean titres increase with advancing stage of the disease in untreated patients. The diagnostic titres for viral capsid antigen and early antigen antibodies are:

<table>
<thead>
<tr>
<th></th>
<th>IgA</th>
<th>IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCA</td>
<td>1/10</td>
<td>1/640</td>
</tr>
<tr>
<td>EA</td>
<td>1/5</td>
<td>1/80</td>
</tr>
</tbody>
</table>
IgA/VA has the highest sensitivity with a nasopharyngeal carcinoma detection rate of 95%, followed by IgA/EA which is highly specific for nasopharyngeal carcinoma with almost no false positives. IgG/VCA has the least discriminatory value as a primary serological diagnostic indicator of nasopharyngeal carcinoma (Ho et al, 1981).

**Clinical course and survival**

The titres of IgA/VCA and IgA/EA are useful clinical indices for the follow-up of nasopharyngeal carcinoma patients after treatment. They decline to a low level after successful treatment (Henle et al, 1977). An upsurge of viral capsid antigen, early antigen and nuclear antigen antibodies would indicate clinical recurrence and/or metastasis. It may be useful to be aware of the occurrence of an occult tumour and this would necessitate careful evaluation of the patient.

The geometric mean titres of early antigen, viral capsid antigen and nuclear antigen (taken at the time of diagnosis) were significantly higher in the patients who died (within 4 years) from the disease compared with those who survived. Antibody-dependent cellular cytotoxicity antibody titre was highest in long-term survivors while viral capsid antigen and early antigen antibody titres showed a progressively inverse relationship to survival. The geometric mean titres of early, viral capsid and nuclear antigens increase stepwise with disease stage but decline towards the end-stage. Antibody-dependent cellular cytotoxicity antibody clearly demonstrates its value as a biological titre in determining the survival of patients (data from Chan et al, 1979).

**Prognostic serological markers**

The prognostic markers of nasopharyngeal carcinoma include specific Epstein-Barr virus antibody titres. The Epstein-Barr virus titres are dependent on the histological types, the availability (load) of various Epstein-Barr virus antigens and host immune competence. The titres may not be elevated in the early and end stages of the disease nor in cases with intracranial extension without significant lymph node involvement.

1. Prognosis and survival is inversely proportional to the geometric mean titres of viral capsid antigen and early antigen antibodies.

2. Good prognosis is indicated by a high antibody dependent cellular cytotoxicity antibody titre. Its titre appears to be independent of the disease stage. This suggests that a parameter independent of the tumour load is involved.

**Other clinical applications**

*Screening for nasopharyngeal carcinoma in high risk populations*

IgA/VCA is of practical value in serological screening for nasopharyngeal carcinoma in endemic regions. A large-scale seroepidemiological survey has been conducted in Guangzi Autonomous Region, China since 1978. A total of 148029 normal subjects over 30 years old were tested for IgA/VCA. A total of 3533 cases (2.4%) were found to be positive and from this group 55 cases of nasopharyngeal carcinoma were detected. Thirty-two more cases of
nasopharyngeal carcinoma were diagnosed in subsequent follow-up. The period between the
detection of raised IgA/VCA and the clinical onset of stage I nasopharyngeal carcinoma
ranged from 8 to 30 months (mean 13). The detection rate of the screened IgA/VCA-positive
population was estimated to be more than 80 times the annual nasopharyngeal carcinoma
incidence of the general population of comparable age (Zeng et al, 1983). This indicates
positively the existence of subclinical and early nasopharyngeal carcinoma in the otherwise
asymptomatic IgA/VCA-positive individuals. The long subclinical period (months or even
years) with raised IgA/VCA probably indicates the slow tumour growth with ample time for
the Epstein-Barr virus antigens to stimulate the immune system. As there is no diagnostic
macroscopic appearance of nasopharyngeal carcinoma, it is likely that tumour in the early
stage is indistinguishable from the normal 'lymphoepithelium' and lymphoid aggregations
commonly seen in the nasopharynx. A raised IgA/VCA titre identifies these high risk
individuals for further clinical and immunohistological evaluation of the nasopharynx
(Desgranges et al, 1982).

**Differential diagnosis of nasopharyngeal carcinoma**

Morphologically nasopharyngeal carcinoma can be confused with lymphoma especially
in the low risk population.

**Occult primary tumour with cervical metastases**

The nasopharynx is still the most frequent site of an occult primary tumour in the head
and neck with cervical metastases. In certain clinical situations where the primary tumour is
difficult to detect, a positive Epstein-Barr virus IgA serology, and positive immunohistological
markers on the metastatic tumour tissue serve as an adjunct to pathological identification
(Coates et al, 1978). Multiple nasopharyngeal biopsies under endoscopic vision are indicated
if the Epstein-Barr virus serological markers are positive. Should the serology be negative and
other head and neck regions are clear, an enlarged lymph node should be excised *in toto*
with the capsule intact. Fresh lymph node tissue is sent for identification of nuclear antigen and
DNA in the tumour cells. If nuclear antigen is demonstrated the primary tumour is most likely
to be a nasopharyngeal carcinoma. Nuclear antigen has so far not been demonstrated in other
carcinomata of the head and neck except some parotid gland tumours reported in Eskimos
(Saemundsen et al, 1982) and, recently, thymic carcinoma (Leyvraz et al, 1985). One must
be aware of the fact that a small primary nasopharyngeal carcinoma is known to give rise to
over tumour deposits in the parotid gland.

Indiscriminate excision biopsy of lymph nodes should be discouraged. Such biopsy
offers little in the clinical management if the primary tumour is still untreated. It would
further compromise the prognosis in nasopharyngeal carcinoma and increases the morbidity
to radiation should the wound break down as a result of tumour seedings.

**Immunogenetics of nasopharyngeal carcinoma**

Patients with nasopharyngeal carcinoma have shown a prominent genetic susceptibility
to this cancer. This is evident by the following observations:
(1) high risk among southern Chinese population

(2) differential high risk in emigrant Chinese in comparison to the indigenous population

(3) family clustering of nasopharyngeal carcinoma in Chinese

(4) elevated risk in people having genetic admixture with Chinese

(5) low risk in other racial groups despite living in high-risk countries, for example Indians in Singapore.

**Genetic markers in nasopharyngeal carcinoma**

Patients with nasopharyngeal carcinoma among the Chinese are found in a genetically distinct subpopulation. HLA is the only genetic system so far shown to have strong association with this cancer.

**HLA (histocompatibility locus antigen)**

The major histocompatibility gene complex on the short arm of chromosome 6 comprises six recognized loci called HLA-A, -B, -C, -DR, -DQ and -DS. There are at least 18 recognized distinct alleles at the HLA-A locus and 32 distinct alleles at HLA-B locus. Each allele determines a product (antigen).

**Haplotype**

Because of their close linkage, the combination of alleles at each locus on a single chromosome is usually inherited as a unit referred to as haplotype (for example A2-BW46). Since one chromosome is inherited from each parent, every person possesses two HLA haplotypes (for example A2-BW46, A11-B40).

Example: AB x CD ==> AC - AD - BC - BD

Paternal haplotype A: A2-BW46 B: A11-B40
Maternal haplotype C: A2-B40 D: AW19-B17

**Linkage disequilibrium**

The alleles for HLA vary in frequency and presence among different ethnic groups. The linkage pattern also differs between different human populations. In the general population, certain alleles of one locus tend to be associated with that of another, with a frequency far exceeding that expected if the two genes were segregated independently and separately. This is called linkage disequilibrium and is observed in Chinese patients with nasopharyngeal carcinoma (A2-BW46, AW19-B17).
HLA and nasopharyngeal carcinoma in Chinese

History of Sin 2 antigen

An oriental B antigen was discovered with high frequency among Singapore Chinese patients with nasopharyngeal carcinoma in a pilot study in 1974. It was designated Singapore-2 (Sin 2) (Simons et al, 1976; Simons and Day, 1977). Meanwhile, an independent study in the USA also found an HLA-antigen (designated HS) occurring with high frequency among the Chinese Cantonese patients with nasopharyngeal carcinoma in California (Payne, Radvany and Grumet, 1975). It is now known that Sin 2 and HS are identical, and it is designated BW46 by the WHO committee on leucocyte nomenclature. There are not three well established associations between HLA and nasopharyngeal carcinoma involving A2, BW46 and B17. Subsequent studies in newly diagnosed Chinese patients with nasopharyngeal carcinoma showed HLA associations with haplotype A2-BW46 and AW19-B17 (Chan and Simons, 1977; Chan et al, 1981) (Table 19.5).

Table 19.5 Summary of HLA types and their relationship to survival pattern and clinical behaviour of nasopharyngeal carcinoma

<table>
<thead>
<tr>
<th>HLA pattern</th>
<th>Clinical behaviour and survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>AW19-B17</td>
<td>Short-term survivals</td>
</tr>
<tr>
<td></td>
<td>Mostly young onset &lt; 30 years</td>
</tr>
<tr>
<td></td>
<td>Poor CMI, PHA and Mantoux</td>
</tr>
<tr>
<td></td>
<td>High VCA/EA titres, low ADCC titre</td>
</tr>
<tr>
<td></td>
<td>Most die within 2 years from onset</td>
</tr>
<tr>
<td>A2-BW46</td>
<td>Intermediate term survivals</td>
</tr>
<tr>
<td></td>
<td>Older onset &gt; 30 years</td>
</tr>
<tr>
<td>A2 without BW46 or B17</td>
<td>Long-term survivals (40% 5-year survival)</td>
</tr>
<tr>
<td></td>
<td>Low VCA/EA titres, high ADCC titres</td>
</tr>
</tbody>
</table>

Differential HLA frequency distribution

Differential frequency distributions of HLA antigen are seen among the newly diagnosed Chinese patients with nasopharyngeal carcinoma with regard to the age of onset of the disease. They are as follows:

(1) BW46 is confined to older patients (> 30 years old)

(2) B17/BW58 is associated with both young and old patients but particularly with younger patients (< 30 years old)

(3) B11 and B13 are associated with decreased risk (B13 is associated with younger patients).
**Haplotype distribution and relative risk**

The association of a particular disease with a particular HLA antigen is quantitated by calculating the relative risk. This can be defined as the chance an individual with the disease-associated HLA-antigen has of developing the disease compared with an individual who lacks the antigens.

**Relative risk**

<table>
<thead>
<tr>
<th>HLA</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>1.5</td>
</tr>
<tr>
<td>BW46</td>
<td>1.9</td>
</tr>
<tr>
<td>B17</td>
<td>2.1</td>
</tr>
<tr>
<td>Haplotype A2-BW46</td>
<td>3.4</td>
</tr>
<tr>
<td>AW19-B17</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Haplotype or joint occurrence of AW19-B17 and A2-BW46 is associated with a higher risk than B17 or BW46 alone (Chan et al, 1983). This suggests that the risk is associated with haplotype rather than individual antigens. These two pairs are known to be in linkage disequilibrium in the general Chinese population.

Despite the occurrence of 50 or more alleles at the HLA-A and -B loci, only a very limited number emerged associated with nasopharyngeal carcinoma. A11 is rarely found with B17 or BW46, while the association of A2 with BW46 in patients with nasopharyngeal carcinoma is stronger than in control patients. No other stronger linkage is seen than the AW19-B17 association. The different HLA association with varying age of onset suggests that there is heterogenicity within the Chinese population with nasopharyngeal carcinoma. Of the racial groups, there are certain similar HLA findings among Malay and Chinese patients with nasopharyngeal carcinoma - the association with B17 (Chan et al, 1985).

BW46 is not found in the Caucasian population. It does not occur commonly nor is it in linkage with HLA-A2 in non-Chinese Asian populations. The HLA gene association is the most convincing evidence for the role of genetics in the aetiology of nasopharyngeal carcinoma.

**Surgical approaches to the nasopharynx**

There are many surgical approaches to the nasopharynx. The various extracranial approaches include:

1. transnasal-maxillary (transnasal and transantral)
2. transpalatal
3. sublabial mid-facial degloving approach
4. others (transpharyngeal, transmandibular, transcervical, infratemporal fossa approach).

The many surgical approaches attest to the difficulty of surgery in the nasopharyngeal region. More than one surgical approach is often needed to provide adequate and optimal exposure. The transnasal and transantral approaches provide good access only for removing
tumours in the maxilloethmoid region. Often they are combined as a transnasal-maxillary approach (resecting the maxilla and lateral nasal wall) to provide a reasonable access to the nasopharynx. With the sublabial mid-facial degloving technique, the nasopharynx is accessible from both sides of the face. Other approaches for example, transmandibular (adopted for palatectomy), transcervical (for high cervical and disc surgery), transpharyngeal (through the floor of the pharynx above the hyoid) and infratemporal fossa approach (radical skull base surgical procedure transecting the auditory canal, zygoma and petrosectomy) are seldom employed nowadays.

Tumours that are limited to the nasopharynx can be removed by the standard transpalatal approach. Such tumours include minor salivary gland tumours (pleomorphic adenoma, mucoepidermoid tumours), haemangioma, inverted papilloma, melanoma and rhinosporidiosis. A combined intra- and extracranial approach may be required for tumours that demonstrate notable intracranial extension, for example craniopharyngioma. The selection of an appropriate surgical approach depends upon the extent of the tumour and which structures and spaces are involved. This can be illustrated in the surgery of angiofibroma. Postoperative haemostasis can be achieved by postnasal packing and/or a Foley catheter (inflated with 20-30 mL of water) brought out through the nose. The advantage of using a Foley catheter is that should bleeding recur on removing the pressure, the balloon can be re-inflated.

Angiofibroma

The angiofibroma is a benign yet biologically aggressive tumour. It originates almost exclusively from the posterior nasal and nasopharyngeal region in adolescent males. Thus it has been known as juvenile angiofibroma, although cases have been reported in older adults and in females as well. The usual clinical behaviour of the tumour is one of expansive growth with a potential for intracranial extension. Histologically, angiofibroma is composed of fibrous connective tissue interspersed with variable proportions of endothelium-lined spaces. A preponderance of fibrous stroma may indeed allow surgical removal with relative ease in some cases. However, even with advances in surgical and arterial embolization technique, the intraoperative blood loss is still a major concern. The capacity for spontaneous regression of angiofibroma at sexual maturity is doubtful.

Incidence and age

Angiofibroma is a relatively rare tumour and the age of onset is in the second decade. The reported incidence ranges from 1/5000 to 1/50.000 of otolaryngological patients in different countries (Table 19.6). Over a 30-year period (1949-1979), the Head and Neck Service of the Sloan-Kettering Memorial Cancer Centre in New York reported only 31 male patients between the ages of 11 and 21 (median age 14 years) (Witt, Shah and Sternberg, 1983).

Pathogenesis

The tissue of origin remains unknown in angiofibroma. Various theories have been proposed. The fibroblastic theory suggests abnormal growth or response of the connective tissues such as the embryonic occipital plate (chondrocartilage between the body of the
sphenoid and the basiocciput) prior to its ossification at the age of 25 years (Bensch, 1878),
the ventral periosteum of the posterior nasopharyngeal wall (Ringertz, 1938) or the fascia
basalis from the fusion of the pharyngeal aponeurosis and the buccopharyngeal fascia near
the base of the skull (Brunner, 1942).

**Table 19.6 Incidence of angiofibroma**

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handousa, Farid and Elwi (1954)</td>
<td>Egypt</td>
<td>1/50,000</td>
</tr>
<tr>
<td>Harma (1959)</td>
<td>Finland</td>
<td>1/6000</td>
</tr>
<tr>
<td>Bhatia, Mishra and Prakash (1967)</td>
<td>India (Lucknow)</td>
<td>92 cases in 27 years</td>
</tr>
<tr>
<td>Witt, Shah and Sternberg (1984)</td>
<td>USA (New York)</td>
<td>31 cases in 30 years</td>
</tr>
</tbody>
</table>

The second theory suggests that angiofibromata are hormone-dependent tumours (based
on their predilection to occur in an age group undergoing endocrine changes) and that the
tumours occur as a result of either oestrogen or androgen stimulation due to oestrogen-
androgen imbalance (Martin, Ehrlich and Abels, 1948). Recent documentation of androgen
receptors in these tumours has lent some support to this theory (Lee et al, 1980). The third
theory is that of hamartomatous origin. Osborne (1959) observed some morphological
similarity between the anomalous vessels in the angiofibroma and that of the nasal erectile
tissue in the lamina propria of the choana and nasopharynx. Hamartomatous proliferation
of such vascular or aberrant erectile tissue may be medicated under hormonal influence (Schiff,
1959).

**Clinical features**

**Signs and symptoms**

The most common presenting symptoms are nasal obstruction and epistaxis. Less
common symptoms include tinnitus, eustachian dysfunction with conductive loss, facial
swelling, proptosis and diplopia. Clinically, the tumour appears as a reddish-purple nodular
mass on one side of the posterior nares and nasopharynx. It may fill the nasopharynx
completely, displacing the soft palate forward. The tumour can be examined quite easily by
posterior rhinoscopy or transnasally with a flexible nasopharyngoscope.

**Site of origin**

Angiofibromata have a broad base. They originate from the posterolateral wall of the
nasal cavity and the adjoining superolateral nasopharyngeal wall. The sphenopalatine foramen
is always involved. After radiation, tumours often involute back towards this region (Sessions

**Tumour spread**

Angiofibromata often grow and extend along natural foramina and fissures, displacing
and distorting the adjacent structures. Larger tumours, however, may erode bone. As they
expand, collateral blood supplies develop. The tumours spread laterally from the
sphenopalatine foramen to the pterygopalatine fossa through the pterygomaxillary fissure.
From this narrow fossa they eventually expand into the infratemporal fossa and the cheek.
They can also extend along the inferior orbital fissure, across the apex of the orbit into the superior orbital fissure. Continued tumour expansion causes pressure erosion of the base of the pterygoid plate and greater wing of the sphenoid. This brings the tumour against the dura of the middle cranial fossa.

Medially, the tumour fills the nasopharynx and distorts the nasal septum, turbinates and the soft palate. It may erode into the posterior ethmoidal and sphenoidal sinuses, allowing direct extension of tumour into the orbit, cavernous sinus and the parasellar region.

**Diagnosis**

The patient's age, sex, symptoms and physical findings are often diagnostic of angiofibroma and allow differentiation from other more common nasopharyngeal tumours, for example nasopharyngeal carcinoma. Nasopharyngeal carcinoma is usually ulcerative and infiltrative with early lymphatic spread. Occasional difficulty arises in clinical diagnosis in a young patient presenting with polypoidal nasopharyngeal carcinoma which may mimic an angiofibroma in symptoms, signs and radiological features. Diagnostic biopsy may be needed prior to planning invasive diagnostic procedures. However, biopsy can cause uncontrollable epistaxis if the tumour is well vascularized. In typical cases of angiofibroma, radiological and angiographic investigations are sufficient to obviate the need for pretreatment biopsy (Sessions et al, 1976).

**Radiological diagnosis**

Radiological findings of the juvenile angiofibroma include:

1. nasopharyngeal soft tissue mass
2. widening of the pterygopalatine fissure (anterior bowing of the posterior wall of the maxillary antrum and posterior bowing of the pterygoid plate) is the classical sign in early angiofibroma - however, it is not pathognomonic; similar radiological features have also been observed in schwannomata, fibrous dysplasia and nasopharyngeal cancer (Schaffer et al, 1978; Som et al, 1981)
3. enlargement of the superior orbital fissure in patients with proptosis
4. distortion of the nasal septum, erosion and opacification of the paranasal sinuses.

Computerized tomographic (axial and coronal) studies with contrast delineate the tumour and its extension. They show, in detail, the bone and soft tissue of the skull base which is hitherto obscure on plain X-rays. Contrast enhancement differentiate sinus opacification due to tumour invasion from opacification as a result of ostial obstruction.

**Angiographic anatomy and therapeutic embolization**

The angiographic features of angiofibroma are consistent. In the arterial phase there is rapid filling of increased numbers of dilated vessels, followed by the characteristic dense homogeneous blush. Subtraction technique gives excellent visualization of the tumour, and
is useful in detecting the pre-existing extra-intracranial anastomoses. The major arterial supply is always from the ipsilateral internal maxillary artery (Roberson et al, 1979). Collateral blood supplies may come from the ascending pharyngeal artery, contralateral internal maxillary artery and branches of the internal carotid system. Large tumours with intracranial extension are likely to receive major collaterals from the internal carotid system. Such collaterals may also occur in patients whose external carotid arteries have been ligated. Thus angiographic study is of particular importance in managing these groups of patients.

Preoperative therapeutic embolization of the major feeding vessels is a major asset in reducing intraoperative blood loss. Embolization with Gelfoam thromboses the vascular bed, whereas in ligation, collaterals open very quickly. Postembolization fever and facial pain are the two common sequela of this procedure. One complication is the escape of emboli into the intracranial circulation due to reflux or via unrecognized external-internal carotid anastomoses (Lasjaunis, 1980).

**Treatment**

Surgery is the treatment of choice for angiofibroma and radiotherapy is generally reserved for unresectable lesions. Primary treatment with radiotherapy has not gained general acceptance despite comparable results (Cummings, 1980; Cummings et al, 1984). The latent effects of radiation on facial skeletal growth and the potential to cause sarcomatous change have dissuaded many from considering this mode of treatment. Cryosurgery, sclerotherapy and electrocoagulation are seldom employed except for treating small accessible recurrences. Androgens or oestrogens, as definitive treatment or as adjuncts in inoperable and recurrent tumours, have produced variable results.

**Surgical approaches**

More than one surgical approach is often needed for complete removal of an angiofibroma. It may recur if not completely removed. Angiofibromata with intracranial extension should be removed with a combined intracranial approach, particularly when the main blood supply is from the internal carotid artery.

**Transnasal-maxillary approach**

Tumour in the maxillary antrum and anterior part of the nose may be removed through the sublabial incision. Preoperative ligation or clipping of the internal maxillary artery can be carried out transantrally. Denker's extension of the Caldwell-Luc procedure, resecting bone from the face of the maxilla and lateral nasal wall provides fair access. Exposure is limited, however, by the soft tissue of the lip and nose. The use of lateral rhinotomy or Weber-Fergusson incision improves the exposure but is limited by its unilateral and mid-facial scarring. Digital manipulation of the lateral tumour extension in the pterygopalatine fossa is made possible by extending the sublabial incision to the maxillary tuberosity. It often needs to be combined with the transpalatal approach to deliver the tumour completely.
Transpalatal approach

This approach exposes the nasopharynx and allows extensions into the sphenoidal and posterior nasal fossa. There are many variations to the palatal incision (Wilson, 1957). The U-shaped incision is preferred as it can be extended around the tuberosity of the maxilla to join the sublabial incision to reach the pterygopalatine fossa. In this procedure, after the mucoperiosteal flap is elevated (preserving the greater palatine neurovascular pedicle), bone from the posterior hard palate is removed. Once the tumour has been completely exposed and mobilized, it is removed with the mucoperiosteum of the nasopharynx.

Sublabial mid-facial degloving approach

This procedure is essentially a bilateral extended sublabial and transnasal-maxillary approach (Casson, Bonormo and Converse, 1974; Conley and Price, 1979). It obviates visible scarring and allows adequate exposure to the nasal complex, nasopharynx and mid-third of the face. The initial gingivolabial incision is across the midline from one maxillary tuberosity to the other. The soft tissue on both sides of the face is then elevated subperiosteally up to the infraorbital foramina. The infraorbital nerves are exposed and preserved. Routine intercartilaginous incisions are used, separating the soft tissue of the nose from the upper lateral cartilage as in rhinoplasty. A transfixing septal incision then separates the cartilaginous septum from the medial crura of the alar cartilage. Finally, an incision along the pyriform aperture connects the circumferential septal-vestibular incisions to the sublabial incision. This allows total mid-facial degloving up to the root of the nose and infraorbital foramen. The necessary bone is then resected from the maxilla, the antrum and the lateral nasal wall to provide access to the nasopharyngeal region. This approach also allows the pterygopalatine and infratemporal fossae to be reached. One of its postoperative complications is vestibular stenosis.

Tumours of lymphoid and haemotopoietic tissue

These tumours possess no gross characteristics which allow differentiation from the epithelial tumours of the nasopharynx. The symptomatology is similar to that of other invasive tumours occurring in this region. Epistaxis and nasal blockage are the usual presenting symptoms. Pain may signify pressure or invasion of adjacent structures. Biopsy is needed for a definitive diagnosis. Patients with no involvement of regional lymph nodes may have disseminated disease at the time of diagnosis. Management requires a multidisciplinary approach involving the radiotherapist and medical oncologist.

Malignant lymphoma

About 25% of malignant lymphomata are of extranodal origin, with Waldeyer's ring, second only to the stomach, as the most common site of involvement (Freeman, Berg and Cutler, 1972). Within the Waldeyer's ring, the faucial tonsil is the most frequent site of lymphomatous involvement, followed by the nasopharynx. In a review of the world literature from 1935 to 1969, Banfi et al (1970) reported malignant lymphoma to represent between 1% (in south-east Asia) to 43% (in Europe) of all nasopharyngeal tumours. The low incidence in the east Asian population is related to the prevalence of nasopharyngeal carcinoma.
Diagnosis and treatment

Advances in immunopathology using tissue markers and monoclonal antisera have further classified lymphomata into various immunological types (Parker, 1979). The normal or reactive lymphocyte population is heterogeneous whereas a malignant, non-Hodgkin's lymphoma is a clone of lymphocytes carrying specific surface markers. These markers enable the non-Hodgkin's lymphoma to be identified and typed as being B or T cell. Hodgkin's disease has no monoclonal marker pattern and is based on a morphological diagnosis. Staging follows the definitive diagnosis. In localized disease, radiation alone is the treatment of choice. For systemic disease, chemotherapy alone or in combination with radiation is the preferred treatment (Jacobs, Weiss and Hoppe, 1986).

Plasmacytoma

Plasmacytic dyscrasia occurs in the bone marrow (medullary) and any structure containing reticulo-endothelial tissues (extramedullary plasmacytoma). They are histologically similar. The extramedullary plasmacytoma occurs most commonly in the head and neck region and has a predilection for the upper aerodigestive tract, especially the nasal sinuses and the nasopharynx (Batsakis and Fries, 1964). It can be solitary or multiple in form. It is relatively rare and the incidence compared to multiple myeloma is 1:40 (Pahor, 1977). Males predominate in the ratio 3:1 and the peak incidence is in the fifth decade.

Diagnosis and treatment

Once the histological diagnosis is confirmed, it is necessary to exclude multiple and systemic involvement. Investigations would include radiological skeletal survey, haematological evaluation, bone marrow trephine biopsy and aspirate, and immunoglobulin electrophoresis study. Solitary plasmacytoma in the head and neck is generally treated by excision (depending on the site and accessibility) or local radiotherapy. The clinical course of plasmacytoma of the nasopharyngeal or upper aerodigestive tract is unpredictable (Booth, Cheesman and Vincenti, 1973). Despite treatment, it may recur or eventually evolve into a systemic form after a variable latent period. Hence long-term follow-up and surveillance is necessary.

Paediatric nasopharyngeal tumours

Paediatric nasopharyngeal tumours are rare. They cause respiratory obstruction, and create problems in diagnosis and management. Besides adenoid hypertrophy (which is unusual in early infancy) and antrochoanal polyp, the differential diagnoses of a nasopharyngeal mass include:

1. teratoid: dermoids, teratoma, epignathi
2. neuroectodermal: encephalocele, brain heterotopia, meningioma
3. dysontogenetic: chordoma, craniopharyngioma
4. miscellaneous: cysts, haemangioma, hamartoma, rhabdomyosarcoma.
**Teratoid tumours**

Most of the tumours arise from the midline or lateral wall of the nasopharynx and may be attacked to the palate. Females outnumber males by 6:1. In contrast to dermoids, teratomata of the nasopharynx are recognized later in infancy (Foxwell and Kelham, 1958).

**Dermoids or hairy polyps**

This is the commonest variety. They probably arise from inclusion errors during the fusion of the lateral palatine process. They are often pedunculated and covered by hairy skin containing dermal glands. Occasionally the main tumour mass is connected to an intracranial portion through a perforation in the skull base. Histologically, they are bidermal with fibroadipose tissue, bone, cartilage and fragments of striated muscles.

**Teratomata**

These are more complex than the dermoids in structure. Histologically, they are tridermal with nervous tissue. They are frequently associated with deformities of the skull (anencephalia, hemicrania and palatal fissures). Teratomata grow aggressively and, in this aspect, are true neoplasms. Unlike teratomata elsewhere in the body, nasopharyngeal teratomata have not been reported to undergo malignant degeneration (Willis, 1968).

**Epignathi**

This is the least common variety. It consists of the well-formed organs and limbs of a parasitic fetus. Highly developed teratoid tumours are much rarer in the head and neck; they often result in stillbirths.

**Basal encephaloceles and brain heterotopia**

The human nasopharynx is closely related to the embryonic development of the neural tube. The juxtaposition of the nasopharynx and the prosencephalon may further account for the very rare nasopharyngeal neuroectodermal tumours, for example basal brain heterotopia. Generally encephaloceles occur in approximately 1/4000 births and less than 10% are of the basal type (Blumenfeld and Skolnik, 1965). Among the basal encephaloceles, the sphenopharyngeal type is the most common. Within the nose and nasopharynx it can cause obstruction and deform the upper airway. The intranasal sac may be mistaken for a nasal polyp. It must be differentiated from nasal glioma and brain heterotopia.

**Chordoma and craniopharyngioma**

Chordoma is a slow-growing tumour of low malignancy. The craniocervical form occurs along the embryonic craniocervical axis of the notochord bar - the clivus, nasopharynx and first two cervical vertebrae. It erodes bone extensively with displacement of the surrounding structures, making complete surgical removal difficult (Mabrey, 1935; Batsakis and Kittleson, 1963). This tumour is not very sensitive to radiotherapy.
Few cases of craniopharyngioma in the nasopharynx have been described (Johnson, 1962). It is probably derived from remnants of the Rathke's pouch and the craniopharyngeal canal. Devoid of a definite capsule, the tumour proper is soft with multiple septa separating the cystic spaces. Calcification may be present. Clinically, the intracranial portion of the tumour may cause increased intracranial pressure, endocrine disturbances and retarded sexual development. Surgical decompression may be required to relieve the raised intracranial pressure. Complete removal of the main cyst necessitates a subfrontal approach and can be difficult (Matson and Crigler, 1969).

Nasopharyngeal cysts

Nasopharyngeal cysts occur in the roof and the lateral wall. They include the Rathke's pouch cyst, Thornwaldt's cyst from the pharyngeal bursa and branchial cleft cyst (on the lateral wall) (Taylor and Burwell, 1954).

Symptomatology

The clinical picture will depend on the size, nature and site of the tumour. Choanal obstruction may give rise to snuffling and rhinorrhoea. Long pedunculated tumours may cause intermittent attacks of coughing, apnoea and dysphagia. Sessile tumours may block the nasopharyngeal airway completely and distort the palate, impeding mouth breathing and feeding. Nasopharyngeal obstruction is often dramatic in the first few months of life as infants are obligate nose breathers (Moss, 1965; Swift and Emery, 1973). The risk of asphyxia and difficulty in feeding is greater in nasopharyngeal tumours than in bilateral choanal atresia. Any intracranial communication of the tumour always predisposes the infant to the threat of cerebrospinal fluid rhinorrhoea and ascending meningitis.

Radiological investigations

Radiological investigations include plain X-ray tomogram and computerized tomographic study.

Plain lateral skull X-ray may show a soft tissue mass obstructing the nasopharynx and displacing the soft palate anteroinferiorly. Adenoid hypertrophy in early infancy is very unusual. A choanogram may outline the attachment of the nasopharyngeal mass and demonstrate the patency of the choana. A tomogram of the base of skull may be necessary to exclude intracranial extension particularly through the sella turcica and sphenoorbital synchondrosis. The most useful investigation is the CT scan. It provides information on the nature of the tumour, its site of origin and both its intra- and extracranial extension.

Surgical management

Large teratoid masses may cause acute respiratory obstruction and need immediate surgical removal. The more common pedunculated 'hairy polyp' can be removed easily by a snare. In less urgent cases of nasopharyngeal tumour, endoscopic assessment under anaesthesia and careful biopsy is required to establish the diagnosis before definitive treatment. Laryngoscopy and bronchoscopy should also be carried out to exclude other causes of upper airway obstruction. The transpalatal approach is used to remove sessile tumours.
Intracranial communication is uncommon but must be excluded prior to any surgery. The existence of such a communication may necessitate combined intra- and extracranial surgery.

Appendix 19.1 Stage classification of nasopharyngeal carcinoma currently in use

(1) UICC TNM Classification

UICC (1978)

(a) Anatomical regions and sites

Posterior-superior wall: extends from the level of the junction of the hard and soft palates to the base of the skull.

Lateral wall: including the fossa of Rosenmüller.

Inferior wall: consists of the surface of the soft palate.

Note: The margin of the choanal orifices including the posterior margin of the nasal septum is included with the nasal fossae.

(b) TNM pretreatment categories

T: primary tumour

Tis pre-invasive carcinoma (carcinoma in situ)
T0 no evidence of primary tumour
T1 tumour confined to one site (including tumour identified from positive biopsy)
T2 tumour involving two sites
T3 tumour with extension to nasal cavity and/or oropharynx
T4 tumour with extension to base of skull and/or involving cranial nerves
Tx the minimum requirements to assess the primary tumour cannot be met

N: regional lymph nodes

N0 no evidence of regional lymph node involvement
N1 evidence of involvement of movable homolateral regional lymph nodes
N2 evidence of involvement of movable contralateral or bilateral regional lymph nodes
N3 evidence of involvement of fixed regional lymph nodes
Nx the minimum requirements to assess the regional lymph nodes cannot be met

M: distant metastases

M0 no evidence of distant metastases
M1 evidence of distant metastases
Mx the minimum requirements to assess the presence of distant metastases cannot be met.
(c) Stage-grouping (1978)

Similar to AJC (1978) stage-grouping.

(2) The American Joint Committee for Cancer Staging and End-Results Reporting Stage Classification

AJC/TNM Stage Classification (1978)

Anatomy

The anterior limit of the nasopharynx is the choana, through which it is continuous with the nasal cavity. Its roof is attached to the base of skull and slopes downward to become continuous with the posterior pharyngeal wall. The lateral wall is composed of the torus tubarius, the eustachian tube orifice, and that portion of the mucosa of the fossa of Rosenmüller extending up to its apex and junction with the roof. The inferior limit of the nasopharynx is level with the plane of the hard palate.

Anatomical site

Posterior-superior wall (vault).
Lateral wall.

TNM categories

T: primary tumour
Tx tumour that cannot be assessed
T0 no evidence of primary tumour
Tis carcinoma in situ
T1 tumour confined to one site of nasopharynx or no tumour visible (positive biopsy only)
T2 tumour involving two sites (both postero-superior and lateral walls)
T3 extension of tumour into nasal cavity or oropharynx
T4 tumour invasion of skull or cranial nerve involvement, or both

N: cervical lymph nodes (midline nodes are considered as homolateral nodes)
Nx nodes cannot be assessed
N0 no clinically positive node
N1 single clinically positive homolateral node 3 cm or less in diameter
N2 single clinically positive homolateral node more than 3 cm but not more than 6 cm in diameter or multiple clinically positive homolateral nodes, none more than 6 cm in diameter
N3 massive homolateral node(s), bilateral nodes or contralateral node(s)
M: distant metastasis

Mx not assessed
M0 no (known) distant metastasis
M1 distant metastasis present

Stage grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T category</th>
<th>N category</th>
<th>M category</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>N0-1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-4</td>
<td>N2-3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-4</td>
<td>N0-3</td>
<td>M1</td>
</tr>
</tbody>
</table>

(3) Ho's classification (Ho, 1978)

TNM categories

Tumour

T1 tumour confined to the nasopharynx (space behind the choanal orifices and nasal septum and above the posterior margin of the soft palate in its resting position)

T2 tumour extending to the nasal fossa, oropharynx or adjacent muscles or nerves below the base of the skull

T3 tumour extending beyond T2 limits and subclassified as follows:

- T3a bone involvement below the base of the skull (including floor of sphenoid sinus)
- T3b involvement of base of skull (including the lateral and posterior walls of sphenoid sinus)
- T3c involvement of cranial nerve(s)
- T3d involvement of orbit, laryngopharynx (hypopharynx) or infratemporal fossa

N: regional lymph nodes

N0 no palpable nodes (excluding nodes thought to be benign)

N1 node(s) wholly in the upper cervical level, bounded below by the neck crease extending laterally and backwards from or just below the thyroid notch (laryngeal prominence)

N2 palpable node(s) between the crease and the supraclavicular fossa, the upper limit being a line joining the upper margin of the sternal end of the clavicle and apex of an angle formed by the lateral surface of the neck and the superior margin of the trapezius

N3 palpable node(s) in the supraclavicular fossa and/or skin involvement in the form of carcinoma en cuirasse or satellite nodules above the clavicles
Stage-grouping

I  tumour confined to the nasopharynx (T1 N0)
II tumour extending to nasal fossa, oropharynx or adjacent muscles or nerves below the base of the skull (T2) and/or N1 involvement (T1 N1, T2 N0 and T2 N1)
III tumour extending beyond T2 limits or with bone involvement (T3) and/or N2 involvement (T1-2 N2, T3 N0-1)
IV N3 involvement, irrespective of the stage of the primary tumour (T1-3 N3)
V haematogenous metastasis and/or involvement of the skin or lymph nod(s) below the clavicle (T1-3 N0-3 M1).