CHAPTER 2

Tumours of the Nasopharynx

A wide variety of tumours can arise in the nasopharynx, but it is nasopharyngeal carcinoma that has fascinated generations of oncologists, pathologists, scientists and epidemiologists. It shows marked geographic differences, with highest incidence rates in Southern Chinese. In some endemic areas, the incidence has declined by about 30% over the past two decades, suggesting that environmental or lifestyle factors may play a major role and that the disease is, to some extent, preventable. Nasopharyngeal carcinoma shows a very strong association with Epstein-Barr virus (EBV) infection, irrespective of the ethnic origin of the patients. This association has pioneered a new paradigm of utilizing viral serological tests for the diagnosis of cancer and for screening in high-risk populations. Nasopharyngeal carcinoma is generally responsive to radiation therapy, and the clinical outcome has greatly improved over the years, due to refinements in staging and to improved therapy protocols.

The unusual and often deceptive histological features of nasopharyngeal carcinoma have generated controversies over the nature of the tumour and still pose a challenge to surgical pathologists. There have possibly been more names invented for the various histological subtypes of nasopharyngeal carcinoma than any other tumour type. The WHO classification presented in this book is expected to become the world-wide standard reference.
### WHO histological classification of tumours of the nasopharynx

#### Malignant epithelial tumours
- Nasopharyngeal carcinoma
  - Nonkeratinizing carcinoma
  - Keratinizing squamous cell carcinoma
  - Basaloid squamous cell carcinoma
  - Nasopharyngeal papillary adenocarcinoma
- Salivary gland-type carcinomas

#### Benign epithelial tumours
- Hairy polyp
- Schneiderian-type papilloma
- Squamous papilloma
- Ectopic pituitary adenoma
- Salivary gland anlage tumour
- Craniopharyngioma

#### Soft tissue neoplasms
- Nasopharyngeal angiofibroma

#### Haematolymphoid tumours
- Hodgkin lymphoma
- Diffuse large B-cell lymphoma
- Extranodal NK/T cell lymphoma
- Follicular dendritic cell sarcoma/tumour
- Extramedullary plasmacytoma

#### Tumours of bone and cartilage
- Chordoma

#### Secondary tumours

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1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (821) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded 0 for benign tumours, 3 for malignant tumours, and 1 for borderline or uncertain behaviour.

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### TNM classification of carcinomas of the nasopharynx

#### TNM classification

<table>
<thead>
<tr>
<th>T-Primary tumour</th>
<th>N-regional lymph nodes**</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Primary tumour cannot be assessed</td>
<td>NX Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>T0 No evidence of primary tumour</td>
<td>N0 No regional lymph node metastasis</td>
</tr>
<tr>
<td>T1 Tumour confined to nasopharynx</td>
<td>N1 Unilateral*** metastasis in lymph node(s), &lt;6 cm in greatest dimension, above the supravacular fossa</td>
</tr>
<tr>
<td>T2 Tumour extends to soft tissues</td>
<td>N2 Bilateral metastasis in lymph node(s), &lt;6 cm in greatest dimension, above the supravacular fossa</td>
</tr>
<tr>
<td>T2a Tumour extends to oropharynx and/or nasal cavity without parapharyngeal extension*</td>
<td>N3 Metastasis in lymph node(s), &gt;6 cm and/or in the supravacular fossa</td>
</tr>
<tr>
<td>T2b Tumour with parapharyngeal extension*</td>
<td>N3a &gt;6 cm in dimension</td>
</tr>
<tr>
<td>T3 Tumour invades bony structures and/or paranasal sinuses</td>
<td>N3b in the supravacular fossa#</td>
</tr>
<tr>
<td>T4 Tumour with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0 Tis N0 M0</td>
<td>M- MX Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>Stage I T1 N0 M0</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>Stage IIA T2a N0 M0</td>
<td>M1 Distant metastasis</td>
</tr>
<tr>
<td>Stage IIB T1 N1 M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2a N1 M0</td>
</tr>
<tr>
<td></td>
<td>T2b N0, N1 M0</td>
</tr>
<tr>
<td>Stage III T1 N2 M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2a, T2b N2 M0</td>
</tr>
<tr>
<td></td>
<td>T3 N0, N1, N2 M0</td>
</tr>
<tr>
<td>Stage IV A T4 N0, N1, N2 M0</td>
<td></td>
</tr>
<tr>
<td>Stage IVB Any T N3 M0</td>
<td></td>
</tr>
<tr>
<td>Stage IVc Any T Any N M1</td>
<td></td>
</tr>
</tbody>
</table>

*Parapharyngeal extension denotes postero-lateral infiltration of tumour beyond the pharyngobasilar fascia.

** The regional lymph nodes are the cervical nodes.

*** Midline nodes are considered ipsilateral nodes.

# Supraclavicular fossa is the triangular region defined by 3 points: the superior margin of the sternal end of the clavicle, the superior margin of the lateral end of the clavicle, the point where the neck meets the shoulder. This includes caudal portions of Levels IV and V.

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1. (947,2418).
The most common type of nasopharyngeal tumour is nasopharyngeal carcinoma, which is remarkable for the striking geographic differences in its incidence as well as the near consistent association with the Epstein-Barr virus (EBV). Nasopharyngeal carcinoma is also the prototype of a family of morphologically distinctive tumours – the lymphoepithelial carcinomas – that can arise in a variety of sites, such as other head and neck mucosal sites, salivary gland, lung and thymus, albeit uncommonly. Interestingly, in contrast to nasopharyngeal carcinoma, lymphoepithelial carcinomas occurring in these sites usually show a strong association with EBV only in Asians, but not in Caucasians.

Besides nasopharyngeal carcinoma, a broad range of neoplasms can arise in the nasopharynx, from epithelial to lymphoid, mesenchymal and neurogenic. Rarely, tumours derived from embryonic remnants either entrapped in their normal pathway of ascent or descent (ectopic pituitary tumour, craniopharyngioma) or dissociated from their normal regulatory influences (germ cell tumour) can occur. Since the nasopharynx is in close proximity to many different anatomic structures, tumours arising in the latter sites can also present clinically as a nasopharyngeal mass, for example, chordoma arising in the clivus.

**Anatomy**

The nasopharynx is the narrow tubular passage behind the nasal cavity. Its sloping roof and posterior wall are formed by the basisphenoid, basis-occiput and the first cervical vertebra. Anteriorly, it communicates with the nasal cavity via the choanae. The orifices of Eustachian tubes are in the lateral walls, and each is shielded superiorly and posteriorly by a comma-shaped elevation called the torus tubarius. Immediately above and behind the torus tubarius is a pharyngeal recess called the fossa of Rosenmüller. The nasopharynx tapers inferiorly, and continues as the oropharynx from the level of the soft palate.

The nasopharynx constitutes part of the Waldeyer ring. Histologically, its mucosa is covered by respiratory-type ciliated epithelium, but variable amounts of squamous epithelium are common. The mucosa exhibits invaginations, forming crypts that abut the underlying stroma. The stroma is rich in lymphoid tissue that often includes reactive lymphoid follicles. The surface or crypt epithelium is commonly infiltrated by many small lymphoid cells, which expand and disrupt the epithelium to produce a reticulated pattern. Some seromucinous glands are present, but they are not as abundant as in the nasal mucosa.

**Clinical features**

**Diagnostic procedures**

Various imaging techniques, such as computed tomography and magnetic resonance imaging, are helpful for detection of the presence of a tumour, as well as in precise delineation of the extent of disease. Endoscopic examination with directed biopsy is the key in obtaining materials for a definitive histological diagnosis.

**Tumour staging**

The TNM staging system for nasopharyngeal tumours (see preceding section) is only applicable for epithelial tumours, and in fact has been developed specifically for nasopharyngeal carcinoma. For lymphomas, the Ann Arbor staging system is recommended [947].

**Classification of nasopharyngeal carcinomas**

In the 1978 WHO classification, three histological subtypes of nasopharyngeal
carcinoma were recognized: squamous cell carcinoma (WHO type 1), nonkeratinizing carcinoma (WHO type 2), and undifferentiated carcinoma (WHO type 3) (2320). In the 1991 WHO classification, the squamous cell carcinoma subtype (keratinizing squamous cell carcinoma) was retained, while the last two subtypes in the previous classification were combined under a single category of “nonkeratinizing carcinoma”, which was further subdivided as being “differentiated” or “undifferentiated”; lymphoepithelioma-like carcinoma was considered a morphologic variant of undifferentiated carcinoma (2317). The use of numerical designation of WHO types 1, 2 and 3 was eliminated. The wide ranging reported figures on the frequencies of various subtypes indicate that the boundaries between the categories are not always clear (such as less well differentiated forms of keratinizing squamous cell carcinoma versus nonkeratinizing carcinoma, and nonkeratinizing carcinoma versus undifferentiated carcinoma), sampling error is a significant problem due to the small size of the biopsies, and intra- and inter-observer reproducibility of the classification is sub-optimal (323,2318, 2497,2735). In fact, squamous cell carcinoma and nonkeratinizing carcinoma have been viewed by some investigators as being merely variants of a fairly homogeneous group of tumours (2318,2577). Notwithstanding these problems, the proportion of keratinizing squamous cell carcinoma among all nasopharyngeal carcinomas is probably higher in low-incidence compared with high-incidence areas.

The current WHO classification maintains the terminology of the 1991 classification, with the addition of one category: basaloid squamous cell carcinoma.
**Nasopharyngeal carcinoma**

**Definition**
A carcinoma arising in the nasopharyngeal mucosa that shows light microscopic or ultrastructural evidence of squamous differentiation. It encompasses squamous cell carcinoma, nonkeratinizing carcinoma (differentiated or undifferentiated) and basaloid squamous cell carcinoma. Adenocarcinoma and salivary gland-type carcinoma are excluded.

**ICD-O codes**
- Nonkeratinizing carcinoma: 8072/3
- Keratinizing squamous cell carcinoma: 8071/3
- Basaloid squamous cell carcinoma: 8083/3

**Synonyms**
Lymphoepithelioma, lymphoepithelioma-like carcinoma, lymphoepithelial carcinoma, Schmincke type lymphoepithelioma, Regaud type lymphoepithelioma, transitional cell carcinoma, intermediate cell carcinoma, anaplastic carcinoma, undifferentiated carcinoma with lymphoid stroma, vesicular nucleus cell carcinoma, squamous cell carcinoma (WHO-1), nonkeratinizing carcinoma (WHO-2), undifferentiated carcinoma (WHO-3).

**Epidemiology**

**Global incidence and mortality**
Nasopharyngeal carcinoma (NPC) shows a distinct racial and geographical distribution and a multifactorial etiology. Globally, there were approximately 65,000 new cases and 38,000 deaths in the year 2000 (730). While rare in most parts of the world (onset rates commonly <1 per 105, or 0.6% of all cancers), there are certain populations for which the incidence is considerably higher, notably native and foreign-born Chinese, Southeast Asians (e.g. in Thailand, Philippines, and Vietnam), North Africans (e.g. in Algeria and Morocco), as well as native peoples of the Arctic region (e.g. in Canada and Alaska). Within these populations, there is a remarkable heterogeneity among ethnic lines (2872). The highest incidence of NPC has long been observed in Hong Kong, where 1 in 40 men develop NPC before the age of 75 years [1981].

**Age and sex distribution**
In high-risk groups, NPC incidence rises after the age of 30 years and peaks at 40-60 years, and thereafter declines [730]. The age distribution is similar in males and females, although rates in men are commonly 2-3-fold those observed in women [1981].

**Migration**
In general, populations that migrate from high to low risk areas retain much of the elevated risk [304] seen in their country of origin, although this, and the extent to which the risk diminishes in successive generations, varies according to ethnicity. Such heterogeneity may be associated with several factors, possibly acting in combination - the degree of genetic predisposition, and the prevalence of certain risk factors related to lifestyle upon migration.

**Time trends**
Recent trends in NPC incidence in high-risk countries reveal convincing evidence of a decline in rates since the mid-1970s in Hong Kong [1446]. The speed of the decline points to the role of changing environmental risk factors. Rates in low-risk areas are, in view of the rarity of the disease, subject to a great deal of random variation, and trends are often difficult to interpret. In U.S. Whites and in England, rates are low and in slow decline. The evolution of trends in U.S. Blacks is unclear.

**Etiology**
The specific geographical and demographic distribution of nasopharyngeal carcinoma (NPC), the time trends, and patterns observed in migrants reflect the interplay of genetic susceptibility, infection by Epstein-Barr virus (EBV) and environmental factors (dietary and non-dietary) in disease causation.
Epstein-Barr virus

The near constant association of EBV with NPC, irrespective of ethnic background, indicates a probable oncogenic role of the virus in the genesis of this tumour (1166,2107).

Environmental factors

Diet

In high incidence regions, high levels of volatile nitrosamines in preserved food have been implicated as the putative carcinogen for NPC development (2063). In the 1960s, it was proposed that the increased incidence of NPC among Hong Kong boat dwellers compared to house dwellers may have been due to their staple diet of salted fish (1108).

Table 2.02 Common presenting symptoms and signs of nasopharyngeal carcinoma. Data from 722 consecutive patients treated at the Pamela Youde Nethersole Eastern Hospital, Hong Kong, during 1994 to 2001.

<table>
<thead>
<tr>
<th>Presenting features</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Neck mass</td>
<td>42%</td>
</tr>
<tr>
<td>Nasal (post nasal drip, discharge, bleeding, obstruction)</td>
<td>46%</td>
</tr>
<tr>
<td>Aural (tinnitus, discharge, ear ache, deafness)</td>
<td>42%</td>
</tr>
<tr>
<td>Headache</td>
<td>16%</td>
</tr>
<tr>
<td>Ophthalmic (double vision, squint, blindness)</td>
<td>6%</td>
</tr>
<tr>
<td>Facial numbness</td>
<td>5%</td>
</tr>
<tr>
<td>Speech / swallowing problem</td>
<td>2%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical signs</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enlarged neck node(s)</td>
<td>72%</td>
</tr>
<tr>
<td>Bilateral neck nodes</td>
<td>35%</td>
</tr>
<tr>
<td>Neck nodes extending to supraclavicular fossa</td>
<td>12%</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>10%</td>
</tr>
<tr>
<td>Deafness</td>
<td>3%</td>
</tr>
<tr>
<td>Dermatomegacysis</td>
<td>1%</td>
</tr>
</tbody>
</table>

\[ISH = \text{in-situ hybridization}; \text{PCR} = \text{polymerase chain reaction}; \text{EBV} = \text{Epstein-Barr virus}\]

\[EBER = \text{EBV-encoded early RNA}, \text{LMP-1} = \text{latent membrane protein-1}\]

\[*\text{Immunohistochemistry (IHC) for early antigen-diffuse and 350/220 kd membrane glycoprotein of EBV}\]
involvement are features of more advanced disease. In endemic areas, NPC is an important underlying malignancy in patients presenting with dermatomyositis, being found in 12% of patients [2005] although only 1% of patients with NPC have dermatomyositis [2573].

**Imaging**

Magnetic resonance (MR) is the study of choice for assessing the loco-regional extent because of its superior sensitivity and multiplanar capability. Although CT is useful in depicting cortical bone erosion, MR is superior in revealing soft tissue infiltration and intracranial extension [442,1880] as well as marrow replacement permitting early recognition of bony involvement [442,1880]. Systemic imaging workup for patients with high metastatic risk include X-ray/CT of chest, ultrasonography/CT of liver, isotope bone scan and positron emission tomography coupled with CT (PET-CT).

**Table 2.03** Structures involved by local infiltration of nasopharyngeal carcinoma at presentation. Source: Magnetic resonance studies of 308 patients from Pamela Youde Nethersole Eastern Hospital, Hong Kong.

<table>
<thead>
<tr>
<th>Structures involved</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjacent soft tissues</strong></td>
<td></td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>87%</td>
</tr>
<tr>
<td>Oropharyngeal wall, soft palate</td>
<td>21%</td>
</tr>
<tr>
<td>Parapharyngeal space, carotid space</td>
<td>68%</td>
</tr>
<tr>
<td>Pterygoid muscle (medial, lateral)</td>
<td>48%</td>
</tr>
<tr>
<td>Prevertebral muscle</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Bony erosion / paranasal sinus</strong></td>
<td></td>
</tr>
<tr>
<td>Nasal septum</td>
<td>3%</td>
</tr>
<tr>
<td>Pterygoid plate(s), pterygo-maxillary fissure, pterygo-palatine fossa</td>
<td>27%</td>
</tr>
<tr>
<td>Maxillary antrum</td>
<td>4%</td>
</tr>
<tr>
<td>Ethmoid sinus</td>
<td>6%</td>
</tr>
<tr>
<td>Sphenoid sinus, sphenoid bone, foramina lacerum, ovale, rotundum</td>
<td>38%</td>
</tr>
<tr>
<td>Clivus</td>
<td>41%</td>
</tr>
<tr>
<td>Petrous bone, petro-occipital fissure</td>
<td>19%</td>
</tr>
<tr>
<td>Jugular foramen, hypoglossal canal</td>
<td>4%</td>
</tr>
<tr>
<td>Pituitary fossa / gland</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Extensive/ intracranial extension</strong></td>
<td></td>
</tr>
<tr>
<td>Cavernous sinus</td>
<td>16%</td>
</tr>
<tr>
<td>Cerebrum, meninges, cisterns</td>
<td>4%</td>
</tr>
<tr>
<td>Infratemporal fossa</td>
<td>9%</td>
</tr>
<tr>
<td>Orbit, orbital fissure(s)</td>
<td>4%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Macroscopy**

The tumour can appear as a smooth bulge in the mucosa, a discrete raised nodule with or without surface ulceration, or a frankly infiltrative fungating mass. Sometimes no grossly visible lesion is seen.

**Tumour spread and staging**

**Tumour spread**

NPC is notorious for its highly malignant behaviour, with extensive loco-regional infiltration, early lymphatic spread, and disproportionately high incidence of haematogenous dissemination. Erosion of skull base and paranasal sinuses, intracranial spread (via eroded bone or basal foramina), infiltration of cranial nerves, and extension to more distant structures (infratemporal fossa, orbit, hypopharynx) occur as tumour invasion advances.

With the rich lymphatic plexus in the nasopharynx, lymphatic spread occurs early in the course of disease. In patients staged by MR, about 20% of patients have no enlarged nodes, and about half have retropharyngeal node involvement [2314]. The jugulo-digastric node is by far the most common palpable node at presentation, and involvement of the posterior cervical chain is more frequent than with other head and neck cancers. The strong association between the topographic level of lymphatic extension and the increased incidence of distant failure reflects that haematogenous dissemination occurs mainly via the draining of the lymphatic trunks at the lower end of the jugular chain into the great vessels. The most common sites of haematogenous deposits are, in descending order of frequency, bone, liver, lung, and distant nodes [2575].

**Serological studies**

Positive serology against Epstein-Barr virus (EBV) is found in close to 100% of patients with non-keratinizing NPC [976]. IgA against viral capsid antigen (VCA) and IgG/IgA against early antigens (EA) are the most extensively used diagnostic tool, with the reported detection rates for NPC varying from 69-93%. Newer antibody tests based on recombinant EBV antigens such as EBV nuclear antigens (EBNA), membrane antigen (MA), thymidine kinase (TK), DNA polymerase (DP), ribonucleotide reductase (RR), DNAase, and Z transactivator protein (Zta) have shown promise when used in combination [378,537].

Another approach is to test for elevated levels of circulating EBV DNA or RNA (BamH1-W, EBERs or EBNA1) by quantitative PCR (Q-PCR) in the plasma or serum, with reported sensitivity in NPC up to 96% [35,1514,1549,2346].

**Relevant diagnostic procedures**

All patients should have complete physical examination and endoscopic examination of the nasopharyngeal region. Biopsies are taken from the gross lesions. In the absence of a gross lesion, multiple biopsies should be taken from the lateral, superior and posterior walls of the nasopharynx for patients with high suspicion of NPC.

**Fig. 2.4** Positron emission tomography coupled with computed tomography (PET-CT) of nasopharyngeal carcinoma. Physical examination and biochemistry did not show any sign suggestive of distant metastases. X-ray chest was normal. PET-CT revealed multiple distant metastases in lung, liver and spleen, in addition to extensive local infiltration and bilateral cervical lymph nodes.

**Fig. 2.5** The relative frequency of cranial nerve palsy due to nasopharyngeal carcinoma at the time of diagnosis. Source: 722 patients treated at the Pamela Youde Nethersole Eastern Hospital, Hong Kong, 1994-2001.
behaviour and therapeutic considerations of NPC are so uniquely different from other head and neck cancers. With accumulation of supporting data from different countries {448,490,1061,1119,1444,1592,1966}, there is little doubt that the current staging system is superior to the past systems, both in terms of improved predictive accuracy and more balanced stage distribution.

Nonkeratinizing carcinoma

**Histopathology**

The biopsies vary in appearance from the presence of a frank tumour with surface ulceration to subtle involvement of the mucosa beneath an intact surface epithelium {2316,2318,2735}. The tumour comprises solid sheets, irregular islands, dyscohesive sheets and trabeculae of carcinoma intimately intermingled with variable numbers of lymphocytes and plasma cells. Subclassification into the undifferentiated and differentiated subtypes is optional, since their distinction is of no clinical or prognostic significance, and different areas of the same tumour or different biopsies taken at different time intervals from the same patient may exhibit features of one or the other subtype. When both subtypes are seen in a specimen, the tumour may be classified according to the prominent subtype, or as nonkeratinizing carcinoma with features of both subtypes. The undifferentiated subtype, which is more common, is characterized by syncytial-appearing large tumour cells with indistinct cell borders, round to oval vesicular nuclei, and large central nucleoli. The cells often appear crowded or even overlapping. Sometimes, the nuclei

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**Fig. 2.6** Nasopharyngeal nonkeratinizing carcinoma. Tumour islands are obvious in the lymphoid stroma.

**Fig. 2.7** Nasopharyngeal nonkeratinizing carcinoma. This example is accompanied by an abundant desmoplastic stroma.

**Fig. 2.8** Nasopharyngeal nonkeratinizing carcinoma. A This example of differentiated subtype is characterized by sheets of tumour separated by a dense infiltrate of lymphocytes and plasma cells. B Tumour island in a lymphoid cell-rich stroma. Some lymphocytes are also seen within the tumour. C This tumour shows an uncommon trabecular growth pattern.

**Fig. 2.9** Cytological spectrum of nasopharyngeal nonkeratinizing carcinoma, undifferentiated subtype. A The cells exhibit a syncytial quality, and possess vesicular nuclei, prominent nucleoli and amphophilic cytoplasm. B The syncytial-appearing cells have vesicular nuclei, distinct nucleoli and lightly eosinophilic cytoplasm. There are some intermingled lymphocytes. C Focally, there can be cells with more distinct cell borders and a moderate amount of eosinophilic cytoplasm.
Nasopharyngeal carcinoma can be chromatin-rich rather than vesicular. The scant cytoplasm is either amphophilic or eosinophilic. There can be small foci of primitive squamous differentiation, where groups of tumour cells exhibit a slightly greater amount of lightly eosinophilic cytoplasm and slightly more distinct cell borders. The differentiated subtype differs from the undifferentiated subtype in showing cellular stratification and pavementing, often with a plexiform growth, reminiscent of transitional cell carcinoma of the bladder [2317]. The tumour cells show fairly well-defined cell borders and sometimes vague intercellular bridges, and there may exceptionally be occasional keratinized cells. Compared with the undifferentiated subtype, the cells are often slightly smaller, the nuclear-cytoplasmic ratio is lower, the nuclei can be more chromatin-rich, and nucleoli are usually not as prominent.

A desmoplastic stroma is uncommon. Areas of coagulative necrosis are sometimes present, and can be extensive. The density of lymphocytes and plasma cells is highly variable. At one extreme, there are no or few lymphocytes within the tumour islands, although some lymphoid cells are present in between, which probably merely represent the native lymphoid tissue in the nasopharyngeal mucosa. At the other extreme, abundant lymphocytes and plasma cells infiltrate the tumour islands, breaking them up into tiny clusters or single cells and obscuring the epithelial nature of the tumour; the term “lymphoepithelial carcinoma” may be applied for such cases. In metastatic sites, the lymphocyte density in the tumour may or may not be maintained. In some cases, scattered epithelioid granulomas are present, and may be so prominent as to mask the small islands of carcinoma [404]. Many admixed eosinophils are seen in about one-fourth of cases [830,1463,1555]. Some cases show a prominent infiltrate of neutrophils even in the absence of ulceration.

There are a number of inconstant features. The carcinoma cells can assume a plump or slender spindle shape focally or extensively, with formation of streaming fascicles. The nucleoli of the spindly cells are often not as prominent as the syncytial-appearing cells. In some cases, isolated or groups of tumour cells may appear shrunken, with dark smudged nuclei and dense amphophilic or eosinophilic cytoplasm; it is unclear whether such changes reflect a degenerative phenomenon in a subpopulation of tumour cells, or a biopsy artefact. There can be Pagetoid spread of the carcinoma into the surface or crypt epithelium. In approximately one-tenth of cases, there are interspersed spherical amyloid globules [2084]. The amyloid globules are usually smaller than a tumour cell, and can be present intracellularly (sometimes causing indentation of the tumour cell nucleus), scattered among the carcinoma cells, or in the adjacent stroma. They are derived from keratins, and are probably of tumour origin. In the uncommon papillary variant, there are papillary fronds comprising delicate stromal cores covered by stratified tumour cells morphologically no different from those of the usual nonkeratinizing nasopharyngeal carcinoma. Rare cases can show cyto-

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**Table 2.04 Frequency of histological subtypes of nasopharyngeal carcinoma.**

<table>
<thead>
<tr>
<th>Current WHO classification</th>
<th>High incidence population</th>
<th>Intermediate incidence</th>
<th>Low incidence population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratinizing squamous cell carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong Kong*</td>
<td>Singapore (2318)</td>
<td>Tunisia (323)</td>
<td>Japan (2497)</td>
</tr>
<tr>
<td>Keratinizing squamous cell carcinoma</td>
<td>1%</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>Nonkeratinizing carcinoma - Undifferentiated</td>
<td>99%</td>
<td>83%</td>
<td>92%</td>
</tr>
<tr>
<td>Nonkeratinizing carcinoma - Differentiated</td>
<td>92%</td>
<td>42%</td>
<td>76%</td>
</tr>
<tr>
<td>Basaloid squamous cell carcinoma</td>
<td>&lt;0.2%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = Not available; *Queen Elizabeth Hospital, 2001-2003

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**Fig. 2.10 Nasopharyngeal nonkeratinizing carcinoma, undifferentiated subtype.**

A So-called lymphoepithelial carcinoma, characterized by lymphoid cells apparently breaking up the tumour into tiny aggregates, rendering it difficult to appreciate the epithelial nature of the neoplasm. B This case comprises spindly cells with dark-staining nuclei and inconspicuous nucleoli. C Among the carcinoma cells with vesicular nuclei, there can be tumour cells with a shrunken appearance and dark-staining nuclei. D Some examples show many amyloid globules among the tumour cells. Some globules are intracellular, and displace the nucleus of the tumour cells to one pole.
plasmic clear cell change, but this is such an uncommon feature that the alternative diagnosis of lymphoma or salivary gland-type carcinoma should always be considered. Exceptionally, there is accumulation of extracellular edema fluid or mucosubstance, breaking up the tumour islands to produce a complex reticulated pattern. Nasopharyngeal carcinoma may contain intracytoplasmic mucin in very rare cells. It has also rarely been reported to occur in combination with a component of adenocarcinoma (1200, 1389).

Nasopharyngeal carcinoma may present initially with cervical lymph node metastases. The lymph nodes can be involved extensively or subtly (such as submergence of the tumour in the lymphocyte-rich paracortex). The tumour takes the form of islands and strands, being intermingled with variable numbers of lymphocytes, plasma cells and eosinophils. Some tumour cells can resemble Reed-Sternberg cells or lacunar cells. Coupled with a dense lymphoid infiltrate, a misdiagnosis of Hodgkin or non-Hodgkin lymphoma is sometimes made (330,1470). A desmoplastic stroma may be present. In approximately one fifth of cases, there are epithelioid granulomas, and in half of these cases, the granulomas show caseous necrosis (1470). Nasopharyngeal carcinoma may also metastasize as a wholly or partly cystic lesion containing necrotic material.

**Immunoprofile**

Practically all tumour cells show strong staining for pan-cytokeratin (AE1/AE3, MNF-116); this uniform staining contrasts with the usually focal staining observed in undifferentiated carcinomas of other sites, such as the lung and thyroid. The staining for high molecular weight cytokeratins (such as cytokeratin 5/6, 34ßE12) is strong, and staining for low molecular weight cytokeratins (such as CAM5.2) is often weaker and sometimes patchy. Cytokeratins 7 and 20 are both negative (801). In undifferentiated nonkeratinizing carcinoma, the cytokeratin immunostain highlights the scanty wisps of cytoplasm that wrap around the large nucleus and extend outward as short narrow processes. As a result of the cell nests being broken up by infiltrating lymphocytes, a distinctive reticulated or meshwork pattern is produced. In differentiated nonkeratinizing carcinoma, the tumour cells, with a broader rim of cytoplasm, are obviously polygonal on immunostaining for cytokeratin.

Immunoreactivity for epithelial membrane antigen in nasopharyngeal carcinoma is often only focal (816). In most cases, the tumour exhibits strong nuclear staining for p63, a basal cell marker that normally highlights the basal and parabasal cells of the overlying stratified squamous epithelium.

The lymphoid cells represent a mixture of T cells and B cells, usually with the former predominating, especially within and around the tumour islands (854,883, 1070,1962,2912). At least a proportion of the T cells are activated cytotoxic cells. The plasma cells are polyclonal. There are variable numbers of scattered S100-positive plasma cells.
protein-positive dendritic cells. Some studies have reported the following features to be associated with a better prognosis: high density of dendritic cells; high number of infiltrating lymphocytes; and low number of granzyme B-positive cytotoxic cells [854,883,1903,1962,2912].

**Epstein-Barr virus detection**

Nonkeratinizing nasopharyngeal carcinoma is associated with Epstein-Barr virus (EBV) in practically 100% of cases, irrespective of the ethnic background of the patient. EBV latent membrane protein-1 (LMP1) is usually positive in only 30-40% of cases, and the immunostaining is often patchy and weak, and thus is not a reliable method to demonstrate the presence of EBV {16,961,1988,2061}. The simplest and most reliable way to demonstrate EBV is in-situ hybridization for EBV encoded early RNA (EBER), which is present in abundance in cells latently infected by EBV. Practically all the tumour cells should show nuclear labelling {1137,1157,1176,2061,2233,2638,2684}. In-situ hybridization for EBER can aid in the diagnosis of nasopharyngeal carcinoma if there are difficulties in distinguishing between carcinoma and reactive epithelial atypia. A positive result also strongly suggests a nasopharyngeal origin (although not entirely specific) for a metastatic nonkeratinizing carcinoma of unknown primary. On the other hand, fine needle aspiration cytological examination of enlarged cervical lymph nodes is invaluable in reaching a diagnosis of metastatic nasopharyngeal carcinoma, either for initial diagnosis or staging {380,1355}. The aspirate smears show, in a background of lymphocytes and plasma cells, irregular clusters of large cells with overlapping vesicular nuclei and large nucleoli. The cytoplasm of these cells is often fragile and barely visible. There are commonly many naked nuclei {1760}. The presence of dispersed large tumour cells among the lymphoid cells may result in a pattern strongly reminiscent of Hodgkin lymphoma {1355}. The diagnosis can be readily confirmed by immunostaining for cytokeratin and in-situ hybridization for EBER either on the cell smears or cell block preparations.

**Electron microscopy.**

Although squamous differentiation is primitive or not evident in most cases of nasopharyngeal carcinoma at the light microscopic level, there is usually convincing evidence of squamous differentiation at the ultrastructural level. At least some carcinoma cells contain small bundles of tonofilaments or tonofibrils, in addition to well-formed desmosomes {1470, 1513,2082,2568}.

**Differential diagnosis**

Crush artefacts are common in nasopharyngeal biopsies, making it difficult to determine whether the observed distorted cells represent carcinoma or merely lymphoid cells. Such biopsies should be scrutinized in the better-preserved areas for tumour cell clusters. If there are uncertainties, immunostaining for cytokeratin is of great help in reaching a diagnosis of nasopharyngeal carcinoma. In the non-neoplastic nasopharyngeal mucosa, cytokeratin immunostaining highlights the sharply delineated surface and crypt epithelium, with no positive cells in the stroma other than those in seromucinous glands. Mucosa involved by nasopharyngeal carcinoma typically shows irregular clusters of cytokeratin-positive cells in the stroma.

**Cytopathology**

Nasopharyngeal aspirate or brush is used in some centres to produce cytologic preparations for diagnosis of nasopharyngeal carcinoma. However, since the diagnostic sensitivity of nasopharyngeal cytology is limited (70-90%) {387,1001}, nasopharyngeal biopsy is the preferred method for obtaining a definitive histological diagnosis {387}. On the other hand, fine needle aspiration cytological examination of enlarged cervical lymph nodes is invaluable in reaching a diagnosis of metastatic nasopharyngeal carcinoma, either for initial diagnosis or staging {380,1355}. The aspirate smears show, in a background of lymphocytes and plasma cells, irregular clusters of large cells with overlapping vesicular nuclei and large nucleoli. The cytoplasm of these cells is often fragile and barely visible. There are commonly many naked nuclei {1760}. The presence of dispersed large tumour cells among the lymphoid cells may result in a pattern strongly reminiscent of Hodgkin lymphoma {1355}. The diagnosis can be readily confirmed by immunostaining for cytokeratin and in-situ hybridization for EBER either on the cell smears or cell block preparations.

**Fig. 2.13** Metastatic nasopharyngeal carcinoma in lymph node. A Fine needle aspiration smear shows tight clusters of tumour cells among small lymphocytes. B In histological sections, examination under medium magnification often reveals areas where cohesive tumour growth is evident. C The epithelial nature of the tumour is readily confirmed by immunostaining for cytokeratin, whereby a meshwork pattern of staining is often observed.

**Fig. 2.14** Nasopharyngeal mucosa. A Germinal centre cells mimicking nasopharyngeal carcinoma. B Nasopharyngeal lymphoid hyperplasia mimicking nasopharyngeal carcinoma. In the left field, the venule with no obvious lumen can also be mistaken for a cluster of carcinoma cells.
A number of benign cellular changes can mimic nonkeratinizing carcinoma. (1) Clusters of germinal centre cells may be mistaken for carcinoma because of the presence of large cells with vesicular nuclei and the absence of a well-defined mantle zone. The identification of admixed centrocytes (smaller “atypical” cells with irregular-shaped or angulated nuclei) and tingible-body macrophages points toward the lymphoid nature of the large cells, which can be confirmed by immunostaining (leucocyte common antigen positive, cytokeratin negative) (2317). (2) A tangentially sectioned crypt harbouring cells with reactive changes that include nuclear enlargement can produce a pattern simulating an island of carcinoma lying in a lymphoid cell-rich stroma. In contrast to nasopharyngeal carcinoma, the nuclei are not as large and thus not so crowded, and the nucleoli are not as prominent. A negative in-situ hybridization for EBER would render a diagnosis of nasopharyngeal carcinoma most unlikely (2318). (3) The nasopharyngeal mucosa can sometimes exhibit reactive lymphoid hyperplasia, accompanied by an increased number of immunoblasts in the lymphoid stroma, raising a suspicion for carcinoma. In contrast to the latter, the large cells are non-cohesive and have well-defined amphophilic cytoplasm. The diagnosis can be confirmed by a lack of cytokeratin immunoreactivity as well as positive immunostaining for lymphoid markers in the large cells (323). (4) The lymphoid tissue-associated venules lined by plump endothelial cells with vesicular nuclei may be mistaken for clusters of carcinoma cells. The presence of distinct basement membrane around the groups of cells, lack of large nucleoli, and negative staining for cytokeratin would be against the diagnosis of carcinoma.

Distinction between nonkeratinizing carcinoma and large cell lymphoma can at times be difficult. In the nasopharyngeal mucosa or metastatic deposit in lymph node, dispersed growth of the carcinoma cells and accompanying eosinophil infiltration may lead to a misdiagnosis of Hodgkin lymphoma (330,394,2880). Features favouring a diagnosis of carcinoma include the presence of cohesive cell groups in some foci (best appreciated at medium magnification) and the generally poorly defined cell borders; the diagnosis can be readily confirmed by immunostaining for cytokeratin. Nasopharyngeal carcinoma with marked cellular spindling can mimic a high-grade sarcoma. In most cases, the diagnosis can be reached by identifying in some foci a component of typical nasopharyngeal carcinoma, and can be further confirmed by cytokeratin immunoreactivity.

Post-treatment biopsies
After treatment by radiation therapy, it may take weeks (up to 10 weeks) for the nasopharyngeal carcinoma to disappear histologically (1401). The radiated carcinoma cells usually show evidence of radiation injury in the form of enlarged and bizarre nuclei, accompanied by an increased amount of cytoplasm that is often finely vacuolated. If biopsy is positive, repeat biopsies should be taken every two weeks – remission is defined by two subsequent negative biopsies (1401,1402,1886). Radiation-induced changes in the normal nasopharyngeal mucosa can be mistaken for malignancy. The surface or crypt epithelium can exhibit enlarged, hyperchromatic or even bizarre nuclei, but such changes can be recognized to be benign because they are limited to some but not all cells (random cytologic atypia) and the normal nuclear-cytoplasmic ratio is maintained. Mucosal epithelial atypia usually does not persist beyond one year. If there are uncertainties as to whether the atypical cells represent residual carcinoma or irradiated normal cells, positive in-situ hybridization for EBER would strongly favour the former interpretation. There can also be bizarre stromal cells (radiation fibrolasts) with large smudged nuclei or large vesicular nuclei with prominent nucleoli; these atypical cells can persist for many years. These cells can be distinguished from residual or recurrent carcinoma by their occurrence as single cells and by the amphophilia of the cytoplasm. The stroma frequently contains ectatic blood vessels showing variable degrees of radiation injury such as enlarged prominent endothelial cells and abundant fibrinoid deposits.

Some patients with nasopharyngeal carcinoma develop local recurrence. The nasopharyngeal biopsies should be interpreted in the same way as for patients without a prior history of nasopharyngeal carcinoma. The recurrence can be morphologically identical to the original tumour, or may show a slightly greater degree of squamous dif-
Keratinizing squamous cell carcinoma

Histopathology

This is an invasive carcinoma showing obvious squamous differentiation at the light microscopic level, in the form of intercellular bridges and/or keratinization over most of the tumour, morphologically similar to keratinizing squamous cell carcinomas occurring in other head and neck mucosal sites [2317]. The degree of differentiation can be further graded as: well differentiated (most common), moderately differentiated and poorly differentiated. The tumour typically grows in the form of irregular islands, accompanied by an abundant desmoplastic stroma infiltrated by variable numbers of lymphocytes, plasma cells, neutrophils and eosinophils [1555]. The tumour cells are polygonal and stratified. The cell borders are distinct and separated by intercellular bridges. The cells in the centres of the islands or facing the surface often show a greater amount of eosinophilic glassy cytoplasm, sometimes with identifiable cytoplasmic tonofibrils, indicative of cellular keratinization. Occasionally keratin pearls are formed [2735]. The nuclei often show hyperchromasia, and the degree of nuclear pleomorphism ranges from mild to marked. The surface epithelium is frequently involved, apparently representing carcinoma in situ.

Keratinizing squamous cell carcinoma can arise de novo or as a radiation-associated carcinoma occurring many years after radiation therapy for nonkeratinizing nasopharyngeal carcinoma [403, 2316, 2735]. Compared with nonkeratinizing carcinoma, keratinizing squamous cell carcinoma shows a greater propensity for locally advanced tumour growth (76% versus 55%) [2136] and a lower propensity for lymph node metastasis (29% versus 70%) [1859]. While some studies suggest that this subtype of nasopharyngeal carcinoma has lower responsiveness to radiation therapy and a worse prognosis compared with nonkeratinizing carcinoma [1122, 1859, 2136, 2318], others have not found this subtype to differ in biological behaviour [363, 778].

Immunoprofile and Epstein-Barr virus detection

Keratinizing squamous cell carcinoma shows immunoreactivity for pan-cytokeratin, high molecular-weight cytokeratin, and focally epithelial membrane antigen. For radiation-induced keratinizing squamous cell carcinoma, there is no association with EBV [403]. However, for de novo keratinizing squamous cell carcinomas, data on the EBV status are conflicting. In general, the patients have lower or negative IgA titres against EBV compared with nonkeratinizing carcinomas [1486, 1860, 2549]. Molecular studies of EBV in the tumour tissues have yielded conflicting results. Summarizing the literature, it appears that EBV is almost always positive in areas endemic for nasopharyngeal carcinoma, EBV is often positive in intermediate incidence areas, while EBV is positive in only a proportion of cases in low incidence areas [405, 580, 599, 961, 1124, 1125, 1157, 1176, 1262, 1885, 1892, 1988, 2894]. Keratinizing squamous cell carcinomas tend to carry lower copy numbers of EBV compared with nonkeratinizing carcinomas [2108]. On in situ hybridization, the nuclear signals of EBER are usually confined to the less differentiated cells (basal cells that surround the individual tumour islands), but not in the cells showing obvious squamous differentiation.

The role of human papillomavirus in keratinizing squamous cell carcinoma remains uncertain [1125].

Differential diagnosis

The frank invasive growth, nuclear atypia and obvious squamous differentiation usually permit a straightforward diagnosis of keratinizing squamous cell carcinoma to be made. However, in some cases, particularly those arising after radiation therapy for nonkeratinizing nasopharyngeal carcinoma, distinction between a very well differentiated keratinizing squamous cell carcinoma and squamous metaplasia/hyperplasia can be extremely difficult, since the nuclear atypia can be very subtle and focal, and invasion may not be obvious in the former. Assessment of invasion is further hampered by the abundant fibrinous deposits in the stroma related to prior radiation, and the usual desmoplastic stroma may be lacking. To arrive at a definitive diagnosis, sometimes multiple biopsies are required to identify convincing stromal invasion as well as focal mild nuclear atypia.

Basaloid squamous cell carcinoma

Several cases of basaloid squamous cell carcinoma, morphologically identical to the same tumour more commonly occur-
ring in other head and neck sites (See chapter on hypopharynx, larynx and trachea for details), have been reported to occur as primary tumours of the nasopharynx \{116,117,1790,1997,2714\}. Among the 6 cases with information, the M:F ratio is 2:1, and patients’ ages ranged from 27-79 years (mean 55 years). Four cases had stage T3 or T4 disease; and two had lymph node metastasis. None had distant metastasis at presentation. On follow-up, three patients had no evidence of disease at 34-52 months; three were alive with disease at 19-46 months. The tumour appears to show a lower clinical aggressiveness compared with basaloid squamous cell carcinoma occurring in other head and neck sites. Among 4 cases tested for EBV, all three Asian cases were positive, while one Caucasian case was negative \{1790,2714\}.

Precursor lesions

In biopsies of nasopharyngeal carcinoma, an in-situ or intraepithelial component is identified in only 3-8% of cases, but it is often difficult to determine whether the invasive carcinoma has originated from the overlying in situ carcinoma or has merely invaded the surface epithelium \{364,1504,1989,2852,2911\}. Pure nasopharyngeal carcinoma in-situ, as confirmed by multiple biopsies to rule out an invasive component, is very rare \{419,1989,2911\}. These findings suggest that most nasopharyngeal carcinomas do not originate from nasopharyngeal carcinoma in-situ, or the evolution from the latter to the former occurs over a short time scale such that the latter is rarely detected.

Histologically, pure nasopharyngeal carcinoma in-situ is characterized by atypical epithelial change confined to the surface or crypt epithelium, and lacking an invasive component. The epithelium is usually slightly thickened, and consists of cells with variable loss of polarity, nuclear enlargement, nuclear crowding and distinct nucleoli. Sometimes there can be scattered amyloid globules. Some attempts have been made to grade the spectrum of intraepithelial neoplastic changes (dysplasia/carcinoma-in-situ, or nasopharyngeal intraepithelial neoplasia) in the nasopharynx, but reproducibility and difficulties in recognizing the lower grade lesions remain an issue. So far, all cases of nasopharyngeal carcinoma in-situ studied have been positive for EBV (EBER), confirming that EBV infection precedes the acquisition of invasiveness by nasopharyngeal carcinoma \{419,1971,2813\}. Analysis of the EBV termini shows the virus to be in a clonal form, providing indirect support for the clonality of the epithelial proliferation \{1989\}. Thus in situ hybridization for EBER may aid in the distinction between carcinoma-in-situ and non-specific reactive atypia of the nasopharyngeal epithelium.

There are only limited data on the natural history of untreated pure nasopharyngeal carcinoma in-situ (or dysplasia). A proportion of patients develop invasive cancer on follow-up \{1971,1989\}.

Histogenesis

Nasopharyngeal carcinoma arises from the surface or crypt epithelium of the nasopharyngeal mucosa. In some cases, the tumour appears to arise from the basal layers of the stratified squamous epithelium, a finding further supported by the strong immunoreactivity for p63 in both the tumour and normal basal cells.

Somatic genetics

Nasopharyngeal carcinoma (NPC) is believed to result from accumulation of multiple genetic alterations and Epstein-Barr virus (EBV) latent infection in the
Inactivation of the P16 tumour suppressor gene has been shown to be early events in NPC tumorigenesis \cite{360,361}. Moreover, deletions on 3p and 9p have important roles in the genesis of NPC. The characteristic LOH on 3p, 9p, and 14q in almost all tumours suggests that the characteristic LOH on 3p, 9p, and 14q in almost all tumours suggests that the characteristic LOH on 3p, 9p, and 14q in almost all tumours suggests that the

Cytogenetics and comparative genomic hybridization (CGH)

Only few well-characterised karyotypes of NPC have been described. Despite the many complex rearrangements found, rearrangement and deletion on chromosome 3 have been consistently noted in this cancer \cite{1141,2707,2813}. The spectral karyotyping (SKY) analyses have defined the common chromosomal regions of loss including 3p12-p21, 11q14-qter as well as the common regions of gain including 7p15-p14, 7q11.2-q21, 8q21.1-q22, 12q22-q24.1 and 20q were frequently detected \cite{2813}. CGH studies have identified multiple recurrent chromosomal aberrations including loss on chromosomes 3p, 9p, 9q, 11q, 13q, 14q and 16q and gains of 1q, 3q, 12p, and 12q. Common regions of loss are 3p14-21, 14q24-qter, 11q21-qter while common regions of gains are 3q21-26 and 12q13-15 \cite{413,1545}. Array-based CGH analyses and fluorescence in-situ hybridization (FISH) analyses have identified a cryp
tics are identified at 3p14–24.2, 11q21–23, 13q12–14, 13q31–32, 14q24–32, and 16q22–23 \cite{1545}. The characteristic LOH on 3p, 9p, and 14q in almost all tumours suggests that the characteristic LOH on 3p, 9p, and 14q in almost all tumours suggests that the characteristic LOH on 3p, 9p, and 14q in almost all tumours suggests that the

Molecular genetic alterations

In concordance with CGH results, loss of heterozygosity (LOH) studies have revealed high frequencies of deletion on chromosomes 3p, 9p, 9q, 11q, 13q, 14q and 16q. Multiple minimally deleted regions are identified at 3p14–24.2, 11q21–23, 13q12–14, 13q31–32, 14q24–32, and 16q22–23 \cite{1545}. The characteristic LOH on 3p, 9p, and 14q in almost all tumours suggests that the characteristic LOH on 3p, 9p, and 14q in almost all tumours suggests that the characteristic LOH on 3p, 9p, and 14q in almost all tumours suggests that the

Expression profiles / Proteomics

In NPC, P53 mutation is rare, but DNA-P63, a P53 homologue, is consistently over-expressed and may block P53-mediated transactivation and apoptotic network in cancer cells \cite{506,2453}. Frequent aberrant expression of the cyclin D1, P27 and BCL-2 may also be involved in dysregulation of cell proliferation and apoptosis pathway \cite{100,1415,1566}. Overexpression of the hypoxia associated proteins, HIF-alpha, CA IX, and VEGF, is common and associated with poor prognosis \cite{1150}. High MET protein expression level correlates with poor survival in late-stage NPC \cite{2094}.

Genetic susceptibility

There is strong evidence that genetic predisposition is involved in the genesis of NPC. Epidemiological studies strongly support the existence of susceptible populations in the world: the prevalence of NPC is highly variable in different ethnic groups \cite{1979}; migrants from high-risk areas continue to exhibit high risk of NPC \cite{952,1501}, familial clustering of NPC is frequently observed \cite{2893}.

HLA

There is an association between HLA phenotype and NPC risk. The association between HLA-A2 and NPC was first reported among Chinese in Singapore \cite{2364}. Subsequent studies have confirmed the association of HLA A2-B46 haplotype with NPC in many different countries \cite{382,1089,1223,1565,1567,2365,2366}. In addition, increased risk of NPC has been found in individuals harbouring HLA B17 in southern China \cite{1567,2874}, Singapore \cite{382} and Malaysia \cite{381}. Haplotypes A2-B17 \cite{2895}, A2-B38 \cite{1565}, and A2-B16 \cite{2827} are also shown to be associated with increased risk of NPC. These findings are further supported by linkage or association studies that provide evidence for a NPC predisposing gene in close linkage with the HLA locus \cite{1565,1567,1947}. There is a negative association with NPC risk for alleles A11, B13.
On the other hand, an association between HLA and NPC has not been found in NPC patients in Alaskan Eskimos, Indians (1427), North Africans (208,1071,1762) and Caucasians (313,314,1769).

GSTM1 and CYP2E1
Polymorphism of some metabolic enzyme genes has been reported to influence susceptibility to NPC. Glutathione S-transferase M1 (GSTM1) detoxifies benzopyrene and other carcinogens in tobacco smoke. Studies on association between absence of GSTM1 and increased risk for NPC are conflicting (415,1857).

The cytochrome P450 2E1 (CYP2E1) enzyme catalyzes the metabolic activation of low-molecular weight nitrosamines such as those detected in NPC-associated foods. A variant form of the gene that is detectable by Rsa I digestion (the c2 allele) has been shown to exhibit higher enzymatic activity. If dietary nitrosamines from preserved foods indeed play a direct role in NPC development, exposed individuals possessing different CYP2E1 genotypes may experience differential levels of NPC risk. In a population-based case-control study from Taiwan, individuals possessing the c2/c2 genotype experienced a 2.6-fold risk relative to those with one or two copies of the wild-type allele (1088). This finding adds to the evidence that nitrosamine-containing preserved foods are important nasopharyngeal carcinogens.

PIGR and TCR
The mechanism of the entry of EBV into the nasopharyngeal epithelium has not yet been conclusively elucidated, but a receptor on nasopharyngeal epithelial cells, namely polymeric immunoglobulin receptor (PIGR), has been proposed to be involved. It has been reported that one single nucleotide polymorphism (SNP) (1739C->T), located on exon 7 of the gene, is significantly associated with increased risk of NPC (1102). The SNP is a missense mutation altering the amino acid alanine to valine, and it occurs adjacent to the endoproteolytic cleavage site of the PIGR extracellular domain. It is hypothesized that the homozygous 1739C state may result in the altered efficiency to release IgA-EBV complex and hence increase the possibility of nasopharyngeal epithelial cells to be infected by EBV.

Since T cell receptor (TCR) may mediate immunity against EBV infection, effort has been made to test the association between polymorphism of TCR and NPC. A study has shown NPC susceptibility to be associated dominantly with a 20-kb fragment (P=0.02, RR=8.2) (412).

Chromosome 4p
With construction of a human genome genetic linkage map and development of methods and algorithms, linkage analysis has become the robust tool to connect phenotypes with genotypes. A whole genome scan for linkage with NPC has been performed on 32 high risk NPC Cantonese pedigrees (729). The marker D4S405 on chromosome 4p12–p15 yielded a maximum multipoint lod score of 3.06, a heterogeneity adjusted lod score (HLOD) of 3.21, and a non-parametric linkage score of 2.75 (P=0.005),...
suggesting that a disease susceptibility gene may be linked with D4S405. Fine mapping and haplotype analysis has localized the NPC predisposing gene to chromosome region 4p15.1–q12.

In summary, NPC development may involve susceptibility gene mutations (major genes) and gene polymorphisms (minor-effect genes). In some familial cases, inherited genetic alterations (major gene transmission) could be the first “hit”, and EBV infection may contribute to the second “hit”. Therefore, familial cases usually have a much younger age of onset. However, some other familial cases and probably most sporadic cases may get the first “hit” from both inherited genetic alterations (minor-effect genes, such as HLA, CYP2E1) and somatic genetic changes. In the high prevalence areas like south China, most of the NPC cases belong to this type and they usually have older age of onset than the familial cases with a major gene transmission [2890].

**Prognosis and predictive factors**

The mainstay of treatment for NPC is radiation therapy. Progressive improvement of treatment results for NPC has been reported both from endemic and non-endemic areas. The average 5-year survival steadily increased from around 35% for patients treated in the 1940–60 (1755,1785,2096), to 55-60% in the 1970–90s [1061,1592,2096,2693]. A recent study of patients without distant metastases treated during 1996–2000 showed that a 5-year disease-specific survival (DSS) of 81% and overall survival 75% can now be achieved [1448]. The presenting stage is the most important prognostic factor. A recent study using the 2002 TNM staging System shows that the 5-year DSS for Stage I is 98%, Stage II A-B 95%, Stage III 86%, and Stage IVA-B 73%. In addition, tumour volume may prove to be useful for predicting local control (447,2520).

The importance of host factors varies among different series. In general, younger age (less than 40 years) and female gender are associated with better prognosis [2574]. Interestingly, the influence of age is mainly on local failure, while that of gender is on distant failure. The values of EBV antibodies for predicting prognosis and monitoring disease progression are rather limited [567, 2855]. High baseline titers often persist even in patients in remission. Although rising titers to VCA, EA and Zta are associated with disease relapse, the elevation is often not consistently high or early enough for disease monitoring.

Circulating plasma/serum EBV DNA is a more promising prognostic factor. High plasma/serum EBV DNA titers are associated with advanced stages [1549]; both pre-treatment and post-treatment titers correlate significantly with survival [362,1547]. The titer is substantially elevated in patients with active disease (especially distant metastasis), and drops to very low titers upon remission [362,1548,1882,2346]. Aneuploid status or high pre-treatment tumour proliferative fractions, as determined by DNA flow cytometry, correlate significantly with poor survival [2854]. Other biological factors that might have prognostic significance include tumour angiogenesis, c-erbB2 [2209], p53 [1658], nm23-H1 [965], interleukin-10 [828], and vascular endothelial growth factor [2095].

Treatment factors affect the ultimate survival. Significant improvements in treatment results have been attributed to refinement of radiotherapy technique [1454], dose escalation [2561,2576], accelerated fractionation [1447,2717], addition of chemotherapy (concurrent + sequential) [29,1515,2180], and combination of new strategies [2803].
Nasopharyngeal papillary adenocarcinoma and salivary gland-type carcinomas

**Nasopharyngeal papillary adenocarcinoma**

**Definition**
A low-grade adenocarcinoma characterized by an exophytic growth comprising papillary fronds and glandular structures.

**ICD-O code**
8260/3

**Epidemiology**
Nasopharyngeal papillary adenocarcinoma is extremely rare (1902,2672,2770). The reported age range is 11-64 years (median 37 years) (1902,2672,2770). Gender distribution is nearly equal (1902,2672,2770).

**Localization**
The tumour most commonly involves the roof, lateral wall and posterior wall of the nasopharynx (2770).

**Clinical features**
Nasal obstruction is the main presenting symptom. The diagnosis can be readily confirmed by endoscopic biopsy.

**Macroscopy**
The tumours are soft or gritty and exophytic, with a papillary, polypoid, or cauliflower appearance. The tumours measure up to 4 cm (median size 2.5 cm) (2770).

**Tumour spread and staging**
The tumours usually remain confined within the nasopharynx except one reported case with extensive local invasion (1902).

**Histopathology**
Nasopharyngeal papillary adenocarcinoma arises from the surface epithelium (2770). The tumour comprises arborizing delicate papillary fronds and crowded glands. The lining columnar or pseud stratified cells have bland, round to oval nuclei and tiny nucleoli. Mitotic figures are rare; necrosis may be focally identified. Psammoma bodies may be found in some cases. The tumours are unencapsulated and infiltrate into the surrounding stroma. Diastase-resistant, periodic acid-Schiff intracytoplasmic positive material is present; intraluminal and intracytoplasmic mucicarmine staining may be focally identified. Immunohistochemical staining shows positive reactivity for epithelial markers (i.e., cytokeratin, epithelial membrane antigen), but there is no reactivity for thyroglobulin and S-100 protein. There is no association with Epstein-Barr virus.

**Genetic susceptibility**
A case has been reported in a patient with Turner syndrome (1902).

**Prognosis and predictive factors**
This is an indolent low-grade malignant neoplasm with no metastatic potential. It has an excellent prognosis if a complete excision can be achieved (2770).

**Salivary gland-type carcinomas**
These are very rare in the nasopharynx (2448). Men are affected nearly three times more frequently than women (1389). The age range is from 15-74 years with a median age of 50 years. The most frequent types are, in order of frequency, adenoid cystic carcinoma, mucoepidermoid carcinoma and adenocarcinoma not otherwise specified (2273). Carcinomas at this site frequently present at an advanced stage and often with invasion of the base of the skull, intracranial extension and involvement of the cranial nerves.

**Adenoid cystic carcinomas** (336,1449,2273,2718) are typically insidious in onset, and symptoms may include middle ear effusion, epistaxis, diplopia and symptoms due to cranial nerve palsy (such as pain, paraesthesia, anaesthesia). The microscopic features are similar to those of adenoid cystic carcinoma elsewhere. The 5 and 10 year survival are 78% and 49.5% respectively, and 35% of patients will develop metastasis to bone or lung (2718).

**Mucoepidermoid carcinomas** (1321, 1389,2273) are microscopically similar to those in other sites but rarely psammoma bodies can be seen.

Other rare salivary gland-type carcinomas of the nasopharynx include epithelial-myoepithelial carcinoma (1174), myoepithelial carcinoma (1899), acinic cell carcinoma (1890) and polymorphous low-grade adenocarcinoma (1469,2763).

![Fig. 2.23 A Nasopharyngeal papillary adenocarcinoma. The tumour comprises complex papillae and glands lined by columnar to spindly cells with bland-looking nuclei. B Mucoepidermoid carcinoma of nasopharynx. There are solid islands of squamoid cells and clear cells.](image-url)
Benign epithelial tumours

Hairy polyp

Definition
A presumed developmental anomaly that clinically manifests as a polyp covered by skin with hair and sebaceous glands.

Synonyms
Teratoid polyp, dermoid polyp.

Epidemiology
Hairy polyps occur in newborns and older infants. There is an unexplained female predominance (female to male ratio 6:1) [1296].

Localization
The lateral wall of the nasopharynx, the superior nasopharyngeal aspect of the soft palate, and the tonsils are classic locations for hairy polyps [1296]. They also have been infrequently reported in the middle ear [1310]. No cases have been reported in the sinonasal tract.

Clinical features
The usual clinical presentation is a pedunculated mass in the oropharynx or nasopharynx of a newborn or older infant. In the middle ear, the hairy polyps cause recurrent otitis media that is not responsive to the usual treatment. There are individual reports of associated cleft palate or multiple congenital anomalies, including the Dandy-Walker malformation [88].

Histopathology
The surface of the polyp is composed of skin with a delicate hyperkeratotic layer and pilosebaceous units. The core is formed by fibroadipose tissue often with foci of cartilage, muscle and bone. Hairy polyps are distinguished from teratomas by a lack of endodermal components.

Histogenesis
It has been argued that these polyps are congenital anomalies of the first branchial cleft or choristomas [1045].

Prognosis and predictive factors
Complete surgical excision is curative.

Schneiderian-type papilloma

Definition
A benign tumour that arises from the surface epithelium of the nasopharynx and resembles Schneiderian papillomas of the sinonasal tract [81,1924].

ICD-O code
8121/0

Synonyms
Fungiform papilloma, inverted papilloma, transitional papilloma, nasopharyngeal papilloma.

Epidemiology
Schneiderian-type papillomas of the nasopharynx are distinctly uncommon. They occur in older individuals (mean 62 years, range 45-79) and are 2-3 times more common in males [2499].

Etiology
Anatomically, the posterior choanae represent the boundary between the ectodermally-derived (Schneiderian membrane) and endodermally-derived respiratory mucosa that, respectively, line the sinonasal tract and nasopharynx. It is thought that aberrant embryologic displacement of normal Schneiderian mucosa might account for these lesions in the nasopharynx.

Clinical features
Most do not exceed two cm in greatest dimension. They are often incidental findings or, at most, result in nasal airway obstruction. The more common Schneiderian papilloma of the sinonasal tract with secondary involvement of the nasopharynx must be excluded before accepting the lesion as primary in the nasopharynx.

Histopathology
They are similar to those occurring in the nasal cavity and paranasal sinuses (see section on sinonasal papillomas). Most are of the inverted type (ICD-O code 8121/1).

Prognosis and predictive factors
Transnasal or transoral excision is the treatment of choice. Local recurrences are not uncommon. At least one case has been associated with a separate focus of nasopharyngeal squamous cell carcinoma [2499].

Squamous papilloma

Squamous papillomas are uncommon in the nasopharynx, and they are morphologically similar to those found in the larynx. See chapter on ‘Tumours of the hypopharynx, larynx and trachea’.

Ectopic pituitary adenoma

Definition
A benign pituitary gland neoplasm occurring separately from, and without involvement of the sella turcica (i.e., with normal anterior pituitary gland).

Fig. 2.24 Ectopic pituitary adenoma. Ectopic pituitary adenoma of the nasopharynx appearing as a submucosal and unencapsulated cellular tumour; the nasopharyngeal surface epithelium is intact and seen on top.
Tumours of the nasopharynx

ICD-O code 8272/0

Synonyms
Extrasellar pituitary adenoma; extrasellar adenohypophysial tissue; extracranial pituitary adenoma; sphenoidal pituitary adenoma; adenomatous pharyngeal pituitary.

Epidemiology
Ectopic pituitary adenomas of the upper aerodigestive tract are rare, and predominantly occur in adults but have been identified over a wide range of ages, from 16 – 84 years, with a reported mean and median age at presentation of 49 years and 58 years respectively [1425, 2752]. Females are affected more often than men [1425, 2752].

Etiology and pathogenesis
The etiology of ectopic pituitary adenomas is unknown. Extrasellar involvement by a pituitary adenoma can result from downward extension of a sellar-based pituitary tumour or occur as an adenomatous tumour arising from ectopic pituitary tissues. The latter may occur from two sources, including embryologic rests along the course of the cephalic invagination of Rathke’s pouch (infrasellar) or anterior pituitary cells attached to the supradiaphragmatic portion of the pituitary stalk. This discussion will be limited to infrasellar-derived ectopic pituitary adenomas.

Localization
In the upper aerodigestive tract, ectopic pituitary adenoma most commonly occurs in the sphenoid bone and sinus [55, 1425, 1538, 2627] and nasopharynx [417, 488, 2752]. Other sites of occurrence include the nasal cavity [1131, 2129, 2752], ethmoid sinus [2752], and temporal bone [2129].

Clinical features
The clinical presentation of ectopic pituitary adenomas is primarily related to its space-occupying effects, and include airway obstruction, chronic sinusitis, headache, epistaxis, cerebrospinal fluid leakage and visual field defects [237, 417, 1425, 1667, 2627, 2752]. Clinical evidence of hormonally active tumours can be identified in over half of the cases [1425] and include Cushing disease [235, 309, 1261, 1538, 2274, 2396], acromegaly [491, 685, 2725] hyperparathyroidism [1538], hyperthyroidism [488], amenorrhea [1051], and hirsutism [2752]. Radiographic imaging is helpful in localizing the lesion and determining the relationship to the sella turcica [2396]. Of note is the fact that the extent of tumour and erosion of bone do not completely correlate with severity of clinical signs and symptoms [1425]. Furthermore, erosion of the sella turcica does not exclude an ectopic origin [1425].

Immunoprofile
Ectopic pituitary adenomas show strong cytoplasmic immunoreactivity for cytokeratin, synaptophysin, chromogranin, neuron specific enolase, and may stain for a variety of pituitary hormones including adrenocorticotropic hormone (ACTH), prolactin, thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), growth hormone (GH), and luteinizing hormone (LH). Tumours may demonstrate immunoreactivity with only a single pituitary hormone (monohormonal pituitary adenoma), multiple hormones (plurihormonal pituitary adenoma) or no pituitary hormone (null cell pituitary adenoma).

Electron microscopy
Intracytoplasmic secretory granules of varying numbers can be identified.

Prognosis and predictive factors
Surgical resection is the treatment of choice for smaller, accessible tumours [1425]; complete surgical eradication is usually curative [2752]. However, complete surgical resection may not be possible for larger, invasive tumours. When resection is incomplete or cannot be accomplished due to size and extent of

Fig. 2.25 Ectopic pituitary adenoma. A Organoid growth pattern. B Growth in the form of ribbons. C Scattered mitotic figures are seen in a tumour that otherwise shows uniform neoplastic cells with minimal pleomorphism and dispersed chromatin. D Extension into bone may be present.

ICD-O code 8272/0

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Epidemiology
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Prognosis and predictive factors
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Benign epithelial tumours

the tumour, postoperative radiotherapy is indicated [55,1425,2627,2666]. Dopamine agonist drugs (e.g., bromocriptine) have been effective in reducing the size (not permanently) in prolactin-secreting adenomas and the mitotic rate of other pituitary adenomas [1425]. Somatostatin analog treatment with octreotide has been shown to reduce tumour size and may, in the proper setting of a pituitary adenoma with high somatostatin receptor content, be administered in lieu of surgery in patients whose tumours are too large to be adequately resected [2093]. A rare example of malignant transformation of an ectopic pituitary adenoma has been reported [1131].

**Salivary gland anlage tumour**

**Definition**
A benign tumour with mixed epithelial and mesenchymal elements, recapitulating the early stages in the embryology of the salivary gland between the 4th and 8th weeks of development.

**Synonym**
Congenital pleomorphic adenoma

**Epidemiology**
Fewer than 20 cases have been reported in the literature [229,233,296,572,1007,1168,1720,1763]. Most patients are diagnosed in the immediate neonatal period or by the age of 6-weeks. Males exceed females by a 13:3 ratio.

**Clinical features**
Almost all patients present with respiratory and feeding difficulties. Bleeding has rarely been reported. Clinical examination reveals a midline pedunculated erythematous polyp [229].

**Macroscopy**
A firm, smooth to lobulated mass measuring between 1.3 and 3 cm in greatest dimension is the typical gross appearance. The surface is usually glistening. The remnants of a stalk may or may not be apparent. A vague nodularity is appreciated on its greyish-tan to reddish cut surface. Cysts and interstitial haemorrhage may occur.

**Histopathology**
A non-keratinizing squamous mucosa overlies multiple contiguous cellular nodules. The nodules are separated by fibrous and myxoid stroma containing duct-like structures and nests of solid or cystic squamous epithelium. In areas, the duct-like structures are connected to the surface epithelium. The epithelial units within the internodular stroma blend into the cellular nodules, which are comprised of fusiform cells forming short fascicles or trabecular structures, interspersed with poorly formed tubules with or without lumens. The fusiform cells have eosinophilic cytoplasm with indistinct cell borders. The nuclei are bland and uniform, and mitotic activity is quite low. The interstitial can show haemorrhage, and rarely bone formation [296].

**Immunoprofile**
The cellular nodules display a mixed pattern of reactivity for vimentin, cytokeratin and actin and are generally non-reactive for S-100 protein and glial fibrillary acidic protein. Nascent tubules and ducts within the stromal nodules show a luminal pattern of positivity for epithelial membrane antigen. The differentiated epithelial components are reactive for pancytokeratin and cytokeratin 7; epithelial membrane antigen positivity is restricted to the tubular structures. Salivary gland amylase is expressed consistently.

**Prognosis and predictive factors**
Complete excision is curative in virtually all cases.

**Craniopharyngioma**

**ICD-O code**
9350/1

Exceptionally, craniopharyngioma can arise in the nasopharynx or involves the nasopharynx through downward invasion from a suprasellar location. The morphological features are identical to the suprasellar counterpart [316,1609,1612,2062,2083,2525].

Fig. 2.26 Salivary gland anlage tumour. **A** The cellular tumour nodules communicate in the form of glandular structures with the surface epithelium. **B** There is merging of spindle cells into abortive tubules.
Tumours of the nasopharynx

The spectrum and clinicopathological features of nasopharyngeal soft tissue tumours are similar to those of other sites in the upper aerodigestive tract, except for angiofibroma, which typically presents in the nasopharynx.

Definition
A benign, highly cellular and richly vascularized mesenchymal neoplasm that involves the nasopharynx in males.

ICD-O code
9160/0

Synonyms
Juvenile nasopharyngeal angiofibroma; angiofibroma; fibroangioma; fibroma

Epidemiology
Nasopharyngeal angiofibroma represents <1% of all nasopharyngeal tumours [190,267,512,1434,1503,1861,2654]. Boys and adolescent to young men are almost exclusively affected, with a peak in the 2nd decade of life. If a female is affected, testicular feminisation has to be excluded. Fair-skinned and red-haired males are more commonly affected.

Etiology
There is no known etiology although testosterone-dependent puberty-induced tumour growth may be ameliorated by blockade of estrogen or progesterone receptors within the tumour [717, 1861].

Localization
This tumour arises in the posterolateral nasal wall or the nasopharynx. There is often extensive infiltration into the surrounding tissues [190,267,512,1434,1503,1861,2654].

Clinical features
Patients usually present with nasal obstruction and/or recurrent, spontaneous epistaxis, nasal discharge, facial deformity (including proptosis), diplopia, exophthalmos, sinusitis, otitis media, tinnitus, rhinolalia, deafness, headaches, dyspnoea, and rarely, anosmia or pain [190,267,512,1434,1503,1861,2654].

Imaging
Routine radiographs reveal a soft tissue density in the nasopharynx in conjunction with anterior bowing of the posterior wall of the maxillary sinus as well as distortion and posterior displacement of the pterygoid plates (Holman-Miller sign). Bony margins may be eroded, but are distinct. Computed tomography allows for accurate determination of the extent of the disease as well as the best possible surgical approach. Angiography allows for identification of the feeding vessel(s) and pre-surgical embolization. Tumour blush on angiogram is characteristic [1434,2654]. Due precautions have to be taken in obtaining biopsies from the lesion because of the risk of life-threatening bleeding.

Macroscopy
The tumours range in size up to 22 cm, with a mean of about 4 cm. They are polyloid with a rounded or multinodular contour, with red, grey-tan cut surfaces [190,267,512,1434,1503,1861,2654].

Tumour spread and staging
The tumour expands in all directions from the nasopharyngeal region, following the path of least resistance: anteriorly into the nasal cavity and maxillary sinuses, laterally into the pterygoid region, temporal fossa and infratemporal fossa (resulting in a cheek or intraoral buccal mass); superiorly into orbit and middle cranial fossa; or to the opposite side. This type of extensive involvement is seen in up to 30% of cases, explaining the potential aggressive nature of this benign neoplasm [190,267,512,1434,1503,1861,2654]. A number of staging systems have been suggested, [384,767,2111,2309] with a modification based on size and location used most frequently.

Histopathology
There is a vascular proliferation set in a fibrous stroma. The vessels are mostly thin-walled, slit-like (“staghorn”) or dilated with calibres ranging from capillary size to large, patulous vessels. The mus-
cicular layer can be absent, focal and pad-like, or circumferential. Endothelial cells may be plump but are usually attenuated. The fibrous stroma consists of plump spindle, round, angular, or stellate shaped cells and a varying amount of fine and coarse collagen fibres; background myxoid degeneration is common (especially in embolized specimens). The nuclei of the stromal cells are generally cytologically bland, but they may be multinucleated or show some degree of pleomorphism in the more cellular areas. Mast cells may be seen, but other inflammatory elements are usually absent (except when there is surface ulceration) (190,267,512,1434,1503,1861,2654). Long-standing lesions show increased fibrosis and diminished vasculature. Treatment with hormones results in increased collagenization of the stroma with fewer, but thicker-walled vessels. In specimens excised after embolization, the tumour often shows areas of infarction, and emboli can be seen in some blood vessels. Sarcomatous transformation is an exceedingly uncommon event, usually following radiation therapy (2431).

**Immunoprofile**
Occasional elastic fibres can be identified in the vessel walls, although they are generally absent in the stroma. The vessel wall cells are immunoreactive with vimentin and smooth muscle actin (SMA), whereas the stromal cells are immunoreactive with vimentin only, except in areas of increased fibrosis, where focal SMA may be identified. Desmin may be focally immunoreactive in larger vessels at the periphery of the tumour. Stromal and endothelial cells are variably reactive with androgen and estrogen/progesterone receptors. Factor VIII R-Ag, CD34 and CD31 highlight the endothelium, but not the stromal cells. The stromal cells are negative for S-100 protein (190,1503). Platelet derived growth factor B and insulin-like growth factor type II are both over-expressed (1812).

**Electron microscopy**
Ultrastructurally, the stromal cells contain lobulated nuclei, intranuclear inclusions, variable amounts of rough endoplasmic reticulum and thin filaments, hemidesmosomes, focal basal lamina and prominent pinocytotic vesicles, suggesting a hybrid mesenchymal cell (myofibroblast) (2565).

**Differential diagnosis**
The differential diagnosis includes lobular capillary haemangioma (pyogenic granuloma), nasal inflammatory polyps with fibrosis or atypical stromal cells, antrochoanal polyps, and peripheral nerve sheath tumour.

**Histogenesis**
It has been proposed that the tumour arises from a fibrovascular nidus that lies dormant until puberty, when testosterone stimulates tumour growth (1861).

**Genetic susceptibility**
There are isolated reports of an association with familial adenomatous polyposis (757,885).

**Prognosis and predictive factors**
This benign tumour is characterized by local aggressive growth, with recurrences in about 20% of patients (>50% in older series), most commonly intracranially, and usually within the first 2 years after diagnosis. Patients may be managed with selective angiographic embolization or hormonal therapy prior to definitive surgical resection. Radiation therapy has been successfully implemented to manage large, intracranial, or recurrent tumours, but surgery is still the therapy of choice (190,267,512,1434,1503,1861,2654).

### Table 2.05 System for staging nasopharyngeal angiofibroma (384,767,2309).

<table>
<thead>
<tr>
<th>Stage Description</th>
<th>Stage I</th>
<th>Tumour limited to the nasopharynx with no bone destruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>Tumour invading the nasal cavity, maxillary, ethmoid, or sphenoid sinuses with no bone destruction</td>
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<tr>
<td>Stage III</td>
<td>Tumour invading the pterygo-palatine fossa, infra-temporal fossa, orbit or parasellar region</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Tumour with massive invasion of the cranial cavity, cavernous sinus, optic chiasm, or pituitary fossa</td>
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</tbody>
</table>

**Fig. 2.28 Nasopharyngeal angiofibroma.**
A Thin walled vessels surrounded by dense, “keloid-like” collagen. Stellate fibroblasts are noted. B Smooth muscle-walled vessels, patulous vessels and capillaries are all surrounded by the characteristic collagenized stroma. C A large thin-walled vessel is associated with fibrous connective tissue, inflammatory cells and stellate fibroblasts. D Heavily collagenized stroma demonstrates only a few stellate fibroblastic cells.
Hodgkin lymphoma

Hodgkin lymphoma only rarely shows primary involvement of the nasopharynx \([1274,1602,1756,1763,1922]\). The patients usually present with nasal obstruction or otitis media, and frequently have low stage (stage I/II) disease. Most of the tumours are of mixed cellularity and nodular sclerosis subtypes. The majority of cases involving the nasopharynx are associated with Epstein-Barr virus \([1274,1756]\). Please refer to ‘Hodgkin lymphoma’ in ‘WHO classification of tumours: Tumours of haematopoietic and lymphoid tissues’ for details.

Non-Hodgkin lymphoma

Definition

Primary non-Hodgkin lymphoma (NHL) of the nasopharynx is defined as a lymphoid cell neoplasm in which the bulk of disease occurs in this site.

Epidemiology

Nasopharyngeal NHL accounts for 2.5% of all extranodal NHLs \([809]\). Most cases have been reported in the literature in combination with either NHL of the nasal cavity or NHL of the Waldeyer ring, rendering it difficult to extract the specific details on nasopharyngeal NHL \([420,1704,2250,2849]\). In some cases, there is simultaneous involvement of both the nasopharynx and nasal cavity, precluding determination of the site of origin of the NHL. In the West, nearly all cases of nasopharyngeal NHL are of B-cell lineage (most commonly diffuse large B-cell lymphoma, DLBCL) \([1704]\). The situation is different in Asia, where B-cell lymphomas account for only 50–60% of cases \([420,2849]\), due to a higher frequency of extranodal NK/T cell lymphomas and peripheral T-cell lymphomas. Most patients with nasopharyngeal NHL are adults. Patients with extranodal NK/T cell lymphoma of nasal-type have a male to female ratio of 3:1, and a median age of 53 years \([420]\). Patients with B-cell lymphomas are generally one decade older (median age of 63 years), and the male to female ratio is only 1.2:1 \([420]\). Burkitt lymphoma occurs more frequently in children and young adults \([2826]\).

Etiology

The etiology is unknown, except that extranodal NK/T cell lymphoma of nasal-type is strongly associated with Epstein-Barr virus (EBV) (>95%) irrespective of the ethnic background of the patients \([1195]\). The association of nasopharyngeal DLBCL with EBV is weak \([376]\).

Clinical features

The patients present with nasal obstruction, epistaxis, hearing impairment, dysphagia, headache or neck mass, similar to the presenting symptoms of nasopharyngeal carcinoma. A small proportion of patients have concurrent cervical lymphadenopathy, a feature seen more frequently in DLBCL than extranodal NK/T cell lymphoma.

Tumour spread and staging

The majority (80%) of patients have localized disease (Stage IE/IIE) at presentation \([420,1500,1505,1550]\). Extranodal NK/T cell lymphoma tends to disseminate to various sites, such as skin, gastrointestinal tract, liver, lymph node and testis, during the course of disease. There is a propensity for DLBCL to spread to the cervical lymph nodes \([420]\).

Histopathology

DLBCL and extranodal NK/T cell lymphoma of nasal-type occurring in the nasopharynx are morphologically and

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Fig. 2.29 Primary non-Hodgkin lymphoma of the nasopharynx. A Diffuse large B-cell lymphoma. A diffuse infiltrate of large lymphoid cells with high nuclear-cytoplasmic ratio and mitotic figures (left). There is strong CD20 immunoreactivity, confirming the B-cell immunophenotype (right). B Extranodal NK/T-cell lymphoma. The neoplastic cells infiltrate the vascular wall (left), and show immunoreactivity for CD3ε (right).

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A.C.L. Chan
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immunophenotypically similar to those seen in the nasal cavity. Other types of NHL, for example, Burkitt lymphoma, follicular lymphoma, mantle cell lymphoma, extranodal marginal zone B-cell lymphoma of MALT type, and peripheral T-cell lymphoma unspecified may also affect the nasopharynx, but at a much lower frequency (420,1704,2849). Please refer to the sections of ‘non-Hodgkin lymphoma’ in ‘Tumours of the nasal cavity and paranasal sinuses’ and ‘Tumours of the oral cavity and oropharynx’ for details.

**Differential diagnosis**

Distinction between nasopharyngeal carcinoma and DLBCL can be difficult at times because the carcinoma cells in nasopharyngeal carcinoma can appear discohesive due to submergence in a dense lymphoplasmatc infiltrate, while DLBCL can sometimes form tight cell clusters. Positive immunostaining for cytokeratin would support the former diagnosis, and expression of lymphoid markers (including CD20) would support the latter. Infectious mononucleosis involving the nasopharynx can also mimic DLBCL (2547), but can be suspected or recognized by the young age of the patient, presence of a range of large cells with apparent maturation to plasmablasts and plasma cells, lack of frank cytologic atypia, and polyclonal immunoglobulin staining in the large cells. Extranodal NK/T cell lymphoma with small cell predominance can be difficult to recognize as being a malignant neoplasm. Histologic features suggestive of the diagnosis include extensive effacement of architecture, marked coagulative necrosis, angiocentric growth, and wide separation of the mucosal glands. The diagnosis is supported by the demonstration of sheets of CD56+, CD3ε+, EBER+ cells. In the rare case of herpes simplex infection involving the nasopharynx, there can be a dense lymphoid infiltrate with extensive CD56 expression, causing confusion with extranodal NK/T cell lymphoma. In contrast to NK/T cell lymphoma, these CD56+ cells express CD4 and CD5, and there is no association with EBV. The diagnosis is confirmed by identifying the herpes simplex virus-infected multinucleated giant cells with ground glass nuclei with or without nuclear inclusions, which can be further confirmed by immunostaining for herpes simplex virus (2523).

**Prognosis and predictive factors**

Radiotherapy is the treatment of choice for extranodal NK/T cell lymphoma, often in combination with additional treatment modalities (421). Chemotherapy and/or radiotherapy is usually given for patients with DLBCL. The overall survival rate for extranodal NK/T cell lymphoma of nasal-type is only 30-50% (421,422,1312,1838). Factors associated with worse outcome include: advanced stage, poor performance status, B symptoms and bulky disease (422). B-cell lymphomas show a slightly more favourable outcome (420).

**Follicular dendritic cell sarcoma / tumour**

Follicular dendritic cell sarcoma/tumour is a rare tumour showing morphologic, immunophenotypic and ultrastructural features of follicular dendritic cells. Primary involvement of the nasopharynx is rare (189,359), and may arise from an underlying hyaline-vascular Castleman disease (359). Please refer to the section of ‘Follicular dendritic cell sarcoma/tumour’ in ‘Tumours of the oral cavity and oropharynx’ for details.

**Extramedullary plasmacytoma**

ICD-O code 9734/3

Approximately 22% of head and neck extramedullary plasmacytomas occur in the nasopharynx, which is the second most common site after the sinonasal tract. See corresponding section in ‘Tumours of the nasal cavity and paranasal sinuses’ for details.

**Other haematolymphoid tumours**

Castleman disease, extramedullary myeloid sarcoma and Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) can occasionally affect the nasopharynx (359,2631,2637,2760). Please refer to Chapter 1 on ‘Tumours of the nasal cavity and paranasal sinuses’ for details.
Tumours of bone and cartilage

The spectrum and clinicopathological features of nasopharyngeal tumours of bone and cartilage are similar to those of other sites in the upper aerodigestive tract, except for chordoma, which typically presents in the nasopharynx.

**Chordoma**

**Definition**
A low-grade malignant tumour that recapitulates the notochord.

**ICD-O code** 9370/3

**Epidemiology**
Chordomas account for approximately 4% of malignant bone tumours [2655]. About a third involve the base of the skull, and a small proportion may involve the nasopharynx and/or paranasal sinuses. There is a male predilection. The patients are predominantly adults, but children can also be affected.

**Clinical features**
Patients usually present with non-specific symptoms, such as headache, nasal obstruction, and symptoms related to cranial nerve involvement. Rarely, they present with nasal polyps [325]. Imaging studies show lytic destruction of the basisphenoid centred in the clivus. The tumour frequently extends into the middle cranial fossa and nasopharynx. Calcification is occasionally seen.

**Histopathology**
Chordomas typically show a lobulated growth pattern. Polygonal or ovoid tumour cells are arranged in cords, lobules and sheets in a myxoid background. The nuclei are typically round and uniform, but may exhibit considerable pleomorphism. The cytoplasm is abundant and eosinophilic, and at times clear. Vacuolated cells (physaliferous cells) are present to a variable degree. The tumour cells are immunoreactive for cytokeratins, epithelial membrane antigen and S100 protein.

The main differential diagnoses are epithelial neoplasms (such as mucinous carcinoma, salivary gland tumours, poorly differentiated carcinoma) and chondrosarcoma. The lobulation, physaliferous cells and diffuse strong S100 protein immunoreactivity distinguish chordoma from carcinoma. Chondrosarcoma is negative for cytokeratin.

**Prognosis and predictive factors**
Chordoma is a low-grade tumour and distant metastases are rare. Chordomas involving the nasopharynx are often treated by radiation therapy because complete surgical resection is practically impossible because of the anatomy [709].

Secondary tumours

**Definition**
Tumours that metastasize to the nasopharynx from other primary malignancies. Direct invasion from tumours of adjacent sites, leukemias and lymphomas are excluded.

**Epidemiology**
Metastases to the nasopharynx are extremely rare [1685]. The majority of patients are over the age of 50 years. Reported primary tumours and tumour sites include malignant melanoma (cutaneous) 9 cases, kidney (3 renal cell, 1 Wilms), lung (4 cases), and one case each of breast, colon and cervical cancer (1685).

**Clinical features**
Patients may be asymptomatic or present with nasal obstruction, epistaxis, unilateral serous otitis media secondary to blockage of the eustachian tube, or otalgia. Large bulky metastases can extend into the nasal cavity or deform the soft palate. A long disease-free interval between treatment of the primary tumour and the appearance of metastasis in the nasopharynx may confuse the diagnosis, raising the possibility of a new primary neoplasm of the nasopharynx. However, this is not uncommon for malignant melanoma and renal cell carcinoma.

**Pathogenesis**
Most metastases to the nasopharynx are haematogenous, possibly arising in some instances through Batson’s paravertebral venous plexus.

**Prognosis and predictive factors**
Metastasis is an ominous sign associated with a poor prognosis.