Tumours of the Nasal Cavity and Paranasal Sinuses

Although the nasal cavity and paranasal sinuses occupy a relatively small anatomical space, they are the site of origin of some of the more complex, histologically diverse group of tumours in the entire human body. These include neoplasms derived from mucosal epithelium, seromucinous glands, soft tissues, bone, cartilage, neural/neuroectodermal tissue, haematolymphoid cells and the odontogenic apparatus. Many of the tumours are similar to those found elsewhere in the body but a few, such as the olfactory neuroblastoma, are unique to this site.
# WHO histological classification of tumours of the nasal cavity and paranasal sinuses

<table>
<thead>
<tr>
<th>Malignant epithelial tumours</th>
<th>Benign tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>Myxoma</td>
</tr>
<tr>
<td>Verrucous carcinoma</td>
<td>Leiomyma</td>
</tr>
<tr>
<td>Papillary squamous cell carcinoma</td>
<td>Haemangioma</td>
</tr>
<tr>
<td>Basaloid squamous cell carcinoma</td>
<td>Schwannoma</td>
</tr>
<tr>
<td>Spindle cell carcinoma</td>
<td>Neurofibroma</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>Meningioma</td>
</tr>
<tr>
<td>Acantholytic squamous cell carcinoma</td>
<td>9840/0</td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma</td>
<td></td>
</tr>
<tr>
<td>Sinonasal undifferentiated carcinoma</td>
<td>8890/0</td>
</tr>
</tbody>
</table>

| Adenocarcinoma               |                |
| Intestinal-type adenocarcinoma | 8144/3        |
| Non-intestinal-type adenocarcinoma | 8140/3      |

| Salivary gland-type carcinomas |                |
| Adenoid cystic carcinoma      | 8200/3         |
| Acinic cell carcinoma         | 8550/3         |
| Mucoepidermoid carcinoma      | 8430/3         |
| Epithelial-myoepithelial carcinoma | 8562/3  |
| Clear cell carcinoma N.O.S.   | 8310/3         |
| Myoepithelial carcinoma       | 8982/3         |
| Carcinoma ex pleomorphic adenoma | 8941/3    |
| Polymorphous low-grade adenocarcinoma | 8925/3|

| Neuroendocrine tumours        |                |
| Typical carcinoid             | 8240/3         |
| Atypical carcinoid            | 8249/3         |
| Small cell carcinoma, neuroendocrine type | 8041/3    |

| Benign epithelial tumours     |                |
| Sinonasal papillomas          |                |
| Inverted papilloma            | 8121/1         |
| Oncocytic papilloma           | 8121/1         |
| Exophytic papilloma           | 8121/0         |

| Salivary gland-type adenomas  |                |
| Pleomorphic adenoma           | 8940/0         |
| Myoepithelioma                | 8882/0         |
| Oncocytoma                    | 8290/0         |

| Soft tissue tumours           |                |
| Malignant tumours             |                |
| Fibrosarcoma                  | 8810/3         |
| Malignant fibrous histiocytoma | 8830/3        |
| Leiomyosarcoma                | 8890/3         |
| Rhabdomyosarcoma              | 8900/3         |
| Angiosarcoma                  | 9120/3         |
| Malignant peripheral nerve sheath tumour | 9540/3     |

| Borderline and low malignant potential tumours |                |
| Desmoid-type fibromatosis       | 8821/1         |
| Inflammatory myofibroblastic tumour | 8825/1        |
| Gliomangiopericytoma            | 9150/1         |
| (Sinonasal-type haemangiopericytoma) | 9150/1     |
| Extrapleural solitary fibrous tumour | 8815/1       |

| Tumours of bone and cartilage |                |
| Malignant tumours             |                |
| Chondrosarcoma                | 9220/3         |
| Mesenchymal chondrosarcoma    | 9240/3         |
| Osteosarcoma                  | 9180/3         |

| Benign tumours                |                |
| Giant cell lesion             | 9250/1         |

| Haematolymphoid tumours       |                |
| Extramedullary NK/T cell lymphoma | 9719/3     |
| Diffuse large B-cell lymphoma | 9680/3         |
| Extramedullary plasmacytoma   | 9734/3         |
| Extramedullary myeloid sarcoma| 9930/3         |
| Histiocytic sarcoma           | 9755/3         |
| Langerhans cell histiocytosis | 9751/1         |

| Neuroectodermal               |                |
| Ewing sarcoma                 | 9260/3         |
| Primitive neuroectodermal tumour | 9364/3      |
| Olfactory neuroblastoma       | 9522/3         |
| Melanotic neuroectodermal tumour of infancy | 9363/0   |
| Mucosal malignant melanoma    | 8720/3         |

| Germ cell tumours             |                |
| Immature teratoma             | 9080/3         |
| Teratoma with malignant transformation | 9084/3   |
| Sinonasal yolk sac tumour (endodermal sinus tumour) | 9071/3   |
| Sinonasal teratocarcinosarcoma|                |
| Mature teratoma               | 9080/0         |
| Dermoid cyst                  | 9084/0         |

| Secondary tumours             |                |
|                             |                |
# TNM classification of carcinomas of the nasal cavity and paranasal sinuses

<table>
<thead>
<tr>
<th>TNM classification of carcinomas of the nasal cavity and sinuses #</th>
<th>T – Primary tumour</th>
<th>Maxillary sinus</th>
<th>Nasal cavity and ethmoid sinus</th>
<th>N – Regional lymph nodes ³</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
<td>T0</td>
<td>No evidence of primary tumour</td>
<td>NX</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour limited to the antral mucosa with no erosion or destruction of bone</td>
<td>T1</td>
<td>Tumour restricted to one subsite of nasal cavity or ethmoid sinus, with or without bony invasion</td>
<td>N0</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour causing bone erosion or destruction, including extension into hard palate and/or middle nasal meatus, except extension to posterior antral wall of maxillary sinus and pterygoid plates</td>
<td>T2</td>
<td>Tumour involves two subsites in a single site or extends to involve an adjacent site within the nasoethmoidal complex, with or without bony invasion</td>
<td>N1</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades any of the following: bone of posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses</td>
<td>T3</td>
<td>Tumour extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate</td>
<td>N2</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour invades any of the following: anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses</td>
<td>T4a</td>
<td>Tumour invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses</td>
<td>N2a</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve V2, nasopharynx, clivus</td>
<td>T4b</td>
<td>Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, clivus</td>
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<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension</td>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
<td>N3</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis as specified in N2a, 2b, 2c below</td>
<td>Note: Midline nodes are considered ipsilateral nodes.</td>
<td></td>
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</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension</td>
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<td></td>
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<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
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<td></td>
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</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
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<tr>
<td>N3</td>
<td>Metastasis in a lymph node more than 6 cm in greatest dimension</td>
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<td></td>
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<tr>
<td>M – Distant metastasis</td>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
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<td>No distant metastasis</td>
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<tr>
<td>M1</td>
<td>Distant metastasis</td>
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### Stage grouping

<table>
<thead>
<tr>
<th>Stage</th>
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<th>N0</th>
<th>M0</th>
</tr>
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<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1, T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T1, T2, T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N0, N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

³ The regional lymph nodes are the cervical nodes.
Tumours of the nasal cavity and paranasal sinuses: Introduction

**Anatomy**

The nasal cavities are separated in the midline by the nasal septum. Each cavity is wide caudally, and narrow cranially. The roof of the nasal cavity is formed by the thin (0.5 mm) cribriform plate. The floor is the hard palate, formed by the palatine processes of the maxillae and the horizontal portions of the palatine bones. The lateral nasal wall contains the maxillary and ethmoid ostia, plus three or four turbinates. These turbinates are delicate scroll-like projections of bone and vascular soft tissue that become smaller as they ascend in the nasal cavity. They attach to the lateral nasal wall anteriorly, and have a free edge posteriorly. The turbinates are covered with a thick mucous membrane and contain a dense, thick-walled venous plexus. The upper margins of the nasal fossa are bound laterally by the superior nasal turbinate and adjacent lateral nasal wall, and medially by the nasal septum. This region is the olfactory recess and it has a yellowish epithelium, the olfactory mucosa (OM). This mucosa contains bipolar olfactory nerve fibers that cross through the cribiform plate. The terminal axons of the olfactory nerves extend to the free surface of the epithelium, where they expand into knob-like protrusions bearing cilia (olfactory cilia). Bowman’s glands, or olfactory glands, within the lamina propria appear similar to serous minor salivary glands.

The nasal cavity and paranasal sinuses are lined by Schneiderian mucosa, consisting of pseudostratified columnar ciliated epithelium with interspersed goblet cells. The lamina propria within the paranasal sinuses, especially the maxillary antrum, is loose and well vascularized, with seromucinous glands, and can easily become polypoid as a result of edema. The goblet cell component of the mucosal surface and seromucinous glands is variable. In chronic sinusitis, goblet cell hyperplasia can result in a papillary mucosal lesion.

The major portion of the nasal septum is formed by the perpendicular plate of the ethmoid bone posteriorly and the septal cartilage anteriorly. The vomer completes the posteroinferior portion of the septum. The septum is lined by relatively thin, ciliated respiratory mucosa, which may regularly undergo squamous metaplasia. The underlying thin lamina propria, although containing seromucinous glands, is tethered to the septal cartilage, restricting reactive polyp formation.

**The frontal sinus**

These paired sinuses reside between the internal and external cranial tables and drain either via a nasofrontal duct into the frontal recess or more directly into the anterior infundibulum, or less often, into the anterior ethmoid cells, which in turn will open into the infundibulum of the bulla ethmoidalis.

**Ethmoid complex**

This paired complex of sinuses contains 3-18 cells that are grouped as anterior, middle, or posterior, according to the location of their ostia. There is an inverse relationship between the number and size of the cells. Generally, the posterior cells are both larger and fewer than the anterior cells. Each ethmoid labyrinth lies between the orbit and the upper nasal fossa. The left and right groups of ethmoid cells are connected in the midline by the cribiform plate (nasal roof) of the ethmoid bone. The cribiform plate is an important landmark in evaluation of sinonasal tumour stage - violation of the cribiform plate signifies direct extension of the tumour into the anterior cranial fossa. The crista galli is a distinctive pointed bony landmark that extends from the midline of the cribiform plate upward into the floor of the anterior cranial fossa. The perpendicular plate of the ethmoid bone extends downward from the cribiform plate to contribute to the nasal septum. The medial wall of each ethmoid labyrinth is formed by a thin lamella of bone from which arise the middle, superior, and supreme turbinates. The lateral ethmoid wall is formed by the thin lamina papyracea, which separates the ethmoid cells from the orbit. This is yet another important landmark for tumour staging. Tumour violation of the lamina papyracea may necessitate including the orbit and globe with the surgical resection. This area should be sampled in a maxillectomy specimen a) if the globe has not been removed (as the lamina papyracea represents the lateral orbital margin), or b) if orbital exenteration has been performed. The roof of the ethmoid complex is formed by a medial extension of the orbital plate of the frontal bone, which projects to articulate with the cribiform plate. This is often referred to as the fovea ethmoidalis.

**Sphenoid sinus**

The average adult sphenoid sinus measures 20 mm high, 23 mm long, and 17 mm wide. The relationship of the posterior extension of the sphenoid in relation to the sella turcica is variable. The sphenoid sinus septum is usually in the midline, and anteriorly aligned with the nasal septum. However, it can also deviate far to one side creating two unequal sinus cavities. With the exception of the sinus roof, the other sinus walls are of variable thickness depending on the degree of pneumatization. The sphenoid roof is thin, often measuring only 1 mm. (planum sphenoidale), and is vulnerable to perforation during surgery. The sinus roof relates to the floor of the anterior cranial fossa, anteriorly; the optic chiasm and
the sella turcica, posteriorly. The lateral sphenoid wall is related to the orbital apex, the optic canal, the optic nerve, and the cavernous sinus, containing the internal carotid artery. The sinus floor is the roof of the nasopharynx, and the anterior sinus wall is the back of the nasal fossa.

Maxillary sinus
The maxillary sinus lies within the body of the maxillary bone. Behind the orbital rims, each sinus roof/orbital floor slants obliquely upward so that the highest point of the sinus is in the posteromedial portion, lying directly beneath the orbital apex. The medial antral wall is the inferior or lateral wall of the nasal cavity ("party wall"). The curved posterolateral wall separates the sinus from the infratemporal fossa. The anterior sinus wall is the facial surface of the maxilla that is perforated by the infraorbital foramen below the orbital rim. The floor of the sinus is lowest near the second premolar and first molar teeth and usually lies 3-5 mm below the nasal floor. The lower expansion of the antrum is intimately related to dentition. The location of the maxillary sinus ostia, is high on the medial wall. They drain through the ethmoidal infundibulum and then the nasal fossa. This pattern of drainage in the erect position is accomplished by intact ciliary action. The maxillary hiatus is a bony window leading to the interior of the maxillary sinus. The hiatus is normally partially covered by portions of four bones: the perpendicular plate of the palatine bone, posteriorly; the lacrimal bone, anterosuperiorly; the inferior turbinate, inferiorly, and above the turbinate attachment, the uncinate process of the ethmoid bone.

Epidemiology
Carcinomas of the nasal cavity and paranasal sinuses account for 0.2-0.8% of all malignant neoplasms and 3% of those occurring in the head and neck (169,2378). Sixty percent of sinonasal tumours originate in the maxillary sinus, 20-30% in the nasal cavity, 10-15% in the ethmoid sinus, and 1% in the sphenoid and frontal sinuses (2378). Malignant neoplasms of this region may lead to significant morbidity and disfigurement.

The incidence of cancer of the nasal cavity and paranasal sinuses (sinonasal cancer) is low in most populations (<1.5/100,000 in men and <1.0/100,000 in women). Higher rates are recorded in Japan and certain parts of China and India. Squamous cell carcinomas are the commonest. Time trends have shown in most populations a stable incidence or a small decline in recent decades.

Imaging
Modern imaging plays a key role in the evaluation of sinonasal tumours (2423). The anatomy of the lesion can be defined with the exact margins clearly delineated in almost every case. Imaging is a dominant factor in determining surgical approach and is an integral part of radiation therapy planning. Computed tomography (CT) and magnetic resonance imaging (MRI) provide significant information about the texture, the margins, the effect on bone and even the vascularity. In addition, some findings are typical for a particular diagnosis, and although biopsy is still required for ascertaining the nature of the lesion, the imaging appearance may help limit the list of differential diagnoses.

Staging and surgical planning
The spread of a sinonasal tumour intracranially or into the orbit and the relationship of tumour to the optic nerve and carotid artery are important features that can be delineated with imaging. Tumour can invade the orbit through the lamina papyracea or the roof of the maxillary sinus. Even if the bony wall is apparently destroyed, orbital fat may not be invaded (515). A smooth bowing of the soft tissue interface with the orbital fat

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suggests that the lesion is contained by periorbital fascia. Infiltration or irregularity of this margin suggests extension into the fat or true orbital invasion. The thin line of fat between the medial rectus muscle and the lamina papyracea is a key landmark in the evaluation of orbital extension of ethmoid neoplasms. The key landmarks for the assessment of intracranial extension of tumour are the roof of the ethmoid, the cribriform plate and the crista galli. Elevation or frank invasion of the dura may be evaluated using MRI.

A tumour in the maxillary sinus region may extend posteriorly and laterally through the bony wall into the pterygopalatine fossa and the infratemporal fossa. Tumour can invade the pterygopalatine fossa area either by direct extension or by following the nerves. From there, perineural extension of tumour in the foramen rotundum and Vidian canal may result in intracranial spread (516).

Radiographic signs
Bone changes can give an indication of the aggressiveness of a tumour (2038). In general, slowly growing lesions, such as Schneiderian papillomas, appear to push bone as they slowly remodel the osseous structure. More aggressive lesions, such as squamous cell carcinoma, can aggressively destroy bony walls leaving only a few remaining fragments (2425). Occasionally, however, malignant lesions can cause bowing rather than infiltrating destruction of bone (2424). The integrity of the thin plates of bone in the ethmoid sinus as well as the bony walls of the sphenoid sinus and the bony nasal septum also suggests that malignancy is unlikely. Mineralization can be seen in several tumours, such as ring-like calcifications in cartilage lesions as well as calcifications in olfactory neuroblastomas (2130). Meningioma can cause hyperostosis and can also calcify. Tumour location plays a significant role in differential diagnosis. Tumours in the region of the cribriform plate and upper nasal cavity suggest diagnoses such as olfactory neuroblastoma or meningioma. Inverted Schneiderian papilloma occurs predominantly along the lateral wall of the nasal cavity or the medial maxillary sinus (534). In the lower maxilla, odontogenic lesions should be considered. Such lesions arise in the bone of the alveolar process and as they grow elevate the floor of the maxillary sinus. Fibroosseous lesions enter the differential diagnosis when a radiodense lesion arises from or follows the contour of bone. Correlation of imaging studies with histologic appearance is crucial in the evaluation of bony lesions.
**Definition**

A malignant epithelial neoplasm originating from the mucosal epithelium of the nasal cavities or paranasal sinuses that includes a keratinizing and a non-keratinizing type.

**ICD-O codes**

Squamous cell carcinoma 8070/3  
Verrucous carcinoma 8051/3  
Papillary squamous cell carcinoma 8052/3  
Basaloid squamous cell carcinoma 8083/3  
Spindle cell carcinoma 8074/3  
Adenosquamous carcinoma 8560/3  
Acantholytic squamous cell carcinoma 8075/3

**Synonyms**

Keratinizing squamous cell carcinoma: squamous cell carcinoma.  
Nonkeratinizing carcinoma: Schneiderian carcinoma, cylindrical cell carcinoma, transitional (cell) carcinoma, Ringertz carcinoma, respiratory epithelial carcinoma.

**Epidemiology**

Sinonasal squamous cell carcinoma is rare, accounting for <1% of malignant tumours and only about 3% of malignancies of the head and neck [169,2758]. The disease appears to be more common in Japan than in the West [2205]. It is extremely rare in children, and men are more commonly affected (about 1.5 times) than women. Patients are generally about 55-65 years of age [502,2758].

**Etiology**

Reported risk factors have included exposure to nickel, chlorophenols, and textile dust, prior Thorotrast instillation, smoking, and a history or concurrence of sinonasal (Schneiderian) papilloma. Human papillomavirus (HPV) has been found in some cases, especially those associated with inverted Schneiderian papilloma [303], but a definite etiologic role has not been clearly established. Formaldehyde, despite the results of animal experiments, has not been found to be a definite risk factor in humans [502,1443,1571,2205,2904].

**Localization**

Sinonasal squamous cell carcinomas occur most frequently in the maxillary sinus (about 60-70%), followed by the nasal cavity (about 12-25%), ethmoid sinus (about 10-15%) and the sphenoid and frontal sinuses (about 1%) [131,502]. Squamous cell carcinoma of the nasal vestibule should be considered a carcinoma of the skin rather than sinonasal mucosal epithelium [2566].

**Clinical features**

Symptoms include nasal fullness, stuffiness, or obstruction; epistaxis; rhinorrhea; pain; paraesthesia; fullness or swelling of the nose or cheek or a palatal bulge; a persistent or non-healing nasal sore or ulcer; nasal mass; or, in advanced cases, proptosis, diplopia, or lacrimation [131,502,2758]. Radiologic studies such as CT scan or MRI may delineate the extent of the lesion, the presence of bony invasion, and extension to neighbouring structures such as the orbit, pterygopalatine or infratemporal spaces.

**Macroscopy**

Sinonasal squamous cell carcinomas may be exophytic, fungating, or papillary; friable, haemorrhagic, partially necrotic, or indurated; demarcated or infiltrative.

**Tumour spread and staging**

Nasal cavity carcinomas can spread to adjacent sites in the nasal cavity or to the ethmoid sinus, or can extend to involve

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Fig. 1.6 A Non-keratinizing papillary squamous cell carcinoma. Multiple complex papillary projections lined by thickened epithelium. Lymphocytic response is present at the pushing border of infiltration. B Squamous cell carcinoma, non-keratinizing. Islands of cohesive tumour cells invading into the underlying stroma. Surface carcinoma in-situ is seen.
the contralateral nasal cavity, bone, maxillary sinus, palate, skin and soft tissues of the nose, lip, or cheek, cribriform plate, or cranial cavity. Maxillary sinus carcinomas may spread to the nasal cavities, palate, other paranasal sinuses, skin or soft tissues of the nose or cheek, orbit, cranial contents, or the pterygopalatine and infratemporal spaces. Lymph node metastases are less common than in squamous cell carcinomas of other sites in the head and neck.

Histopathology

**Keratinizing squamous cell carcinoma**
This tumour is histologically identical to squamous cell carcinomas of other mucosal sites in the head and neck. There is histologic evidence of squamous differentiation, in the form of extracellular keratin or intracellular keratin (pink cytoplasm, dyskeratotic cells) and/or intercellular bridges. Tumour cells are generally apposed to one another in a "mosaic tile" arrangement. The tumour may be arranged in nests, masses, or as small groups of cells or individual cells. Invasion occurs as blunt projections or ragged, irregular strands. There is often a desmoplastic stromal reaction. The carcinomas may be well, moderately, or poorly differentiated.

**Non-keratinizing (cylindrical cell, transitional) carcinoma**
This is a distinctive tumour of the sinonasal tract characterized by a plexiform or ribbon-like growth pattern. It invades into the underlying tissue with a smooth, generally well-delineated border. Therefore, definite evidence of stromal invasion may be difficult to appreciate, although a degree of invasion by irregular small nests or strands may be present. There is typically a lack of maturation in the epithelial nests or ribbons, as in transitional cell carcinoma of the urinary tract, which this tumour subtype resembles. Cytologic atypia is present to a significant degree. As its name implies, this tumour does not generally evince histologic evidence of keratinization, although some degree may be seen. When keratinization is significant, there is morphologic overlap with keratinizing squamous cell carcinoma. Occasional mucus-containing cells can be seen. The tumour may be moderately or poorly differentiated; the latter type is difficult to recognize as squamous, and must be differentiated from olfactory neuroblastomas or neuroendocrine carcinomas.

**Variants of squamous cell carcinoma**
Variants of squamous cell carcinoma are rare in the sinonasal tract. They are similar to the analogous tumours occurring with greater frequency in other sites in the head and neck and are more completely described in the corresponding sections. Verrucous carcinoma of the nasal and paranasal sinuses is very rare. It is a low-grade variant of squamous cell carcinoma characterized by a papillary or warty exophytic mass of very well-differentiated, keratinized epithelium. The maxillary sinus is the most common site, followed by the nasal fossa. Rare nasopharyngeal lesions have encroached on the nasal sinus. Papillary squamous cell carcinoma is an exophytic squamous cell carcinoma with a papillary configuration composed of thin fingers of tumour surrounding fibrovascular cores. Basaloid squamous cell carcinoma is uncommon in the sinonasal tract. It is an aggressive variant of squamous cell carcinoma that is characterized by rounded nests of cytologically highly atypical and mitotically-active basaloid epithelial cells, with high nuclear/cytoplasmic ratios and hyperchromatic nuclei. There is often comedo-type necrosis. A pseudoglandular or strand-like arrangement, reminiscent of the architecture of an adenoid cystic carcinoma, is often present, as is the production of basement membrane-like material. Squamous differentiation is invariably present, either in basaloid nests, as separate foci of tumour, or as surface epithelial carcinoma or carcinoma in-situ. Spindle cell carcinoma is characterized by a biphasic pattern of squamous cell carcinoma as well as a generally much larger component of malignant spindled cells, reminiscent of a sarcoma. The squamous component may be scant or even inapparent on light microscopy. In the latter circumstance, immunohisto-
chemical or ultrastructural evidence of epithelial differentiation is required for the diagnosis. The spindle cell component is characteristically immunohistochemically vimentin-positive, and keratin positivity may be scant, difficult to demonstrate, or even absent.

Adenosquamous carcinoma is uncommon in the sinonasal tract, and is more completely described in the sections on oral and laryngeal tumours. Briefly, it is generally considered as a variant of squamous cell carcinoma in which a surface mucosal component of squamous cell carcinoma is present. There is also a component of carcinoma with definite glandular differentiation in the form of ductules or tubules, often intimately admixed with the squamous cell carcinoma. The mere presence of intracellular mucin is not sufficient for the diagnosis.

Acantholytic squamous cell carcinoma is exceedingly rare in the sinonasal tract.

Precursor lesions
Precursor lesions for sinonasal squamous cell carcinomas are considerably less well defined than for oral or laryngeal carcinomas. The sinonasal Schneiderian (inverted) papilloma appears to be a precursor lesion; the frequency of association has been estimated at about 10% [173]. Although squamous metaplasia may precede the development of sinonasal squamous carcinoma, a predisposing role for such metaplasia in the development of carcinoma has not been clearly established.

Prognosis and predictive factors
Patients with nasal squamous cell carcinomas generally present earlier than patients with maxillary cancers and, not surprisingly, fare better than the latter group. Nasal squamous cell carcinomas rarely metastasize to lymph nodes, and recurrences, when they occur, do so quickly [131]. Advanced local disease worsens the prognosis. The overall 5-year survival for nasal squamous cell carcinoma is about 60%. Squamous carcinomas of the maxillary sinus have a more ominous prognosis. They are likely to be large and extensive when diagnosed. Prognosis correlates with stage. Patients with the non-keratinizing type of carcinoma tend to do better than those with the keratinizing type [502]. The overall 5-year survival of patients with maxillary sinus squamous carcinoma is about 42% [131].

Fig. 1.8 Schneiderian papilloma with keratinization is associated with an area of malignant transformation into a squamous cell carcinoma with severe cytologic atypia.
Lymphoepithelial carcinoma

Definition
Lymphoepithelial carcinoma is a poorly differentiated squamous cell carcinoma or histologically undifferentiated carcinoma accompanied by a prominent reactive lymphoplasmacytic infiltrate, morphologically similar to nasopharyngeal carcinoma.

ICD-O code 8082/3

Synonyms
Undifferentiated carcinoma; undifferentiated carcinoma with lymphocytic stroma; undifferentiated carcinoma of nasopharyngeal type; lymphoepithelioma-like carcinoma

Epidemiology
Sinonasal lymphoepithelial carcinoma is rare, and most reported cases have originated from Southeast Asia, where nasopharyngeal carcinoma is also prevalent [1216,1480,1558,2910]. It affects adults in the fifth to seventh decades, and there is a male predominance of approximately 3:1.

Etiology
Nearly all sinonasal lymphoepithelial carcinomas show a strong association with Epstein-Barr virus (EBV) [801,1216,1480,1558,2910].

Localization
Sinonasal lymphoepithelial carcinomas are more common in the nasal cavity than in the paranasal sinuses, although both sites may be involved simultaneously. The tumours may show local invasion of the palate, orbit, and base of skull.

Clinical features
Patients present with nasal obstruction, bloody nasal discharge or epistaxis. Intracranial extension of tumour may cause proptosis and cranial nerve palsy [1216,1480]. There may be cervical lymph node and/or distant metastasis at presentation. Examination and biopsy of the nasopharynx is required to exclude loco-regional spread from a primary nasopharyngeal carcinoma.

Histopathology
The tumour infiltrates the mucosa in the form of irregular islands and sheets, usually without a desmoplastic stroma. The tumour cells possess relatively monotonous vesicular nuclei with prominent nucleoli. The cytoplasm is lightly eosinophilic, with indistinct cell borders, resulting in a syncytial appearance. The tumour cells may also appear plump spindlely, with streaming of nuclei. Intraepithelial spread of tumour may sometimes be seen in the overlying epithelial lining. Necrosis and keratinization are usually not evident. The tumour is infiltrated by variable numbers of lymphocytes and plasma cells. In general, the inflammatory infiltrate is less prominent than that seen in nasopharyngeal carcinoma. In some cases, the inflammatory cells may even be sparse [1216,1480]. The epithelial nature of the tumour can be confirmed by immunostaining for pan-cytokeratin and epithelial membrane antigen. EBV encoded RNA (EBER) is strongly expressed by the tumour cells in most cases [801,1216,1480,1558,2910].

Differential diagnosis
Sinonasal lymphoepithelial carcinoma must be distinguished from the vastly more aggressive sinonasal undifferentiated carcinoma (SNUC). The presence of lymphoplasmacytic infiltrates, although helpful, cannot be relied on solely in making the distinction. SNUC is characterized by tumour cells with nuclear pleomorphism, high mitotic rate and frequent necrosis. EBV status is also helpful since SNUC, except for rare cases from Asians, are EBV-negative [1216,1480,1558]. Other important differential diagnoses are malignant melanoma and non-Hodgkin lymphoma.

Prognosis and predictive factors
The tumour responds favourably to local-regional radiotherapy even in the presence of cervical lymph node metastasis [623,1216,1480]. Distant metastasis (most often to bone), however, is associated with a poor prognosis.

Fig. 1.9 Primary lymphoepithelial carcinoma of the nasal cavity. A The intimate intermingling of the carcinoma cells with lymphoid cells imparts a lymphoma-like appearance. B Large carcinoma cells with indistinct cell borders, vesicular nuclei and prominent nucleoli are admixed with numerous small lymphocytes.
Sinonasal undifferentiated carcinoma

H.F. Frierson, Jr.

Definition
A highly aggressive and clinicopathologically distinctive carcinoma of uncertain histogenesis that typically presents with locally extensive disease. It is composed of pleomorphic tumour cells with frequent necrosis, and should be differentiated from lymphoepithelial carcinoma and olfactory neuroblastoma.

ICD-O code 8020/3

Synonym
Anaplastic carcinoma

Epidemiology
The tumour is rare, with fewer than 100 reported cases. The age range is broad (third to ninth decade), and the median age is in the sixth decade [350,1216]. There is a male predominance (2-3:1).

Etiology
The neoplasm is typically negative for Epstein-Barr virus [350,1216]. Some cases have occurred after prior radiation therapy for nasopharyngeal carcinoma [1216].

Localization
The nasal cavity, maxillary antrum, and ethmoid sinus are typically involved alone or in combination. The neoplasm also commonly extends to other contiguous sites.

Clinical features
Patients have multiple nasal/paranasal sinus symptoms, usually of relatively short duration, including nasal obstruction, epistaxis, proptosis, periorbital swelling, diplopia, facial pain, and symptoms of cranial nerve involvement.

Macroscopy
The tumour is usually larger than 4 cm. It is fungating, with poorly defined margins, bone destruction, and invasion of adjacent structures [2038].

Tumour spread and staging
In addition to involvement of multiple sinuses, the neoplasm destroys sinus walls and orbital bones. Penetration into the cranial cavity is frequent. Less often, there is extension into the nasopharynx or oral cavity. The tumour can metastasize to cervical lymph nodes and distant sites (such as liver, lung, bone) [1216].

Histopathology
Sinonasal undifferentiated carcinoma forms nests, lobules, trabeculae and sheets, in the absence of squamous or glandular differentiation. Severe dysplasia of the overlying surface epithelium has been noted in a few instances. The nuclei are medium to large-sized, surrounded by small amounts of eosinophilic cytoplasm that lacks a syncytial quality. The nucleoli are variable in size, but most often, they are single and prominent. The mitotic rate is very high and there is often prominent tumour necrosis and apoptosis. Lymphovascular invasion is often prominent.

Immunohistochemistry
The carcinoma is immunoreactive for pan-cytokeratins and simple keratins (CK7, CK8 and CK19), but not CK4, CK5/CK6 and CK14 [801]. Less than half of the cases have been reported to be positive for epithelial membrane antigen, neuron specific enolase, or p53 [350]. The tumour is negative for CEA, while positivity for synaptophysin, chromogranin, or S100 protein is only rarely observed [350,1216].

Electron microscopy
Ultrastructurally, cells with occasional small desmosomes and rare dense core granules have been noted [819].

Histogenesis
This is a tumour of uncertain histogenesis, but with unique clinicopathologic characteristics. It should be differentiated from other specific types of carcinoma and non-epithelial tumours with round cells.

Prognosis and predictive factors
Despite aggressive management, the prognosis is poor, with median survival of less than 18 months [350,1216], and 5-year survival of less than 20% [856]. Recent results suggest that more promising outcome may be achieved by combining chemoradiation and radical resection [1802].

Fig. 1.10 Sinonasal undifferentiated carcinoma. A Small nests of tumour cells with or without interconnections are frequently observed. B The cells usually have prominent nucleoli. The mitotic rate is high. C Conspicuous invasion of vascular spaces.
These are glandular malignancies of the sinonasal tract, excluding defined types of salivary gland carcinoma. Two main categories are recognized: (1) intestinal-type adenocarcinoma, and (2) non-intestinal-type adenocarcinoma, which can be further divided into low-grade and high-grade subtypes. Overall, adenocarcinomas and salivary-type carcinomas comprise 10-20% of all sinonasal primary malignant tumours.

**Intestinal-type adenocarcinomas**

**Definition**
A primary malignant glandular tumour of the nasal cavity and paranasal sinuses histologically resembling adenocarcinoma or adenoma of the intestines, or exceptionally normal small intestinal mucosa.

**ICD-O code** 8144/3

**Synonyms**
Colonic-type adenocarcinoma, enteric-type adenocarcinoma.

**Epidemiology**
The frequency of intestinal type adenocarcinomas (ITACs) among primary sinonasal malignancies is difficult to ascertain. Most series report a pronounced male predominance, possibly because of occupational exposure. Patients have ranged in age from 12 to 86 years at the time of diagnosis (mean 58 years) [124].

**Etiology**
The causal relationship of wood dust and leather dust with the development of sinonasal ITACs has been established by several epidemiological studies from different countries [1594]. In this setting, dust particle size is important because those smaller than 5 µm reach the lower respiratory tract, while larger particles are accumulated in the nasal mucosa. However, the carcinogens involved in the onset of ITACs in wood workers and leather workers have not yet been clearly identified. Biologically active substances which can be present in wood and leather dusts include alkaloids, saponins, stilbenes, aldehydes, quinones, flavonoids, resins, oil, steroids, terpenes, fungal proteins, and tannins [1341]. Association has also been reported for agricultural workers, food manufacturers, and motor-vehicle drivers among men, and for textile occupations among women [1443].

**Localization**
ITACs involve the ethmoid sinus, nasal cavities and maxillary sinus in approximately 40%, 27% and 20% of cases, respectively. In the nasal cavities, the inferior and middle turbinates are the sites of predilection. For larger destructive lesions it may be impossible to ascertain the exact site of origin. Advanced tumours tend to invade the orbit, the pterygopalatine and infratemporal fossae, and the cranial cavity. About 10% of cases show lymph node involvement at presentation [124,1341,2234].

**Clinical features**
Most patients present with unilateral nasal obstruction, rhinorrhea and epistaxis. Advanced tumours may cause pain, neurologic disturbances, exophthalmos and visual disturbances.

**Imaging**
Computed tomography (CT) and magnetic resonance imaging (MRI) are used for diagnosis of early lesions, defining the extent of disease and detection of early recurrence. CT best shows sites of bone destruction, while MRI best delineates soft tissue extension [1537].
Macroscopy
ITACs present as an irregular exophytic pink or white mass bulging in the nasal cavity or paranasal sinus, often with a necrotic friable appearance. Some lesions are gelatinous.

Histopathology
Two classifications of ITACs have been proposed. Barnes divided these tumours into 5 categories: papillary, colonic, solid, mucinous and mixed. Kleinsasser and Schroeder divided ITACs into four categories: papillary tubular cylinder cell (PTCC) types I-III (I = well-differentiated, II = moderately-differentiated, III = poorly-differentiated) {799,804,1333}, alveolar goblet type, signet-ring type and transitional type. Either classification is acceptable, but for simplicity the Barnes classification is preferred and will be the one utilized in this description. The most common histologic types seen in association with wood workers as well as in sporadic cases are the papillary and colonic types {124,1333}.

The papillary type (papillary tubular cylinder cell I or well-differentiated adenocarcinoma), which accounts for approximately 18% of cases, shows a predominance of papillary architecture with occasional tubular glands, minimal cytologic atypia, and rare mitotic figures. The colonic type (papillary tubular cylinder II or moderately-differentiated adenocarcinoma), representing approximately 40% of cases, shows a predominance of tubulo-glandular architecture, rare papillae, increased nuclear pleomorphism and mitotic activity.

The solid type (papillary tubular cylinder III or poorly-differentiated adenocarcinoma), representing approximately 20% of cases, shows a loss of differentiation, characterized by solid and trabecular growth with isolated tubule formation, marked increase in number of smaller cuboidal cells with nuclear pleomorphism, round vesicular nuclei, prominent nucleoli and increased mitotic figures. Analogous to colonic adenocarcinoma, some ITACs are predominantly comprised of abundant mucus and are classified as the mucinous type. The mucinous type (alveolar goblet cell and signet ring) includes two growth patterns. In one pattern, there are solid clusters of cells, individual glands, signet ring cells, short papillary fronds with or without fibrovascular cores; mucin is predominantly intracellular and a mucinomyxoid matrix may be present. The other pattern shows the presence of large, well-formed glands distended by mucus and extracellular mucin pools {799,804,1333}. In the latter type, pools of extracellular mucin are separated by thin connective tissue septa creating an alveolar type pattern. Predominantly cuboidal or goblet tumour cells are present in single layers at the periphery of mucus lakes.

Mucus extravasation may elicit an inflammatory response that can include multinucleated giant cells. {799}.

The mixed type (transitional) is composed of an admixture of two or more of the previously defined patterns. Irrespective of the histologic type, ITACs histologically simulate normal intestinal mucosa and may include villi, Paneth cells, enterochromaffin cells and muscularis mucosae {1739}. In rare instances, this is well differentiated that it is composed of well-formed villi lined by columnar cells resembling normal absorptive cells; in some cases, bundles of smooth muscle cells resembling muscularis mucosae may also be identified under the villi.

Immunohistochemistry
ITACs are diffusely positive for epithelial markers including pancytokeratin, epithelial membrane antigen, B72.3, Ber-EP4, BRST-1, Leu-M1, and human milk fat globule (HMFG-2) {1687}. They show CK20 positivity (73%) and variable CK7

Table 1.1 Classification and survival of intestinal-type adenocarcinoma

<table>
<thead>
<tr>
<th>Classification</th>
<th>Barnes (124)</th>
<th>Kleinsasser and Schroeder (1333)</th>
<th>3-year cumulative survivalb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary-type</td>
<td>PTCC-Ia</td>
<td></td>
<td>82%</td>
</tr>
<tr>
<td>Colonic-type</td>
<td>PTCC-II</td>
<td></td>
<td>54%</td>
</tr>
<tr>
<td>Solid-type</td>
<td>PTCC-III</td>
<td></td>
<td>36%</td>
</tr>
<tr>
<td>Mucinous type</td>
<td>Alveolar goblet Signet-ring</td>
<td></td>
<td>48% 0%</td>
</tr>
<tr>
<td>Mixed</td>
<td>Transitional</td>
<td></td>
<td>71%</td>
</tr>
</tbody>
</table>

aPTCC, papillary tubular cylinder cell
bSurvival data derived from Kleinsasser and Schroeder (1333)
reactivity (43% to 93% of cases) [800]. CDX-2, a nuclear transcription factor involved in the differentiation of intestinal epithelial cells and diffusely expressed in intestinal adenocarcinomas, is commonly expressed in ITACs [800]. Information on CEA staining in ITACs is conflicting [1687,2660]. Scattered or groups of chromogranin-positive cells are frequently identified [1687]; these neuroendocrine cells may express a variety of hormone peptides, including serotonin, cholecystokinin, gastrin, somatostatin and leu-enkephalin [163].

Electron microscopy
ITAC demonstrates features of the intestinal epithelium [163]. Columnar cells present regular microvilli with cores of microfilaments that combine to form a band that inserts into the zonula adherens of the junctional complexes. Glycocalyx bodies as characteristic of intestinal-type epithelium may be identified between the microvilli. Endocrine cells with neurosecretory granules, Paneth cells with large exocrine granules, and goblet cells containing several mucin droplets in the apical cytoplasm are present in variable numbers.

Precursor lesions
The frequent presence of squamous metaplasia and/or dysplasia of the sinonasal epithelium in the vicinity of the tumour impairs mucociliary clearance, resulting in prolonged contact of carcinogenic substances with the mucosa [2789].

Histogenesis
It has been hypothesized that ITAC derives from a stem cell capable of undergoing differentiation into various type of epithelial cells (resorptive cells, goblet cells, neuroendocrine cells, Paneth cells) [1739].

Genetics
Genetic data are limited [2012,2013,2218,2829]. K-RAS or H-RAS mutation has been detected in only about 15% of cases [2012,2218]. TP53 mutations are reported in 18-44% of cases [2013,2829]; mutations consist more frequently of C:G to A:T transitions and involve the CpG dinucleotides. Other gene alterations include loss of heterozygosity (LOH) at 17p13 and 9q21, and promoter methylation of p14(ARF) and p16(INK4a). A close association between TP53, p14(ARF) and p16(INK4a) gene deregulation has been found in tumours from individuals occupationally exposed to dusts [2013].

Prognosis and predictive factors
Sinonasal ITACs are generally locally aggressive tumours with frequent local failure (about 50% of cases), whereas metastasis to cervical lymph nodes and spread to distant sites are infrequent (about 10% and 20%, respectively) [124,799,804,1333]. The 5-year cumulative survival rate is around 40%, with most deaths occurring within 3 years. Since most patients present with advanced local disease, clinical staging generally has no relevant prognostic significance.

The histologic subtype has been identified as indicative of clinical behaviour in different series [124,799,804,1333]. The papillary type (papillary tubular cylinder cell adenocarcinoma I = well-differentiated adenocarcinoma) has a more indolent course, with little tendency to distant spread (5-year survival rate of about 80%). Conversely, the solid type (papillary tubular cylinder cell adenocarcinoma II = poorly differentiated adenocarcinoma) and mucinous type adenocarcinoma III = poorly differentiated adenocarcinoma) and mucinous type adenocarcinoma have a very poor survival. Other factors that have been associated with a more aggressive behaviour are: H-RAS mutation, chromogranin expression and c-erbB-2 expression [855,1687,2012]. Although it has been suggested that ITACs occurring in occupational exposed individuals have a better prognosis than sporadic ITACs [124], this has not been confirmed in other reports [799].

Sinonasal non-intestinal-type adenocarcinoma

ICD-O code 8140/3

Synonyms
Sinonasal low-grade adenocarcinoma, terminal tubulus adenocarcinoma, sinonasal tubulopapillary low-grade adenocarcinoma.

Definition
Adenocarcinomas arising in the sinonasal tract that are not of minor salivary gland origin and do not demonstrate histopathologic features of the sinonasal intestinal-type adenocarcinoma. These adenocarcinomas are divided into low- and high-grade subtypes.

Epidemiology
Sinonasal non-intestinal-type adenocarcinomas predominantly occur in adults but have been identified over a wide age range from 9-80 years [1044]. The average patient age at presentation of low-grade adenocarcinomas is 53 years while that of high-grade ones is 59 years [1044]. There is a slight male predominance for the low-grade adenocarcinomas but a more marked male predilection in the high-grade ones [1044].

Etiology
There are no known occupational or environmental etiological factors.

Localization
The low-grade non-intestinal-type adenocarcinomas predilect to the ethmoid sinus (to a lesser extent as compared with the intestinal-type), and the high-grade non-intestinal-type adenocarcinomas predilect to the maxillary sinus.

---

Fig. 1.13 Sinonasal high-grade non-intestinal-type adenocarcinoma. Solid areas of the tumour show marked nuclear pleomorphism as well as an area of comedo-type necrosis.
Either tumour type may also originate in the nasal cavity, other paranasal sinuses, or in multiple sinonasal sites in various combinations [1044].

Clinical features
For low-grade adenocarcinomas, patients primarily present with nasal obstruction and epistaxis. Pain is an infrequent feature [1044]. The duration of symptoms ranges from 2 months to five years, with a median of 5.5 months. For high-grade adenocarcinomas, the presenting symptoms include nasal obstruction, epistaxis, pain and facial deformity (e.g., proptosis). The duration of symptoms ranges from two weeks to five years with a median of 2.5 months [1044].

Macroscopy
The appearance varies, including well demarcated to poorly-defined and invasive, flat to exophytic or papillary growths with a tan/white to pink colour and a friable to firm consistency.

Histopathology
The low-grade non-intestinal-type adenocarcinomas are circumscribed or invasive, and have a glandular or papillary growth. Numerous uniform small glands or acini are arranged in a back-to-back or coalescent pattern with little or no intervening stroma. Occasionally, large, irregular cystic spaces can be seen. The glands are lined by a single layer of non-ciliated columnar cells with uniform, round nuclei, granular eosinophilic cytoplasm. The cells vary from orderly linear arrangement to stratification with loss of nuclear polarity.

The high-grade non-intestinal-type adenocarcinomas are invasive tumours with a predominantly solid growth pattern, but glandular and papillary patterns can also be present. These tumours are characterized by moderate to marked cellular pleomorphism, high mitotic activity, including atypical forms, and necrosis.

Prognosis and predictive factors
The treatment for sinonasal non-intestinal-type adenocarcinomas is complete surgical excision generally via a lateral rhinotomy; depending on the extent and histology of the neoplasm, the surgery varies from local excision to more radical procedures (maxillectomy, ethmoidectomy and additional exenterations). Radiotherapy may be utilized for extensive disease or for higher-grade neoplasms. The low-grade neoplasms have an excellent prognosis, while high-grade neoplasms have a dismal prognosis with a 3-year survival rate of only approximately 20% [1044].
Salivary gland neoplasms of the sinonasal tract are uncommon, and the majority are malignant [1039]. For details see Chapter 5 on tumours of salivary glands.

**ICD-O codes**
- Adenoid cystic carcinoma 8200/3
- Acinic cell carcinoma 8550/3
- Mucoepidermoid carcinoma 8430/3
- Epithelial-myoepithelial carcinoma 8562/3
- Clear cell carcinoma 8310/3

**Adenoid cystic carcinoma**
Adenoid cystic carcinoma is the most frequent malignant salivary gland-type tumour of the sinonasal tract. The age range is from 11-92 years [1039]. The majority develop in the maxillary sinus (about 80%) and nasal cavity (about 25%) [130]. The disease is often insidious, and symptoms include nasal obstruction, epistaxis, and pain, paraesthesia or anaesthesia. Swelling of the palate or face, and loosening of the teeth may be the presenting symptom. Many tumours are large and extensively infiltrative at the time of diagnosis. These tumours can be difficult to detect on plain film radiographs and often extend widely through bone before there is radiographical evidence of osseous destruction. In addition, the true extent of tumour spread is often underestimated by imaging techniques. The long-term prognosis is poor and the 10-year survival rate is only 7% [2444]. Most patients die as a result of local spread rather than metastatic disease [2799].

**Acinic cell carcinoma**
Acinic cell carcinoma is rare in the sinonasal tract and cases have been reported in the nasal cavity [996,1950, 2014,2244,2698] and maxillary sinuses [829,2860]. The signs and symptoms are non-specific but they include nasal obstruction and epiphora.

**Mucoepidermoid carcinoma**
Mucoepidermoid carcinomas are rare at this site, and should be distinguished from the more aggressive variants of squamous cell carcinoma, especially adenosquamous carcinoma [1039, 1291,2588].

**Epithelial-myoepithelial carcinoma**
Epithelial-myoepithelial carcinoma is rare in the sinonasal tract. Cases have been reported to involve the nasal septum, nasal cavity and maxillary sinus [1011,1221,1450,2506]. Signs and symptoms are non-specific but have
included the formation of polypoid masses and nasal obstruction.

**Clear cell carcinoma**
Clear cell carcinoma, N.O.S., of the sinonasal tract is rare (1757,1874) and it is important to exclude metastatic renal clear cell carcinoma (1664,2918). Microscopically, these tumours consist of closely packed, polygonal clear cells arranged in sheets and theques. They contain glycogen but no mucin.

**Other tumours**
A variety of other salivary gland-type carcinomas have been rarely reported in the nasal cavity and paranasal sinuses. These include: malignant myoepithelioma (2918), carcinoma ex pleomorphic adenoma (435), polymorphous low-grade adenocarcinoma (1536) and basal cell adenocarcinoma (785).

### Table 1.2 Sinonasal glandular tumours*

<table>
<thead>
<tr>
<th>Tumour types</th>
<th>No of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleomorphic adenoma</td>
<td>73</td>
<td>23%</td>
</tr>
<tr>
<td>Oncocytic tumours</td>
<td>7</td>
<td>2%</td>
</tr>
<tr>
<td>Low-grade adenocarcinoma (including acinic cell carcinoma)</td>
<td>67</td>
<td>21%</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>17</td>
<td>5%</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>54</td>
<td>17%</td>
</tr>
<tr>
<td>High grade adenocarcinoma</td>
<td>93</td>
<td>30%</td>
</tr>
<tr>
<td>Total</td>
<td>311</td>
<td>100%</td>
</tr>
</tbody>
</table>

* Modified from Heffner (1039)
Neuroendocrine tumours are very rare in the nasal cavity, paranasal sinuses or nasopharynx. The recognizable types are typical carcinoid, atypical carcinoid and small cell carcinoma neuroendocrine type. It is unclear whether large cell neuroendocrine carcinoma that corresponds to the pulmonary counterpart occurs in these sites. There are also rare cases that do not fit these categories, and the diagnostic label “neuroendocrine carcinoma, not otherwise specified” may be applied.

**Carcinoid tumour**

**ICD-O codes**
- Typical carcinoid: 8240/3
- Atypical carcinoid: 8249/3

Typical and atypical carcinoids of the nasal cavity and paranasal sinuses are exceedingly rare, possibly because they are under-reported or have been included under other non-descriptive categories, such as “neuroendocrine carcinoma” (1676, 2007, 2384, 2776). They are otherwise similar to carcinoids in other sites.

Patients have ranged in age from 13-65 years, and present with nasal obstruction, epistaxis and/or facial pain. Most tumours arise in the nasal cavity but may extend into adjacent sinuses. A patient with two carcinoids - nasal and pulmonary - has been described (2384). Another individual with the Multiple Endocrine Neoplasia Type I (MEN1) has been reported to have a carcinoid of the sphenoid sinus (2776). Paucity of cases and lack of significant follow-up preclude definitive statements about the prognosis. The tumours are at least locally aggressive.

**Small cell carcinoma, neuroendocrine type (SCCNET)**

**Definition**
Small cell carcinoma, neuroendocrine type is a high-grade carcinoma composed of small to intermediate sized cells resembling those of small cell carcinoma of pulmonary or extrapulmonary origin. Necrosis, large numbers of apoptotic cells, high mitotic rate, and lack of neurofibrillary stroma are microscopic hallmarks of this tumour.

**ICD-O code**
8041/3

**Synonyms**
Small cell carcinoma, small cell neuroendocrine carcinoma, oat cell carcinoma, poorly differentiated neuroendocrine carcinoma.

**Epidemiology**
SCCNET of the sinonasal tract is a rare tumour with no sex, racial, or geographic predilection and no known association with smoking or radiation. The age range is from 26-77 years with a mean of 49 years.

**Localization**
SCCNET most commonly arise in the superior or posterior nasal cavity, and often extend into the maxillary or ethmoid sinuses. Primary tumours of the maxillary or ethmoid sinuses without nasal involvement can be seen in approximately 45% of cases. Secondary involvement of the nasopharynx is present in a minority of patients. Advanced tumours may invade the skull base, orbit, or brain.

**Clinical features**
The most common symptoms are epistaxis and nasal obstruction, followed by facial pain, palpable facial mass, and exophthalmos. Rare tumours have shown elevated serum levels of ACTH, calci-
Neuroendocrine carcinomas

tonin, pro-gastrin releasing peptide (pro-GRP), or antidiuretic hormone with syndrome of antidiuretic hormone and hyponatremia [1259,1901,2042].

Pathology
See Chapter 3 under “Neuroendocrine Neoplasms of the Larynx.” An important differential diagnosis is olfactory neuroblastoma.

Prognosis and predictive factors
SCCNET are aggressive tumours with a poor prognosis and frequent local recurrence and distant metastasis despite multimodal therapy. Among twenty reported patients [849,1259,1358,1901,2009,2042,2134,2153,2728,2742], twelve (60%) died of disease, three (15%) were alive with no evidence of disease, four were alive with disease (20%), and one died of other causes. In a study of extrapulmonary small cell carcinomas [845], which included seven cases involving the paranasal sinuses, the median survival of 14 patients with primary head and neck small cell carcinomas was only 14.5 months [845]. Follow-up data have shown a local recurrence rate of 45% and a distant metastasis rate of 35%. Common sites of metastases include cervical lymph nodes, lung, liver, bone marrow, and vertebrae.
Schneiderian papillomas

The ectodermally derived ciliated respiratory mucosa that lines the nasal cavity and paranasal sinuses, so-called Schneiderian membrane, gives rise to three morphologically distinct types of papillomas. These are referred to individually as inverted, oncocytic, and exophytic papillomas or, collectively, as Schneiderian papillomas. As a group, the Schneiderian papillomas are uncommon, representing only 0.4-4.7% of all sinonasal tumours (1423).

Inverted papilloma (Schneiderian papilloma, inverted type)

Definition
A papilloma derived from the Schneiderian membrane in which the epithelium invaginates into and proliferates in the underlying stroma.

ICD-O code 8121/1

Synonyms
Inverting papilloma, Schneiderian papilloma, papillomatosis

Epidemiology
Inverted papillomas are two to five times more common in males, and are found primarily in the 40-70 year age group. They are distinctly uncommon in children.

Table 1.3 Distribution of Schneiderian papillomas

<table>
<thead>
<tr>
<th>References</th>
<th>Total cases</th>
<th>Inverted</th>
<th>Oncocytic</th>
<th>Exophytic</th>
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<tbody>
<tr>
<td>Hyams (1158)</td>
<td>315</td>
<td>149</td>
<td>10</td>
<td>156</td>
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<tr>
<td>Michaels and Young (1714)</td>
<td>191</td>
<td>139</td>
<td>16</td>
<td>36</td>
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<tr>
<td>Buchwald et al. (302)</td>
<td>82</td>
<td>58</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Sarkar et al. (2246)</td>
<td>35</td>
<td>24</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Weiner et al. (2737)</td>
<td>105</td>
<td>82</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>728 (100%)</strong></td>
<td><strong>452 (62%)</strong></td>
<td><strong>42 (6%)</strong></td>
<td><strong>234 (32%)</strong></td>
</tr>
</tbody>
</table>

Etiology
Although a viral origin of inverted papillomas has long been suspected, viral inclusions have never been unequivocally demonstrated by light or electron microscopy. In addition, they are almost invariably negative when stained for human papillomavirus (HPV) by the immunoperoxidase technique. HPV genomes, however, have been demonstrated in inverted papillomas by in situ hybridization or the polymerase chain reaction, particularly HPV 6 and 11, sometimes HPV 16 and 18, and exceptionally, HPV 57. The frequency of finding the virus by these specialized techniques is highly variable, ranging anywhere from 0-100% (127). In a collective review of 341 inverted papillomas evaluated for the presence of HPV by a variety of sophisticated molecular techniques, 131 (38%) were positive. Whether the virus is a passenger or etiologically related to the papilloma is unclear (1596). Epstein-Barr virus (EBV) DNA has been identified in 65% of inverted papillomas by polymerase chain reaction (PCR), raising the possibility that this virus might be involved in its pathogenesis (1596). A subsequent study utilizing in-situ hybridisation found no evidence of EBV in the tumour cells, suggesting that the reported PCR positivity might be related to the presence of EBV-positive lymphocytes in the tissues (842). There is no known association of inverted papilloma with allergy, inflammation, smoking, noxious environmental agents or occupation (1158).

Fig. 1.27 Inverted papilloma. Coronal CT. The tumour bows the bone. The calcification (white arrowhead) may represent a sclerotic fragment of inferior turbinate.

Fig. 1.28 Inverted papilloma. A Specimen removed intact. Note the opaque yellow-tan nodular polyloid appearance. B Cut surface of the lesion shown in A. Close inspection shows well-demarcated islands of epithelium which extend endophytically into the stroma.
**Localization**

Inverted papillomas characteristically arise from the lateral nasal wall in the region of the middle turbinate or ethmoid recesses, and often extend secondarily into the sinuses, especially the maxillary and ethmoid and, to a lesser extent, the sphenoid and frontal. Isolated lesions of the paranasal sinuses without nasal involvement however, do occur. Almost none arise primarily on the nasal septum [1297]. Exceptionally, inverted papillomas may arise in sites other than the sinonasal tract. They have been recorded in the middle ear-mastoid [2757], pharynx [2499], nasopharynx [81], and lacrimal sac [2217]. It has been suggested that ectopic migration of the Schneiderian membrane during embryogenesis could account for these aberrant papillomas in sites contiguous with the sinonasal tract [1158]. Whether all of these ectopic cases are bona fide inverted papillomas is uncertain. Although overwhelmingly unilateral, rare cases of bilateral inverted papillomas have been described [211]. Such occurrence, however, should always arouse the suspicion of septal erosion and perforation from unilateral disease.

**Clinical features**

**Signs and symptoms**

Nasal obstruction is the most common presenting symptom. Other manifestations include nasal drainage, epistaxis, anosmia, headaches (especially frontal), epiphora, proptosis, and diplopia. Pain, on the other hand, is an uncommon initial complaint, occurring in only about 10% of all cases. When present, it should always arouse suspicion of secondary infection or malignant change.

On physical examination, inverted papillomas present as pink, tan, or grey; non-translucent; soft to moderately firm, polypoid growths with a convoluted or wrinkled surface.

**Imaging**

Findings on imaging vary with the extent of disease. Early on, there may be only a soft tissue density within the nasal cavity and/or paranasal sinuses. Later, with more extensive disease, unilateral opacification and thickening of one or more of the sinuses is common, as are expansion and displacement of adjacent structures. Pressure erosion of bone may also be apparent and must be distinguished from the destructive invasion associated with malignancy, such as de novo carcinoma or carcinoma arising in and/or associated with an inverted papilloma.

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**Fig. 1.29** Inverted papilloma  
**A** Low magnification showing hyperplastic aggregates of well-demarcated squamous and respiratory epithelium extending throughout the stroma. Note the absence of mucouserous glands.  
**B** Papilloma composed partially of hyperplastic, ciliated respiratory epithelium. Note the epithelial transmigration of neutrophils and the delicate basement membrane.  
**C** HPV nuclear and cytoplasmic reactivity can be seen in some inverted papillomas, usually in the same nuclei which exhibit features of “koilocytic” atypia (right).  
**D** Inverted papilloma and carcinoma. Note the inverted papilloma on the left and the normal ciliated respiratory epithelium of the sinonasal tract in the middle of the illustration. The carcinoma at the right shows both in-situ and invasive components.
Histopathology

Inverted papillomas are composed exclusively or almost exclusively of hyperplastic ribbons of basement membrane-enclosed epithelium that grow endophytically into the underlying stroma. Infrequently, a minor exophytic component may be seen. The epithelium is multilayered, usually 5-30 cells thick, and formed of squamous or ciliated columnar (respiratory epithelial) cells admixed with mucocytes. Nonkeratinizing squamous or transitional-type epithelium tends to predominate, and is frequently covered by a single layer of ciliated columnar cells. An occasional case may be composed almost entirely of respiratory epithelium. Gradations between these two extremes are not uncommon, resulting in a transitional epithelium reminiscent of that seen in the urinary tract. All of these epithelial types may be present in the same lesion, and their proportions may vary widely in different lesions or even in different areas of the same papilloma. Mitoses are not numerous and, if present at all, are seen primarily in the basal and parabasal epithelium.

Ten to 20% of inverted papillomas may show focal surface keratinisation, and 5-10% varying degrees of dysplasia (127). These are not necessarily signs of malignancy, but they should alert the pathologist of the need of thorough evaluation of the papilloma. The stroma ranges from dense and fibrous to loose and myxoid, with or without an inflammatory component. The inflammatory cells, especially neutrophils, often transmigrate through the epithelium. Basement membrane thickening is not typically seen. Normal appearing seromucinous glands are sparse to absent, because the neoplastic epithelium uses the ducts and glands as scaffolds to extend into the stroma. As inverted papillomas enlarge, they may obstruct the drainage of nearby sinuses. As a result, it is not uncommon to also find ordinary nasal polyps in inverted papilloma specimens. They can usually be identified grossly by their more myxoid appearance and the fact that they will transilluminate, whereas inverted papilloma will not.

Rarely, an inverted papilloma will exhibit focal surface changes reminiscent of a verruca vulgaris; that is, it shows focal papillary squamous epithelial hyperplasia with marked keratosis and/or parakeratosis, with a prominent granular cell layer, and often contains numerous vacuolated cells suggestive of koilocytes. Although this might be a viral effect, immunohistochemical stains for HPV are invariably negative. When this change is observed, the diagnosis of “inverted papilloma with focal verrucous hyperplasia” is appropriate and the patient should be followed closely for possible development of carcinoma, either verrucous carcinoma or squamous cell carcinoma.

Inverted papilloma and carcinoma

Inverted papillomas are occasionally complicated by carcinomas, especially squamous cell carcinoma and, to a much lesser extent, verrucous, mucopusidermoid, spindle and clear cell carcinomas, as well as adenocarcinomas. The incidence of malignant change in individual series of inverted papillomas has ranged from 2-27% (127). In a collective review of 1390 inverted papillomas reported in the literature, 150 (11%) were associated with carcinoma and, of these, 61% of the carcinomas were synchronous and 39% metachronous (127). For metachronous carcinomas, the mean interval from onset of the inverted papilloma to the development of the carcinoma is 63 months (range, 6 months to 13 years) (1477). Carcinomas complicating inverted papilloma vary from well to poorly differentiated and exhibit a broad range of behaviour. Some are in situ and of little consequence, whereas others are locally aggressive or may even metastasize. The carcinomas may actually arise within the papilloma, as evidenced by a gradation of histological changes ranging from dysplasia to carcinoma in-situ to frankly invasive carcinoma; whereas in others, the carcinoma is merely associated with a histologically bland inverted papilloma. Staining for CD44s may be helpful in identifying a malignant component. It is diffusely expressed in typical inverted papillomas, whereas its expression is reduced or absent in the associated carcinomatous component (1175).

There is no correlation between the number of local recurrences of an inverted papilloma and the subsequent development of carcinoma. There is some evidence, however, to suggest that HPV 16 and 18 may be more carcinogenic than HPV 6 and 11 (1334). Preliminary data suggest that alterations in TP53, manifested by an increased protein expression or genetic mutation, can be used to predict which lesions are at risk for malignant change (715,765).

Differential diagnosis

The differential diagnoses include nasal polyp with squamous metaplasia, respiratory epithelial adenomatoid hamartoma (REAH) and invasive carcinoma. Nasal polyps with squamous metaplasia show thickening and hyalinization of the basement membrane, a prominent component of normal seromucinous glands and, often, a large number of stromal inflammatory cells. These features are typically absent in inverted papilloma. In addition, the surface epithelium of nasal polyps is thin, contains more mucocytes, and does not show the characteristic epithelial transmigration of neutrophils. In contrast to inverted papilloma, REAH occurs primarily on the posterior nasal septum rather than the lateral nasal wall and/or paranasal sinuses (2766). REAH is also composed of numerous glands lined by respiratory epithelial cells, surrounded by thick hyalinized basement membranes, features not seen in inverted papilloma.
Invasive carcinoma can be distinguished from inverted papilloma by the presence of the following features: cellular pleomorphism, atypical mitoses, keratin pearls, loss of basement membranes, and stromal invasion associated with an inflammatory-desmoplastic response.

**Prognosis and predictive factors**

Though histologically benign, they have an unlimited growth potential and, if neglected, can cause considerable morbidity or even death by extending into contiguous structures. Attempts to remove these lesions intranasally by snare and avulsion have resulted in recurrence (or persistence) rates of 0-74% (average, 60%) [1442]. The preferred treatment for most lesions is a lateral rhinotomy and medial maxillectomy with meticulous removal of all mucosa in the ipsilateral paranasal sinuses. With this approach, the recurrence rate is usually <20% [1442]. Selected small tumours can be effectively removed by a less aggressive approach using endoscopic sinonasal surgery. Recurrences typically appear within 2-3 years of therapy but, in some instances, are delayed for many years. Attempts to correlate histological features with risk of recurrence have resulted in conflicting data [1158,1442,2417]. Even those with prominent mitotic activity and dysplasia do not invariably show an increased recurrence or malignancy. Nevertheless, dysplasia, especially if moderate to severe, demands thorough microscopic evaluation of all resected tissue to avoid overlooking small foci of carcinoma. The association between presence of HPV and the risk of recurrence is debatable [185,839].

**Oncocytic papilloma (Schneiderian papilloma, oncocytic type)**

**Definition**

A papilloma derived from the Schneiderian membrane composed of both exophytic fronds and endophytic invaginations lined by multiple layers of columnar cells with oncocytic features. Intraepithelial microcysts containing mucin and neutrophils are characteristic.

**ICD-O code** 8121/1

**Synonyms**

Oncocytic Schneiderian papilloma, cylindrical cell papilloma, columnar cell papilloma, papillomatosis.

**Epidemiology**

Oncocytic papilloma is equally distributed between the sexes, and the majority of the patients are aged over 50 years.

**Etiology**

In contrast to exophytic and inverted papilomas, HPV has not been identified in oncocytic papillomas [127].

**Localization**

Oncocytic papilloma almost always occurs unilaterally on the lateral nasal wall or in the paranasal sinuses, usually the maxillary or ethmoid. It may remain localized, involve both areas, or if neglected, extend into contiguous areas such as the orbit or cranial cavity.

**Clinical features**

Oncocytic papilloma presents as a fleshy, pink, tan, red-brown, or grey papillary or polypoid growth associated with nasal obstruction and intermittent epistaxis.

**Histopathology**

The oncocytic papilloma exhibits both exophytic and endophytic patterns of growth. The epithelium is multilayered, 2-8 cells thick, and is composed of tall columnar cells with swollen, finely granular cytoplasm reminiscent of oncocytes. The high content of cytochrome c oxidase and presence of numerous mitochondrial ultrastructurally clearly establish their oncocytic character [129]. The nuclei are either small dark and uniform or slightly vesicular with barely discernible nucleoli. Cilia in varying stages of regression may be observed in a few of the outermost cells. The epithelium characteristically contains numerous small cysts filled with mucin or neutrophils (microabscesses). The stroma varies from edematous to fibrous, and may contain modest numbers of lymphocytes, plasma cells, and neutrophils, but few eosinophils. Seromucinous glands are sparse to absent.

**Oncocytic papilloma and carcinoma**

Four to 17% of all oncocytic papillomas harbour a carcinoma [1158,1266,1611,2723]. Most of these are squamous, but mucoepidermoid, small cell and sinonasal undifferentiated carcinomas have also been described. As in inverted papilloma, the carcinoma complicating oncocytic papilloma may arise within the papilloma, as evidenced by a gradation of histologic changes ranging from dysplasia to in situ to invasive carcinoma, or it may only be associated with the papilloma. Prognosis depends on the histologic type, degree of invasion, and the extent of tumour. In some instances, the carcinoma is in situ and of little consequence to the patient, whereas others are locally aggressive and may metastasize.

**Differential diagnosis**

The intraepithelial mucin-filled cysts of an oncocytic papilloma are often mistaken for rhinosporidiosis. In rhinosporidiosis, the organisms are not limited to the epithelium but also involve stroma, and do not induce a diffuse oncocytic change. Oncocytic papilloma is also occasionally confused with a low-grade papillary ade-
Tumours of the nasal cavity and paranasal sinuses

carcinoma. The presence of intact basement membranes and absence of infiltrative growth are features that indicate a benign lesion. In addition, the presence of intraepithelial mucin-filled cysts and microabscesses and the stratified oncocytic epithelium of a papilloma are rarely seen in a low-grade adenocarcinoma.

Prognosis and predictive factors
The clinical behaviour parallels that of the inverted papilloma. If inadequately excised, at least 25-35% will recur, usually within 5 years. Smaller tumours can be resected endoscopically.

Exophytic papilloma (Schneiderian papilloma, exophytic type)

Definition
A papilloma derived from the Schneiderian membrane composed of papillary fronds with delicate fibrovascular cores covered by multiple layers of epithelial cells.

ICD-O code 8121/0

Synonyms
Fungiform papilloma, everted papilloma, transitional cell papilloma, septal papilloma, squamous papilloma, papillomatosis, Ringertz tumour

Epidemiology
Exophytic papillomas are 2-10 times more common in men, and occur in individuals between 20 and 50 years of age (2-87 years) [1158,1908].

Etiology
There is increasing evidence to suggest that exophytic papillomas may be etiologically related to HPV, especially types 6 and 11, rarely types 16 and 57b. In a collective review of exophytic papillomas evaluated for the presence of HPV by in situ hybridization and/or the polymerase chain reaction, about half of the cases were HPV positive [131].

Localization
Exophytic papillomas arise on the lower anterior nasal septum with no significant lateralization. As they enlarge, they may secondarily involve, but only infrequently originate from the lateral nasal wall.

Involvement of the paranasal sinuses is practically non-existent. Bilateral lesions are exceptional.

Clinical features
Epistaxis, unilateral nasal obstruction, and the presence of asymptomatic mass are the typical presenting symptoms. On physical examination, they appear as papillary or warty, grey, pink or tan, non-translucent growths attached to the nasal septum by a relatively broad base.

Histopathology
Most exophytic papillomas range up to about 2 cm. Microscopically, they are composed of papillary fronds with fibrovascular cores covered by epithelium, 5-20 cells thick, that vary from squamous to transitional (intermediate) to ciliated pseudostratified columnar (respiratory). Scattered mucocytes are common. Surface keratinization is absent or scant, unless the lesion has been irritated or if the papilloma is unusually large and hangs into the nasal vestibule, where it is exposed to the drying effect of air. Mitoses are rare and never atypical. Unless infected or irritated, the stroma contains few inflammatory cells.

Malignant change in exophytic papilloma is exceptional [301,1908].

Differential diagnosis
Exophytic papillomas must be distinguished from the much more common, keratinizing cutaneous papillomas (e.g. verruca vulgaris) occurring in the nasal vestibule. The lack of extensive surface keratinization, presence of mucocytes, and presence of ciliated and/or ‘transitional’ epithelium help to confirm a diagnosis of exophytic papilloma. The presence of seromucinous glands and septal cartilage further indicate that the lesion is of mucosal rather than cutaneous origin.

Prognosis and predictive factors
Complete surgical excision is the treatment of choice. Inadequate excision rather than multiplicity of lesions probably accounts for the local recurrence of 22-50% [1158,1908].
Respiratory epithelial adenomatoid hamartoma

Definition
Benign nonneoplastic overgrowth of indigenous glands of the nasal cavity, paranasal sinuses and nasopharynx associated with the surface epithelium, and devoid of ectodermal neuroectodermal, and/or mesodermal elements.

Synonyms
Glandular hamartoma; seromucinous hamartoma.

Epidemiology
Hamartomas of the sinonasal tract and nasopharynx are uncommon. The majority of them are of pure epithelial type (respiratory epithelial adenomatoid hamartoma) [2766], although pure mesenchymal hamartomas or mixed epithelial-mesenchymal hamartomas may also rarely occur [14,106,933,2766]. Respiratory epithelial adenomatoid hamartomas predominantly occur in adult patients with a decided male predominance; patients range in age from the 3rd to 9th decades of life, with a median age in the 6th decade [2766].

Etiology
Respiratory epithelial adenomatoid hamartomas often arise in the setting of inflammatory polyps, raising a possible developmental induction secondary to the inflammatory process [2766].

Localization
The majority occur in the nasal cavity, in particular the posterior nasal septum; involvement of other intranasal sites occurs less often and may be identified along the lateral nasal wall, middle meatus and inferior turbinate [2766]. Other sites of involvement include the nasopharynx, ethmoid sinus, and frontal sinus. Most are unilateral, but some may be bilateral.

Clinical features
Patients present with nasal obstruction, nasal stuffiness, epistaxis and/or chronic (recurrent) rhinosinusitis. The symptoms may occur over months to years. Associated complaints include allergies.

Macroscopy
Lesions are typically polypoid or exophytic with a rubbery consistency, tan-white to red-brown appearance, measuring up to 6 cm in greatest dimension [933,2766].

Histopathology
The lesions are dominated by a glandular proliferation composed of widely-spaced, small to medium-sized glands separated by stromal tissue. In areas, the glands arise in direct continuity with the surface epithelium, which invaginate downward into the submucosa. The glands are round to oval, and composed of multilayered ciliated respiratory epithelium often with admixed mucocytes. Glands distended with mucus can be seen. A characteristic finding is stromal hyalinization with envelopment of glands by a thick, eosinophilic basement membrane. Atrophic glandular alterations may be present in which the glands are lined by a single layer of flattened to cuboidal epithelium. Small reactive seromucinous glands can be seen. The stroma is oedematous or fibrous, and contains a mixed chronic inflammatory cell infiltrate. Additional findings may include inflammatory sinonasal polyps, hyperplasia and/or squamous metaplasia of the surface epithelium unrelated to the adenomatoid proliferation, osseous metaplasia, rare association with inverted type Schneiderian papilloma, and rare association with a solitary fibrous tumour [2766].

Prognosis and predictive factors
Conservative but complete surgical excision is curative.

Fig. 1.33 Respiratory epithelial adenomatoid hamartoma (REAH). A The glandular proliferation arises in direct continuity with the surface epithelium with invagination downward into the submucosa. Clusters of seromucinous glands are seen (arrow). B Pseudostratified epithelium with cilia within the adenomatoid collections of a REAH hamartoma. C Cilia along the luminal border of the cells (arrows). D Atrophic changes in which the glands are lined by a single layer of flattened to cuboidal-appearing epithelium. Note the prominent thickened stromal hyalinization enveloping the glands.
Among glandular tumours of the sinonasal tract, about one-quarter of cases are benign, and practically all of them are salivary gland-type neoplasms \(\{1039\}\). For details see Chapter 5 on ‘Tumours of salivary glands’.

**ICD-O codes**

- Pleomorphic adenoma 8940/0
- Myoepithelioma 8982/0
- Oncocytoma 8290/0

**Pleomorphic adenoma**

Most patients are between 20 and 60 years of age. Signs and symptoms are non-specific, and include unilateral nasal obstruction, epistaxis and a discernible mass. The tumour may resorb bone and extend into the maxillary sinuses. Most cases arise from the submucosa of the bony or cartilaginous nasal septum, but some arise in the lateral nasal wall \(\{483,974,1210,1506\}\). The size varies from 0.5-5 cm \(\{483\}\) and tumours usually form polypoid, sessile swellings. Microscopically, they are unencapsulated, and tend to be cellular with predominance of modified myoepithelial cells often of plasmacytoid hyaline type; stromal elements are sparse. Exceptionally, focal skeletal muscle differentiation can occur \(\{1419\}\). If treated by wide surgical excision, recurrence is uncommon \(\{483\}\).

**Myoepithelioma**

Myoepithelioma, including the spindle cell variant, of the sinonasal tract is very rare \(\{188\}\).

**Oncocytoma**

Oncocytomas of the sinonasal tract are rare, and most arise from the nasal septum \(\{1039\}\). They are usually small, but some extend posteriorly and can cause bone resorption \(\{470,480,998\}\). The nasolacrimal duct may be involved, causing unilateral epiphora and purulent rhinorrhea \(\{555\}\). Those examples that have behaved aggressively \(\{470\}\) are more appropriately considered low-grade oncocytic adenocarcinomas rather than adenomas \(\{449,605,1044\}\).
Fibrosarcoma

Definition
A malignant tumour of fibroblastic/myofibroblastic phenotype.

ICD-O code 8810/3

Synonyms
Fibromyxosarcoma; chondromyxofibrosarcoma.

Epidemiology
The incidence of sinonasal tract fibrosarcomas is difficult to determine because the diagnosis is often one of exclusion. These tumours are rare, accounting for <3% of all non-epithelial tumours. However, they are considered the second most common soft tissue sarcoma after rhabdomyosarcoma in the head and neck (168,345,826,1041,1317,2438). They occur in all ages, with a peak in the 5th decade. There is a 3:2 female:male gender predilection (168,345,826,1041,1317,2438,2511).

Etiology
A few patients have developed fibrosarcoma within the field of prior irradiation.

Localization
Most fibrosarcomas originate in one or more paranasal sinuses, while origination confined to the nasal cavity alone is less common (168,345,826,1041,1317,2438). The “infantile-type” fibrosarcoma in the sinonasal tract is exceedingly uncommon in the sinonasal tract and occurs near the choana (349,1041,1317).

Clinical features
Nearly all patients have nasal obstruction, often associated with epistaxis, while pain, sinusitis, nasal discharge, swelling, anosmia, and proptosis are less common. The median duration of symptoms is quite short.

Macroscopy
The tumours are smooth, nodular, pedunculated, fungating or ulcerating. The lesions range in size between 2 and 8 cm, with the cut surface revealing a circumscribed but not encapsulated, fleshy, homogeneous white-tan to yellow-pink mass, variably firm dependent upon the collagen content. Necrosis and haemorrhage may be present in higher-grade tumours.

Histopathology
The tumours are unencapsulated, sometimes sharply circumscribed, although often infiltrative and occasionally ulcerating. Bone invasion is common. Surface epithelial invagination into the tumour can be prominent, simulating an inverted papilloma. Spindle cells are arranged in compact fascicles, intersected by various amounts of delicate thin to dense keloid-like collagen. The cell bundles are arranged at acute angles to one another, occasionally giving rise to a “herringbone” or “chevron” pattern, while in most areas there is a more subtle fasciculation. A prominent storiform pattern is not seen. There is a marked variability in the cellularity within and between tumours. The cells are fusiform with a centrally placed hyperchromatic, needle-like nucleus surrounded by tapering cytoplasm which is often indistinct, creating a syncytial appearance to the fascicles. Most sinonasal tract fibrosarcomas are low grade. Nuclear pleomorphism is usually slight to moderate, but occasionally prominent. Mitotic figures are found in variable numbers. Haemorrhage and necrosis can be found in the poorly differentiated forms, with areas of myxoid degeneration. Focal osteo-cartilaginous differentiation has been described (168,345,826,1041,1317,2438). Fibrosarcomas are immunoreactive with vimentin, and sometimes focally with actin (1041).
Differential diagnosis
The differential diagnoses include malignant fibrous histiocytoma, spindle cell carcinoma, spindle malignant melanoma, malignant peripheral nerve sheath tumour, monophasic synovial sarcoma, rhabdomyosarcoma, glomangiopericytoma, desmoid fibromatosis, and nodular fasciitis {168,826,1041, 2332}.

Histogenesis
The (myo)fibroblast is considered the progenitor cell for these tumours.

Prognosis and predictive factors
Surgery is the treatment of choice, often followed by radiation therapy, yielding an overall long-term survival of 75% in low grade and localized tumours. The high incidence of recurrence (about 60%) is perhaps related to the complexity of the anatomy of the sinonasal tract and consequent difficulties of complete excision. Recurrence usually precedes metastasis, which occurs in about 15% of cases, most commonly to the lungs and bones and only rarely to lymph nodes. Poor prognostic factors include male gender, large tumour size, involvement of more than one contiguous site (nasal cavity and sinus, multiple sinuses), high histologic grade, and positive surgical margins {168,345,826,1041,1317,2438}.

Malignant fibrous histiocytoma
Definition
Malignant fibrous histiocytoma (MFH) is currently used as a diagnosis of exclusion for sarcomas composed largely of myofibroblasts or undifferentiated mesenchymal cells.

ICD-O code 8830/3

Synonyms
Fibroxanthosarcoma, malignant fibrous xanthoma, myxofibrosarcoma, myxoid malignant fibrous histiocytoma

Epidemiology
Although once considered the most common sarcoma of adults, the frequency of its diagnosis has diminished since the introduction of immunohistochemistry has allowed assignment of some pleomorphic sarcomas to specific sarcoma entities. Only 3% of MFH occur in the head and neck, with 30% of these arising in the sinonasal area {2187}. MFH rarely occurs in the nasopharynx {1032,1923}. Sinonasal MFH most commonly occurs in adults with a male predominance {2433}.

Etiology
Many sinonasal and nasopharyngeal MFH are a result of previous radiation, after a long latency period {1180,1345}.

Localization
The maxillary sinus is most commonly affected, followed by the ethmoid sinuses and nasal cavity, whereas the frontal and sphenoid sinuses and nasopharynx are affected far less commonly {279,536,581,1032,1923,1936,2256,2426,2433}.

Immunohistochemistry
MFH are usually positive for vimentin and focally for actins. Importantly, MFH is a diagnosis of exclusion and is generally negative for desmin, skeletal muscle specific markers, S100 protein, HMB-45, epithelial markers and lymphoid markers.

Differential diagnosis
The differential diagnoses include fibrosarcoma, rhabdomyosarcoma, leiomyosarcoma, monophasic synovial sarcoma, malignant peripheral nerve sheath tumour, spindle cell carcinoma, spindle cell malignant melanoma and anaplastic large cell lymphoma.

Prognosis and predictive factors
Compared with other anatomical sites, MFHs of the head and neck generally have a slightly lower rate of recurrence and metastasis {133}.
**Leiomyosarcoma**

**Definition**
A malignant tumour of smooth muscle phenotype.

**ICD-O code**
8890/3

**Epidemiology**
Only a small number of sinonasal leiomyosarcomas have been reported [151, 824, 840, 1144, 1395, 1416, 1529, 2147, 2240, 2553], accounting for <1% of all non-epithelial tumours. They occur in all ages, with a peak in the 6th decade (mean, 53 years) without a gender difference.

**Etiology**
There are a few reported cases with a prior history of radiation [824, 1416, 2147] or chemotherapy (cyclophosphamide specifically) [1416, 2147].

**Localization**
Involvement of both the nasal cavity and paranasal sinuses is more common than involvement of the nasal cavity alone [824, 840, 1144, 1395, 1416, 1529, 1745].

**Clinical features**
Nearly all patients have nasal obstruction, frequently associated with epistaxis and pain, while nasal discharge, swelling, and blurred vision are less common. The duration of symptoms is usually long [824, 840, 1144, 1395, 1416, 1529, 2147, 2240, 2553]. There is usually no lymphadenopathy. Plain radiographs show opacification of the nasal cavity or sinus(es), often suggesting sinusitis [1144, 1395, 1529, 2553].

**Macroscopy**
These tumours range in size up to 7 cm, with an average of about 4 cm. They are more likely infiltrative than circumscribed, and occasionally polypoid. The surface is typically ulcerated and crusted. These bulky tumours have a cut surface which reveals a soft to firm, grey-white and fleshy appearance. Haemorrhage, necrosis and cystic change are common.

**Histopathology**
Leiomyosarcomas are infiltrative neoplasms accompanied by surface ulceration. Bone or cartilage invasion is more frequent than surface or seromucinous gland invasion. Leiomyosarcomas are composed of right-angle intersecting bundles of spindle cells. Palisading, storiform and “haemangiopericytoma-like” patterns can occur. The tumours are hypercellular, but coagulative tumour necrosis and haemorrhage can create a hypocellular appearance. The tumour cells have elongated, vesicular to hyperchromatic, lobulated or indent ed nuclei with blunt ends (“cigar-shaped”). The cytoplasm is fibrillar and eosinophilic, with frequent perinuclear vacuolation. Mitoses, both typical and atypical, are present to a variable degree [824, 840, 1144, 1395, 1416, 1529, 2147, 2240, 2553].

**Histochemistry and immunoprofile**
Intracytoplasmic glycogen can be demonstrated with a PAS stain. Masson trichrome stain demonstrates red, longitudinally oriented parallel fibrils within the cytoplasm. Tumour cells are diffusely and strongly immunoreactive for vimentin, actin (smooth muscle or muscle-specific), desmin and h-caldesmon. There is generally no reactivity with keratin, CD34, CD117, S-100 protein or HMB-45 [1144, 1395, 2702]. The Ki-67 index is usually >15% [1144].

**Electron microscopy**
Electron microscopy reveals variable features of smooth muscle cells, including myofilaments arranged in parallel arrays, dense bodies within the filaments, cell junctions, pinocytotic vesicles and basal lamina [1395, 1529, 1933].

**Differential diagnosis**
The differential diagnoses include sinonasal glomangiopericytoma, periph-
eral nerve sheath tumour, fibrosarcoma, spindle cell carcinoma and melanoma {824,840,1144,1416,1529,2147,2240,2553,2603}.

**Genetic susceptibility**
There are isolated cases of children with leiomyosarcomas who have preexisting hereditary retinoblastomas {627}.

**Prognosis and predictive factors**
About half of the reported cases develop local recurrence, often within one year, and nearly 1/3 of these patients will subsequently develop metastasis (mostly to the lungs and liver). Complete surgical excision is difficult to achieve, and radiation and chemotherapy are used with variable results. {824,1416,2501}.

Poor prognostic factors include involvement of more than one contiguous site, large tumour size (>5 cm), high mitotic count (>20/10 high power field), tumour necrosis, and tumour stage {824,840,1144,1395,1416,1529,2147,2240,2553}. There is an overall slight male predominance {825}.

**Rhabdomyosarcoma**

**Definition**
A malignant tumour of skeletal muscle phenotype.

**ICD-O code**
8900/3
(Also see subtypes: 8910/3, 8912/3, 8920/3, 8901/3 in WHO Tumours of Soft Tissue)

**Synonyms**
Myosarcoma, malignant rhabdomyoma, rhabdosarcoma, embryonal sarcoma, rhabdomyoblastoma

**Epidemiology**
Approximately 40% of rhabdomyosarcomas occur in the head and neck {1978}, with about 20% in the nasal cavity, nasopharynx, and nasal sinuses {2745}. Rhabdomyosarcoma is the most common sarcoma in childhood. The embryonal subtype predominates in children, while the alveolar subtype predominates in adults {825,1273}. The pleomorphic subtype is rare {836,837}. There is an overall slight male predominance {825}.

**Localization**
The nasopharynx is more commonly involved than the sinonasal tract {326,724}. In adults, rhabdomyosarcoma is more common in the ethmoid sinuses, followed by the maxillary sinuses and nasopharynx {1856}.

**Clinical features**
Signs and symptoms include difficulty in breathing, epistaxis, facial swelling, visual disturbances, and sinusitis often of short duration. Tumours may appear as a large, polypoid sinonasal mass or may occasionally protrude as a gelatinous mass from the nares {825}.

CT and MRI imaging delineate the size and extent of the tumour {1453,2846}. The botryoid type shows grape-like rings and heterogeneous enhancement {980}.

**Macroscopy**
The embryonal subtype is generally poorly circumscribed, fleshy, pale and tan; the spindle cell variant is firm, fibrous, and tan-yellow with a whorled cut surface. The botryoid variant has a grape-like or polypoid appearance {825}. The alveolar subtype is fleshy to firm tan-grey.

**Tumour spread and staging**
These tumours often spread to contiguous sites including base of the skull, temporal bones, and orbit {724,825}. About 40% metastasize to lymph nodes, bones, and lungs, and less commonly bone marrow, soft tissue, liver and brain {1441,1856}. The tumours are staged according to the Intergroup Rhabdomyosarcoma Study. Group I includes local disease, Group II residual disease or local spread, Group III incomplete resection or biopsy with gross residual disease, and Group IV metastatic disease at onset {613}. Most adult sinonasal and nasopharyngeal rhabdomyosarcomas are staged as Group III or IV at presentation {1856}.

**Histopathology**
Embryonal rhabdomyosarcoma has round to spindled cells with hyperchromatic nuclei. Larger rhabdomyoblasts with eosinophilic cytoplasm are usually identified, but cross striations are difficult to recognize. Myxoid stroma is common. The spindle cell variant, characterized by spindled cells in fascicular to storiform growth patterns, can be deceptively bland. The botryoid variant is polypoid with a submucosal hypercellular cambium layer, a myxoid hypocellular zone, and a deep cellular component. Alveolar rhabdomyosarcoma typically has fibrous septa separating clusters of loosely cohesive groups of small to medium round tumour cells with hyperchromatic nuclei and scant eosinophilic cyto-
plasm. Multinucleated giant cells with overlapping peripheral nuclei are often present. The solid variant grows in sheets and lacks septa. Rarely, the tumour can be composed exclusively or predominantly of clear cells. A mixed alveolar and embryonal pattern may occur. Mitotic figures are usually easy to identify. Pleomorphism is occasionally observed focally. After treatment, there is often increased cytodifferentiation, with the cells exhibiting abundant eosinophilic fibrillary cytoplasm (2644). Pleomorphic rhabdomyosarcoma is rare and uncommon in this location.

**Immunohistochemistry**

There is immunoreactivity for desmin, muscle specific actin, myoglobin, fast myosin, nuclear MyoD1 and nuclear myogenin (skeletal muscle myogenin, myf4) (2619). CD99 can be positive in 16% of cases (1084).

**Electron microscopy**

Electron microscopy shows some degree of skeletal muscle differentiation ranging from well-formed Z-bands to incomplete sarcomeres with thick and thin filaments and ribosome-myosin complexes (724,837).

**Differential diagnosis**

The differential diagnoses of embryonal rhabdomyosarcoma include sinonasal polyp with stromal atypia (1840) and various sarcomas. The differential diagnoses of alveolar rhabdomyosarcoma include various round blue cell tumours, including lymphoma, sinonasal undifferentiated carcinoma, small cell carcinoma of neuroendocrine type, mesenchymal chondrosarcoma, PNET/Ewing sarcoma, olfactory neuroblastoma, and mucosal malignant melanoma.

**Somatic genetics**

Embryonal rhabdomyosarcoma shows allelic loss at 11p15 (271,925). Alveolar rhabdomyosarcoma has a consistent translocation, usually t(2:13) (PAX3-FKHR), or less commonly t(1:13) (PAX7-FKHR) which can be performed on paraffin-embedded sections (141).

**Genetic susceptibility**

Germline mutations of TP53 in Li-Fraumeni syndrome are found in some children with rhabdomyosarcoma.

**Prognosis and predictive factors**

Prognosis is determined by patient age, histologic subtype, and tumour clinical group (2123). Younger patients have a more favourable prognosis than older
patients in all rhabdomyosarcoma subtypes. Currently, the 5-year survival is 44-69%, and 90% for clinical Group I disease (322,1084). Adults have a poor prognosis, with 5-year survival of <10% (1841,1856). Embryonal rhabdomyosarcoma has a better prognosis than alveolar rhabdomyosarcoma (2123). Botryoid and spindle cell variants (346) have a better prognosis than embryonal rhabdomyosarcoma. Furthermore, alveolar rhabdomyosarcomas with PAX7/FKHR are thought to have better prognosis than PAX3/FKHR tumours (1298).

**Angiosarcoma**

**Definition**
A malignant neoplasm of vascular phenotype whose constituent tumour cells have endothelial features.

**ICD-O code**
9120/3

**Synonyms**
Malignant haemangioendothelioma; malignant angioendothelioma; lymphangiosarcoma, haemangiosarcoma.

**Epidemiology**
Angiosarcoma is uncommon, accounting for less than 1% of all sinonasal tract malignancies (89,1603,1640,1848). They occur in all ages, with a peak in the 5th decade, and a male predilection (male:female = 2:1). Females tend to be younger at presentation by up to a decade (823,1848,2633,2795,2812).

**Etiology**
Radiation exposure (1556,1603,1848), Thorotrast, arsenic and vinyl chloride are reported risk factors (2795).

**Localization**
The maxillary sinus is most frequently affected. Other sites that may be involved primarily or secondarily include the nasal cavity and other paranasal sinuses (823,1848,2633,2795,2812).

**Clinical features**
Patients present with recurrent epistaxis, profound pallor, a mass lesion, pain (including headache, otalgia, toothache), nasal obstruction, sinusitis, nasal discharge (often described as foul-smelling and blood tinged), paraesthesia and/or loose teeth. The duration of symptoms ranges from weeks to months, but is generally short (median, 4 months).

**Macroscopy**
The tumours range up to 8 cm, with a mean of about 4 cm. They are nodular, polypoid and morulated, soft and friable, purple to red, often ulcerated with associated haemorrhage or clot and necrosis (823,1848,2633,2795,2812).

**Histopathology**
Most sinonasal angiosarcomas are histologically low-grade. They infiltrate the adjacent tissues and bone, accompanied by necrosis and haemorrhage. They comprise tortuous anastomosing vascular channels that dissect the stroma, capillary-sized vessels and cavernous vascular spaces. The lining endothelial cells range from flat to plump spindly to epithelioid, and often form papillary tufts. Intracytoplasmic vacuoles (neolumen), often containing erythrocytes, are characteristic of the epithelioid variant. The degree of nuclear pleomorphism is variable. Mitotic figures, including atypical forms, are variably present (823,1848,2633,2795,2812).

**Immunohistochemistry**
Angiosarcomas are immunoreactive for CD34, CD31, Factor VIII R-Ag and vimentin, and focally keratin (especially the epithelioid variant) and actin (2812).

**Differential diagnosis**
The differential diagnoses include granulation tissue, intravascular papillary
Malignant soft tissue tumours

endothelial hyperplasia, haemangioma, nasopharyngeal angiofibroma, angiolymphoid hyperplasia with eosinophilia, glomangiopericytoma, Kaposi sarcoma, malignant melanoma, carcinoma and large cell lymphoma [30,1388,1976, 2469,2764].

Prognosis and predictive factors

Patients are usually treated by surgical resection with radiation and/or chemotherapy. Recurrences are common (50%), likely due to incomplete excision or possible multifocality. Metastasis is uncommon, and the predilection sites are the lung, liver, spleen, and bone marrow (1976). The outcome is more favourable compared with the almost uniformly fatal outcome for cutaneous and soft tissue angiosarcomas [823, 1848,2633,2795,2812].

Malignant peripheral nerve sheath tumour

Definition

A malignant tumour of nerve sheath phenotype.

ICD-O code 9540/3

Synonyms

Neurogenic sarcoma, malignant schwannoma, neurofibrosarcoma.

Epidemiology

Malignant peripheral nerve sheath tumours (MPNSTs) comprise 2-14% of all head and neck sarcomas [1231,1562], arising de novo or less commonly in the setting of neurofibromatosis type 1 (NF1) [1059,1231,1795]. De novo MPNST peaks in the fourth decade, while those in the setting of NF1 occur at an earlier age. There is a female predominance for de novo sinonasal MPNST [1041], and a male predominance in NF1-associated MPNST [774].

Etiology

Radiation and possibly immunosuppression may be etiologic factors [1562].

Localization

They commonly arise from the ophthalmic and maxillary branches of the trigeminal (5th) cranial nerve, but can involve all of the sinonasal tract and nasopharynx [756,1153,1795,2018].

Clinical features

Presenting symptoms include mass, pain, epistaxis, deviation or swelling of tonsils, nasal obstruction, and sinusitis [27,1319,1891,1964,2119].

Macroscopy

MPNST is generally globoid to fusiform, pseudoencapsulated, cream-grey and firm, occasionally associated with surface ulceration. Infiltration into the surrounding soft tissues and bone is common. The tumours are often large (>5 cm) and may be attached to a nerve. Foci of cyst formation, necrosis and/or haemorrhage are frequent.

Tumour spread and staging

Local extension into contiguous structures along the path of the trigeminal nerve or through the foramen ovale are characteristic [1452]. MPNSTs metastasize to the lungs, bones, and/or liver, [1041] while the epithelioid variant tends to involve regional lymph nodes [1437].

Histopathology

MPNSTs can either be spindled (95%) or epithelioid (5%) [1437]. At low magnification, both types show alternating areas of dense cellularity with less cellular myxoid areas. Geographic necrosis and perivascular accentuation of tumour cells are common. The tumour cells are fusiform and plump, arranged in tightly packed fascicles woven into a vague “herringbone” pattern, while in other areas the cells are wavy with fibrillar cytoplasmic extensions, arranged in a loose myxoid.
Tumours of the nasal cavity and paranasal sinuses

**background matrix. Focal palisading of nuclei may be present.** The tumour cells are variably pleomorphic, with a high nuclear to cytoplasmic ratio and mitotic activity. Many sinonasal tract MPNSTs, in contrast to those occurring in other anatomic sites, are histologically and biologically low-grade {1041}. An origin from a nerve may or may not be apparent. MPNST with rhabdomyoblasts are known as malignant Triton tumours.

**Immunohistochemistry**

The spindle cell variant is usually focally positive for S100 protein and occasionally positive for glial fibrillary acidic protein (GFAP). However, up to 30% of MPNST may be negative for S100 protein {2784A}. The epithelioid variant is diffusely immunoreactive for S100 protein and may mimic malignant melanoma, {583,756,2603} but other melanoma markers are negative. In malignant Triton tumour, the rhabdomyoblasts are positive for desmin and other skeletal muscle markers.

**Differential diagnosis**

The differential diagnoses include synovial sarcoma, fibrosarcoma, spindle cell carcinoma, leiomyosarcoma and mucosal malignant melanoma {1041,2550, 2603}.

**Precursor lesions**

MPNST may arise from neurofibroma (especially in the setting of NF1) and only exceptionally from classic schwannoma.

**Somatic genetics**

Both NF1 alleles must be inactivated for MPNST to occur in NF1. Malignant progression from neurofibroma in NF1 is related to alterations of genes controlling cell cycle regulation, including TP53 {1459} and CDKN2A (which encodes p16) {1361,1895}.

**Genetic susceptibility**

MPNST of the sinonasal tract may be associated with NF1, typified by germline mutation of the NF1 tumour suppressor gene located on chromosome 17 {454}.

**Prognosis and predictive factors**

Surgery is the treatment of choice, although radiation and chemotherapy may have a palliative role. De novo sinonasal MPNSTs have a 5-year survival rate of about 90%, which is superior to that of 50-65% for MPNSTs arising in other anatomic locations {1041,1562,2715}. However, NF1-associated sinonasal MPNSTs have a 5-year survival rate of only about 15% {2119}. Poor prognostic factors include male gender, high tumour cellularity and high mitotic activity {1041}.
**Desmoid-type fibromatosis**

**Definition**
A locally aggressive, cytologically bland tumour of (myo)fibroblastic phenotype.

**ICD-O code** 8821/1

**Synonyms**
Extra-abdominal desmoid, extra-abdominal fibromatosis, desmoid tumour, aggressive fibromatosis, juvenile desmoid-type fibromatosis, infantile fibromatosis.

**Epidemiology**
Although 15% of cases of desmoid-type fibromatosis occur in the head and neck, the sinonasal tract is uncommonly involved. All ages can be affected, especially children. There is a male predilection.

**Localization**
The maxillary sinus and turbinates are usually affected, and the involvement can occasionally be bilateral.

**Clinical features**
Symptoms include nasal obstruction, epistaxis, mass, facial pain, tooth displacement, and a non-healing tooth extraction site.

**Macroscopy**
The lesion is tan-white, glistening, and rubbery to firm, and is often infiltrative. It measures up to 7 cm. Fibromatosis may be multicentric, especially in the setting of Gardner syndrome.

**Histopathology**
This is an infiltrative growth with low to moderate cellularity, comprising broad fascicles of bland-looking spindle cells and collagen fibers often arranged in a uniform direction. Elongated blood vessels are frequently observed running parallel to each other. The spindle cells have a myofibroblastic appearance, with low nuclear to cytoplasmic ratio and uniformly bland ovoid nuclei with indistinct nucleoli. Mitotic figures are infrequent and never atypical. The matrix is collagenized to focally myxoid, and keloid-like collagen may be present. The main differential diagnoses include hypertrophic scar and fibrosarcoma. Diagnosis does not require immunohistochemistry, but vimentin and actins are positive. Desmin may be focally positive.

**Prognosis and predictive factors**
Fibromatosis can be locally aggressive and involve contiguous structures, with approximately 20% recurrence rate, but it does not metastasise. Recurrence generally occurs within the first few years and is related to inadequacy of surgical margins.

**Inflammatory myofibroblastic tumour**

**ICD-O code** 8825/1

Inflammatory myofibroblastic tumour uncommonly occurs in the sinonasal tract. Please see corresponding section in 'Tumours of the hypopharynx, larynx and trachea'.

**Glomangiopericytoma**

**Definition**
A sinonasal tumour demonstrating perivascular myoid phenotype.

**ICD-O code** 9150/1

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*Fig. 1.50* Desmoid-type fibromatosis. Heavily collagenized stroma with spindle cells with bland nuclei and elongated vessels.

*Fig. 1.51* Glomangiopericytoma. Characteristic diffuse growth within the submucosa, with effacement of the normal components of the submucosa and preservation of mucoserous glands. The overlying respiratory epithelium remains intact.
Tumours of the nasal cavity and paranasal sinuses

Synonyms
Sinonasal haemangiopericytoma; hae-mangiopericytoma-like tumour, sinonasal glomus tumour; haemangiopericytoma.

Epidemiology
Sinonasal glomangiopericytomas predilect to the nasal cavity and paranasal sinuses, where they comprise <0.5% of all neoplasms \(\{343,482,2600\}\). There is a very slight female predominance. All ages can be affected (in-utero to 86 years), but the peak is in the 7th decade.

Localization
Tumours most frequently arise unilaterally in the nasal cavity alone, although extension into paranasal sinuses can occur. Isolated paranasal sinus involvement is uncommon. Rarely, large tumours may appear to arise bilaterally \(\{216,343,482,638,649,1364,1779,1846,2276,2600,2729\}\).

Clinical features
The majority of patients present with nasal obstruction, epistaxis, or non-specific findings, such as a mass, polyp, difficulty breathing, sinusitis, headache and nasal congestion, present for an average duration of <1 year. Imaging studies show nasal cavity or paranasal sinus opacification by a polypoid mass lesion, frequently accompanied by sinusitis, bone erosion and sclerosis \(\{482,2600,2729\}\).

Macroscopy
The generally polypoid tumours range up to 8 cm, with a mean size of about 3 cm. The tumours are beefy red to greyish pink, soft, edematous, fleshy to friable masses, often demonstrating haemorrhage.

Histopathology
This is a subepithelial well-delineated but unencapsulated cellular tumour, effacing or surrounding the normal structures. It is comprised of closely packed cells, forming short fascicles and sometimes exhibiting a storiform, whorled or palisaded pattern, interspersed with many vascular channels. The latter are in the form of capillary-sized to large patulous spaces that may have a “staghorn” or “antler-like” configuration. A prominent peritheliomatous hyalinization is characteristic. The neoplastic cells are uniform, elongated to oval, and possess vesicular to hyperchromatic, round to oval to spindle-shaped nuclei, and lightly eosino-

phile cytoplasm. Mild nuclear pleomorphism and occasional mitotic figures may be present, but necrosis is not found. Extravasated erythrocytes, mast cells, and eosinophils are nearly ubiquitously present. Occasionally, tumour giant cells, fibrosis or myxoid degeneration may be seen.

Immunohistochemistry
Immunohistochemically, glomangiopericytoma is distinctly different from soft tissue haemangiopericytoma by yielding diffuse reactivity for actsins, factor XIIIA and vimentin, and lacking strong diffuse staining for CD34. Bcl-2, FVIII-R Ag, CD99 and CD117 are negative \(\{343,638,1364,2070,2600\}\).

Differential diagnosis
The differential diagnoses include haemangioma, solitary fibrous tumour, glomus tumour, leiomyoma, synovial sarcoma and leiomyosarcoma.

Histogenesis
This tumour has been known as haemangiopericytoma-like tumour or sinonasal haemangiopericytoma, but it is clinically, morphologically and biologically distinct from soft tissue-type or dura-based haemangiopericytoma \(\{446,544,773,936,1723,1724,2276,2386,2689\}\). The proposed cell of origin is a modified perivascular glomus-like myoid cell.

Prognosis and predictive factors
Sinonasal glomangiopericytoma is indolent, with an overall excellent survival (>90% 5-year survival) achieved with complete surgical excision. Recurrence, which develops in up to 30% of cases, may occur many years after the initial surgery \(\{216,343,638,649,2600\}\). Aggressive-behaving glomangiopericytomas (malignant glomangiopericytomas) are uncommon \(\{216,343,482,556,1779,2600\}\), and usually exhibit the following features: large size (>5 cm), bone invasion, profound nuclear pleomorphism, increased mitotic activity (>4/10 high power fields), necrosis, and proliferation index >10% \(\{216,343,1364,2600\}\).
Extrapleural solitary fibrous tumour

ICD-O code 8815/1
Solitary fibrous tumours are tumours of CD34-positive fibroblasts which often show a prominent haemangiopericytoma-like vascular pattern. They are exceedingly uncommon in the upper respiratory tract, where they comprise <0.1% of all neoplasms. All ages can be affected without a gender predilection. Tumours can affect the nasal cavity, nasopharynx or paranasal sinuses. Patients present with nasal obstruction, epistaxis or other nonspecific symptoms. The tumour is usually polypoid and firm. It is composed of a variably cellular proliferation of bland spindle-shaped cells with nondescript growth pattern associated with “ropy” keloidal collagen bundles and interlaced thin-walled vascular spaces. The latter may be prominent and exhibit a haemangiopericytoma-like pattern. Solitary fibrous tumours are immunoreactive for CD34 and bcl-2, and generally lack actin immunoreactivity. The diagnosis rests on a combination of architectural, cytomorphic, and immunophenotypic features. The differential diagnoses include sinonasal glomangiopericytoma, fibrous histiocytoma, leiomyoma, schwannoma, synovial sarcoma, and fibrosarcoma. Complete surgical removal yields the best patient outcome. Occasional cases may potentially show a malignant behaviour {158,834,997,1706,2600,2800, 2914}. See WHO Classification of Tumours of Soft Tissue and Bone [775].

Fig. 1.53 Solitary fibrous tumour of nasal cavity. A Circumscribed tumour beneath epithelium. B Bland-looking spindly cells are tightly intertwined with collagen fibers.

Fig. 1.54 Solitary fibrous tumour A Cytologically bland cells are arranged in streaming fashion, with collagen deposited between the cells. Haemorrhage is seen.. B A solitary fibrous tumour strongly and diffusely immunoreactive for CD34.
**Myxoma**

Myxoma is a benign soft tissue tumour characterized by bland spindle shaped cells embedded in hypovascular, myxoid stroma. For details see Chapter 6 (Odontogenic tumours).

**Leiomyoma**

**Definition**
A benign tumour of smooth muscle phenotype.

**ICD-O code**
8890/0

**Synonyms**
Angioleiomyoma; vascular leiomyoma; leiomyoblastoma

**Epidemiology**
Primary leiomyomas of the sinonasal tract are very rare [824,1144,1307,1535,1796,2114,2635,2695]. There is a peak in the 6th decade, although men are younger than women by a decade at initial diagnosis. There is a female predilection, with a ratio of 3.5:1.

**Etiology**
Other than prior radiation, there are no known risk factors.

**Localization**
The turbinates are affected most frequently, [824,1144,1307,1535,1796,2114,2635,2695] with isolated cases reported in the paranasal sinuses alone or in combination with the nasal cavity [1842].

**Clinical features**
Nearly all patients have nasal obstruction, although nasal discharge, epistaxis, headaches and pain are also common [824,2114,2635,2695].

**Macroscopy**
These tumours have an average size of 2 cm, but rare ones may be as large as 10 cm. They are sessile or polypoid, with a smooth, well circumscribed border.

**Histopathology**
Leiomyomas are located in the submucosa, separated from a typically intact mucosa. They are composed of spindled cells arranged in orderly fascicles, whorls and intersecting bundles. The cells have elongated, vesicular to stippled nuclei with blunt ends (“cigar-shaped”), surrounded by spindled, bipolar, fibrillar eosinophilic cytoplasm. They are highly differentiated, with little or no atypia, although rare cells may exhibit nuclear pleomorphism [2695]. Necrosis and invasion are absent, and mitotic activity is scarce. Mucinous degeneration, hyalinization or fibrosis, and adipocytes can be seen, but these features are usually focal and more likely seen in larger lesions [1144,1535,1796,2695]. Vascular leiomyoma (angiomyoma) contains capillary, cavernous or venous vascular spaces, with the smooth muscle cells being associated with the vessel walls and represents the most common type of benign smooth muscle tumour in this region.

**Immunoprofile**
The tumour cells are diffusely and strongly immunoreactive for actins, desmin, h-caldesmon and vimentin. The Ki-67 index is usually <5% [1144].

**Differential diagnosis**
The differential diagnoses include sinonasal glomangiopericytoma, haemangioma, peripheral nerve sheath tumour and leiomyosarcoma.

**Prognosis and predictive factors**
Complete excision is curative.

**Haemangioma**

**Definition**
A benign neoplasm of vascular phenotype.

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**Fig. 1.55 A** Myxoma. The stellate cells have thin processes which extend out into the background mucinous matrix. **B** Vascular leiomyoma. Spindle tumour cells are identified scrolling off thick muscle-walled vessels.
Synonyms
Lobular capillary haemangioma; pyogenic granuloma; capillary haemangioma; cavernous haemangioma; epulis gravidarum.

Epidemiology
Mucosal haemangiomas of the nasal cavity, paranasal sinuses and nasopharynx account for 10% of all head and neck haemangiomas and approximately 25% of all non-epithelial neoplasms of this anatomical region. The haemangiomas occur in all ages, although there is a peak in children and adolescent males, females in the reproductive years, and then an equal distribution beyond 40 years of age. Patients with cavernous haemangiomas tend to be men in the 5th decade. (166,167,658,823,1037,1189,1270,1738,2056,2333).

Etiology
Lobular capillary haemangioma (pyogenic granuloma) has an association with injury and hormonal factors (pregnancy or oral contraceptive use) (2158).

Localization
The septum is most frequently affected (specifically, the anterior septum in Little's area), followed by the turbinates (usually the tip) and the sinuses (658,823,1037,1189,1270,1738,2056,2333).

Clinical features
Patients present with unilateral epistaxis and/or an obstructive painless mass. Sinus lesions present as sinusitis, proptosis, mass, anaesthesia or pain.

Symptoms are usually present for a short duration (658,823,1037,1189,1270,1738,2056,2333,2753).

Macroscopy
The tumours range up to 5 cm, with a mean size of <1.5 cm. Grossly, they appear as a red to blue submucosal soft, compressible, flat or polypoid lesion, often with an ulcerated surface. Cavernous haemangiomas are spongy on sectioning (658,823,1037,1189,1270,1738,2056,2333,2753).

Histopathology
Haemangiomas are usually localized and can be divided into capillary and cavernous types based on the size of the blood vessels. Haemangiomas are a more diffuse lesion often involving contiguous structures (823,1270,2126).

Lobular capillary haemangioma is a circumscribed lesion comprising lobules of capillaries lined by plump endothelial cells and supported by prominent pericytes. The lobules are separated by a fibromyxoid stroma. The cellularity of the lobules may be quite high. Mitotic figures are often observed, but are never atypical. The surface epithelium often forms collarettes around the lesion (658,823,1037,1189,1270,1738,2056,2333). If the lesion is ulcerated and inflamed, the term ‘pyogenic granuloma’ has been applied.

Cavernous haemangiomas are frequently intraosseous or involve the turbinates or lateral nasal wall. They are composed of multiple, large thin-walled, dilated blood vessels separated by scant fibrous stroma (658,823,1037,1189,1270,1738,2056,2333).

Venous haemangiomas are composed of thick-walled veins with abundant smooth muscle, but rarely occur in this location.

Immunoprofile
The tumour cells are immunoreactive for Factor VIII related antigen, CD34, CD31 and Ulex europaeus I lectin. The proliferated blood vessels are enwrapped by actin-positive pericytes.

Differential diagnosis
Haemangiomas should be distinguished from granulation tissue, telangiectasias, vascular malformations, vascular polyps (haemorrhagic type), papillary endothelial hyperplasia, angiofibroma, bacillary angiomatosis, angiolymphoid hyperplasia with eosinophilia, glomus tumour, sinonasal glomangiopericytoma, lymphangioma, Kaposi sarcoma, and angiosarcoma. Haemangiomas can be distinguished from granulation tissue by the lobular arrangement of the capillaries in the former and the more parallel arrangement of vessels in the latter. The distinction between a haemangioma and telangiectasias may be difficult but is facilitated in a patient with a known family history of hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) (658,823,1037,1189,1270,1738,2056,2073,2333,2600).

Prognosis and predictive factors
Haemangiomas are generally easy to remove, although larger tumours may be complicated by excessive bleeding. They should be removed in all ages, especially in children since aplasia of the nasal cartilages may cause eventual disfigurement. If the tumour is pregnancy-
related, regression will often occur after parturition. Multiple recurrences are more common in children if the lesional bed is not completely eradicated.

**Schwannoma**

**Definition**
A usually encapsulated, benign tumour composed of differentiated, neoplastic Schwann cells.

**ICD-O code**
9560/0

**Synonyms**
Neurilemoma, neurilemmoma, benign peripheral nerve sheath tumour.

**Epidemiology**
Less than 4% of schwannomas involve the nasal cavity and paranasal sinuses [1091,2351], and they occur in middle-aged adults with an equal gender distribution [2351].

**Localization**
Sinonasal schwannomas arise from the branches of the trigeminal (5th) nerve and autonomic nervous system, and most commonly involve the ethmoid and maxillary sinuses, followed by the nasal cavity, sphenoid and frontal sinuses [1023,1091,2018,2351]. Cellular schwannoma tends to be located in the midline.

**Clinical features**
The presenting symptoms include obstruction, rhinorrhea, epistaxis, anosmia, headache, dysphagia, hearing loss, facial or orbital swelling, and pain [2018,2351].

**Macroscopy**
Sinonasal schwannoma ranges in size up to 7 cm. It is a well-delineated but non-encapsulated globular, firm to rubbery yellow-tan mass. The cut surfaces show tan-grey, yellowish, solid to myxoid and cystic tissue, commonly with haemorrhage.

**Tumour spread and staging**
The tumour can expand into the orbit, nasopharynx, pterygomaxillary fossa and cranial cavity [2351].

**Histopathology**
Schwannoma is composed of cellular Antoni A areas with Verocay bodies and hypocellular myxoid Antoni B areas. The cells are fusiform with elongated fibrillary cytoplasm, and buckled to spindled nuclei which show little pleomorphism, although scattered large pleomorphic or bizarre cells can be present in some cases. Nuclear palisading is often evident in some foci. There are frequently small to medium-sized vessels with ectasia, thrombosis and perivascular hyalinization in the Antoni B areas. Extensive degenerative changes can occur, and may result in only a thin rim of recognizable tumour. Cellular variants exhibit only the Antoni A pattern, but no fascicular growth or Verocay bodies.

**Immunoprofile**
The tumour cells are strongly and diffusely immunoreactive for S100 protein. CD34 only stains some more slender cells in the Antoni B areas. Neurofilament is absent. GFAP and keratins may be positive.

**Prognosis and predictive factors**
Schwannoma is a benign tumour with a very low recurrence potential. Malignant transformation is exceptional [1690].

**Neurofibroma**

**Definition**
A benign tumour of peripheral nerve sheath phenotype with mixed cellular components, including Schwann cells, perineurial hybrid cells and intraneural fibroblasts.

**ICD-O code**
9540/0

**Epidemiology**
Neurofibromas are extremely rare in the sinonasal tract. In NF1-related neurofibromas, patients tend to be younger, with a male predominance [2745]. For the more common sporadic neurofibromas,
all ages may be affected, although patients tend to be older with an equal gender distribution.

**Localization**
The tumour arises from the ophthalmic or maxillary branches of the trigeminal (5th) nerve and is most commonly located in the maxillary and ethmoid sinuses and/or nasal cavity [288]. Plexiform neurofibroma may occur in the sinonasal area where it is found in the maxillary sinus [817], usually associated with NF1.

**Clinical features**
Symptoms include epistaxis, rhinorrhea, swelling, mass, obstruction, and pain [61,2018].

**Macroscopy**
The tumour is firm, glistening, grey-tan, fusiform, and sometimes polypoid, in a submucosal location with an intact surface epithelium [61,1095].

**Histopathology**
Neurofibromas are generally submucosal paucicellular lesions. They are composed of spindled cells with wavy, dark-staining nuclei and scanty cytoplasm, in a background of wavy collagen fibres, myxoid stroma and mast cells. The centre of the lesion usually shows residual neurites.

**Immunoprofile**
The tumour is diffusely immunoreactive for S100 protein, but the proportion of positive cells is lower than that in schwannoma. CD34 stains the admixed fibroblasts.

**Genetic susceptibility**
Sinonasal neurofibromas are generally not associated with NF1 [1091,1095, 2018].

**Prognosis and predictive factors**
Neurofibromas are benign and have a very low recurrence rate. A small percentage of cases may undergo malignant transformation.

**Meningioma**

**Definition**
A benign neoplasm of meningothelial cells.

**ICD-O code**
9530/0

**Epidemiology**
Primary extracranial (ectopic, extracavarial) meningiomas of the sinonasal tract are rare, comprising <0.5% of non-
epithelial neoplasms \{814,873,1109,1781,2019,2221,2599\}. They should be distinguished from intracranial meningiomas with extracranial/extraspinal extension into the sinonasal tract \{721,814,2599\}. Any age can be affected, and there is a slight female predilection. Men tend to be younger than women by about a decade.

**Localization**

Sinonasal tract meningiomas involve both the nasal cavity and paranasal sinuses more frequently than either location alone. Most tumours are left-sided \{814,873,1109,1781,2019,2221,2599\}.

**Clinical features**

Symptoms include a mass (often polypoid), nasal obstruction, epistaxis, sinusitis, pain, headache, seizure, exophthalmos, periorbital edema, visual disturbance, ptosis, and facial deformity \{814,873,1109,1781,2019,2221,2599\}. Symptoms are present for an average of 4 years.

**Macroscopy**

The tumours range up to 8 cm, with a mean of about 3 cm. They may infiltrate bone and rarely ulcerate the mucosa. The cut surface is grey-white, tan or pink, gritty, firm to rubbery. Calcifications and fragments of bone are frequently visible.

**Tumour spread and staging**

Primary extra-cranial meningiomas have not been reported to metastasize \{814,873,2019,2599\}.

**Histopathology**

Sinonasal meningiomas can exhibit a variety of histological patterns, most commonly meningotheliomatous, characterized by lobules of cells with whorl formation, indistinct cell borders, and bland nuclei with delicate chromatin \{1329,2599\}. Intranuclear pseudoinclusions and psammoma bodies are common. Other variants can also occur in the sinonasal tract, such as transitional, metaplastic (lipidized cells within tumour), and psammomatous type \{1329\}.

**Immunoprofile**

Meningiomas are immunoreactive for epithelial membrane antigen and vimentin, but usually negative for cytokeratin, although rare lesions can exhibit focal and weak cytokeratin immunoreactivity. They are frequently positive for progesterone receptor (50%) and occasionally for oestrogen receptor (25%). Glial fibrillary acidic protein and smooth muscle actin are negative.

**Differential diagnosis**

The differential diagnoses include carcinoma, melanoma, aggressive psammomatoid ossifying fibroma and follicular dendritic cell sarcoma/tumour \{2599,2771\}.

**Histogenesis**

Meningiomas are derived from arachnoid cap cells located extra-cranially within the sheaths of nerves or vessels.

**Prognosis and predictive factors**

Complete surgical extirpation is sometimes difficult, and accounts for the up to 30% recurrence rate \{1109,2019,2599\}. The rare deaths are related to compromise of mid-facial structures or complications of surgery, rather than the aggressive nature of the tumour. Histologic features (such as hypercellularity, nuclear pleomorphism, necrosis), proliferation index and progesterone receptor status do not influence prognosis \{1138,1139,1426,1666,2599\}. 
Chondrosarcoma, including mesenchymal chondrosarcoma

Definition
Chondrosarcoma is a malignant tumour of hyaline cartilage. Mesenchymal chondrosarcoma is a malignant small round cell neoplasm with focal cartilaginous differentiation, and often with a pericytomatosus vascular pattern.

ICD-O codes
Chondrosarcoma 9220/3
Mesenchymal chondrosarcoma 9240/3

Synonym
Polyhistioma

Epidemiology
These tumours are rare in the facial skeleton. Chondrosarcomas account for <16% of all sarcomas of the nasal cavity, paranasal sinuses and nasopharynx (256,463,1367,4045). Chondrosarcoma affects older adults, with a male predilection. Mesenchymal chondrosarcoma is extremely rare, and affects young adults, with a female predilection.

Localization
Chondrosarcoma involves the alveolar portion of the maxilla, the maxillary sinus or the nasal septum. Mesenchymal chondrosarcoma involves the mandible and maxilla almost equally.

Clinical features
Patients with involvement of the nose present with nasal obstruction. Painful swelling is common with other sites of involvement.

Imaging
On plain radiographs, both tumours show osteolysis with stippled calcification, cortical destruction and possible soft tissue extension. Computerized tomograms and magnetic resonance images are useful in evaluating the extent of disease (463).

Macroscopy
Chondrosarcomas are lobulated pale-blue glistening masses that may show cystic change. Mesenchymal chondrosarcomas have the fish-flesh appearance of high-grade sarcomas; chalky foci of calcification may offer a diagnostic clue.

Histopathology
Chondrosarcomas are often lobulated, and show round to oval cells in lacunae with a blue chondroid matrix that may show myxoid changes. Most are low-grade. Increased cellularity and permeation of the intertrabecular spaces of bone, if identified, are the most important features that distinguish chondrosarcoma from chondroma. Radiological correlation is required for a definitive diagnosis (4045).

Mesenchymal chondrosarcomas show a mixture of hyaline cartilage and small round to oval cells with hyperchromatic nuclei, frequently arranged in a pericytomatosus vascular pattern. These cells
are frequently immunoreactive for CD99. The relative amounts of the two elements are quite variable. The chondroid lobules have the appearance of well-differentiated chondrosarcoma.

**Prognosis and predictive factors**

Chondrosarcomas are associated with an excellent prognosis if the lesions are completely resected. Approximately 20% of patients die of tumour, most often with uncontrolled local recurrence. Mesenchymal chondrosarcoma is a high-grade tumour with an unpredictable prognosis. Patients with tumour of the facial skeleton do better than those with tumours of the remainder of the skeleton.

**Osteosarcoma**

**Definition**

Osteosarcoma is a primary malignant tumour of bone in which the neoplastic cells produce osteoid or bone.

**ICD-O code**

9180/3

**Synonym**

Osteogenic sarcoma

**Epidemiology**

Osteosarcomas of the jaws are very rare, with an incidence of 0.7 per million. They are extremely rare in other head and neck sites. Patients are a decade older than those with extragnathic osteosarcomas. There is a modest male predilection.

**Etiology**

Over 10% of tumours are post-radiation, including Thorotrast exposure.

**Localization**

The maxilla and the mandible are affected almost equally. In the maxilla, the alveolar ridge and the antrum are predominantly involved, whereas in the mandible, the body is the main site.

**Clinical features**

Symptoms include swelling with or without pain and loosening of teeth. On plain radiograph, the tumour is usually lytic but may be sclerotic or mixed. In over half of the lesions, there is soft tissue extension. Computerized tomogram is better in demonstrating matrix mineralization and soft tissue extension.

**Macroscopy**

The tumours vary from the lobulated blue colour of cartilage to fleshy white to densely sclerotic masses.

**Histopathology**

Osteosarcomas of the jaws are generally better differentiated than extragnathic osteosarcomas. There is commonly chondroblastic differentiation, characterized by lobules of atypical-appearing chondrocytes in lacunae. There is a typical condensation of nuclei toward the periphery of the lobules, where sheets of spindle cells may be seen. The centre of the chondroid lobules shows bone formation in the form of trabeculae. The remainder show osteoblastic or fibroblastic features. It is unusual to see benign giant cells within the tumour.

**Prognosis and predictive factors**

Some studies have shown that patients with osteosarcoma of the jaws have a better survival than those with extragnathic osteosarcomas. However, some other studies have not confirmed this finding. Complete surgical resection is associated with better prognosis.
**Fibrous dysplasia**
See Chapter 6 for details.

**Giant cell lesion**

**Synonym**
Giant cell granuloma.

Extragnathic giant cell lesion may rarely involve the paranasal sinuses [2161, 2243, 2479, 2648, 2839]. Symptoms include pain, visual disturbances, exophthalmos, epistaxis, lacrimation, anaesthesia and swellings [728, 1867, 2322, 2839]. Plain radiographs show nonspecific osteolytic defects. Their extent and possible impingement on brain or orbital contents is better visualized in cross-sectional studies (CT, MRI) [2322, 2839]. Brown tumour of hyperparathyrodism should be excluded.

Please refer to Chapter 6 for details.

**Giant cell tumour of bone**

**Definition**
An aggressive but benign neoplasm containing spindle-shaped stromal cells, mononuclear round to oval cells resembling histiocytes, and abundant evenly distributed osteoclastic giant cells.

**ICD-O code**
9250/1

**Epidemiology**
Giant cell tumour (GCT) accounts for about 5% of all bone tumours. Most cases occur in patients between 20 and 50 years [523, 775, 1146, 1369]. CGT is slightly more common in women than in men [523, 775, 2831].

**Localization**
In the skull, in the absence of Paget disease, the bones developing from endochondral ossification, i.e. sphenoid, ethmoid and temporal bone, are almost exclusively involved [207, 496, 870, 875].

**Clinical features**

**Signs and symptoms**
Clinical symptoms of GCTs depend on the site of occurrence. Sphenoidal lesions are associated with headache, diplopia and vision impairment or cranial nerve palsies (II, III, IV, V, VI and combinations). Temporal bone involvement causes deafness (conductive: middle ear and mastoid; sensorineural combined with vertigo: petrous bone), retroauricular pain, or swelling [676, 2328]. Duration of symptoms ranges from weeks to years [207].

**Imaging**
On plain radiographs and CT, GCT presents with a nonspecific expansile and destructive osteolysis, generally lacking any matrix mineralization. The lesion shows contrast enhancement on CT [207, 2177, 2806]. A soft tissue mass in the sphenoid sinus or the sella turcica, displacing the pituitary gland, is best seen on cross-sectional studies (CT, MRI) [983, 2177, 2556].

**Histopathology**
The tumour is characterized by abundant multinucleated osteoclastic giant cells, with up to 50-100 nuclei, that are evenly distributed among sheets of stromal cells. In some areas, ovoid to plump spindled stromal cells are more prominent, and giant cells may be lacking. Regressive changes, including fibrosis, foam cell aggregates, haemosiderin deposits, and even necrosis may be present. Small foci of reactive woven bone are often seen. Mitoses are easily

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Fig. 1.67 Giant cell tumour. Large geographic osteolytic lesion (OL) at the base of the skull with an irregular dorsal margin.

Fig. 1.68 Central giant cell lesion/granuloma. A Osteodestructive lesion of the right maxillary sinus extending into the nasal cavity, eroding the orbital floor and destroying the alveolar process of the maxilla with protrusion into the oral cavity. B On T1 images the signal intensity is low. C Fluid levels are indicative for a pseudocystic (ABC-like) component.
Tumours of the nasal cavity and paranasal sinuses

found in the mononuclear cells, but atypical ones do not occur and, if present, are a strong indicator for progression to malignant GCT [272]. Intravascular growth, particularly in the tumour periphery, may be noted, but has no prognostic relevance [207,775,2831].

Histogenesis
The ovoid to plump spindled stromal cells represent the active proliferating tumour cell pool [2190], capable of secreting cytokines and differentiation factors, including receptor activator of nuclear factor \( \kappa \) ligand (RANKL) [2207]. These factors attract monocytes, the second cell type in GCT, and promote fusion to osteoclasts, the third cell type in GCT. The monocytes and osteoclast-like giant cells represent a non-neoplastic tumour component [775,2831].

Genetics
Cytogenetic studies reveal telomeric associations (TAS) as the most frequent chromosomal aberration [272]. Some GCTs show rearrangements in 16q22 or 17p13, similar to aneurysmal bone cyst, which is often associated with GCT. These rearrangements may indicate the possible presence of an aneurysmal bone cyst component [775].

Prognosis and predictive factors
GCT of the skull is a locally aggressive lesion. Treatment consists of complete removal, if possible. Radiotherapy is also applied [207,1146]. Histologically malignant GCT of the skull has been rarely described; sometimes associated with Paget disease [365,1474].

Chondroma
Chondromas of the sinonasal tract are extremely rare, and any cartilaginous tumour greater than 2 cm occurring in this site should be considered potentially malignant until proven otherwise.

ICD-O code 9220/0

Osteoma
Definition
A benign lesion composed of mature bone with a predominantly lamellar structure.

ICD-O code 9180/0

Synonyms
In the jaws and calvaria, the terms exostosis and osteoma have been used interchangeably [131]. The term ‘osteoma’ should be used in a restricted sense limited to lesions of the paranasal sinuses, facial bones and orbit, although it has been used in the literature to describe calvarian and mandibular ivory exostosis, surface (juxtacortical) osteoma of the long bones, torus palatinus and torus mandibularis.

Epidemiology
Among patients with sinonasal radiographs taken for a variety of reasons, up to 1% have been found to have osteomas. It may occur at any age, but especially in young adults. There is a 2:1 male predominance.

Localization
The osteomas may be single or multiple; central or on the bone surface, where they can be sessile or rarely pedunculated. They occur most commonly in the frontal and ethmoid sinuses. The maxillary and sphenoid sinuses are infrequently involved. In the jaws, the angle of the mandible is more frequently involved than the coronoid process or condyle.

Clinical features
Osteomas are often asymptomatic and incidentally discovered. However they can produce pain or symptoms related to the location. Multiple jaw osteomas are a frequent component of the Gardner syndrome (a form of familial adenomatous polyposis), being found in 70-90% of patients. Osteomas are radiodense, sharply defined, well-circumscribed lesions occurring in either a central or peripheral location.

Macroscopy
The lesion is a well-circumscribed white bony mass, which is occasionally polypoid or exophytic.

Histopathology
Osteoma is characterised by compact cortical bone with scanty intervening fibrovascular stroma. In some cases, there is a peripheral rim of dense sclerotic lamellar bone surrounding trabeculae of lamellar or occasionally woven bone separated by fibrofatty vascular tissue.

Genetic predisposition
The presence of multiple osteomas is an
important clue that the patient may have Gardner syndrome.

**Prognosis and predictive factors**

No therapy is required unless the lesion causes cosmetic or functional problems. A local resection is the treatment of choice in such circumstances.

### Chondroblastoma and chondromyxoid fibroma

**ICD-O codes**

- Chondroblastoma 9230/0
- Chondromyxoid fibroma 9241/0

Chondroblastomas and chondromyxoid fibromas are rare in the head and neck (177,988,1024,1120,1185,1348,1349,1356,1466,2559,2683,2730). See WHO Classification of Tumours of Soft Tissue and Bone (775).

### Osteochondroma (exostosis)

**Definition**

A pedunculated or sessile exophytic bony projection with a cartilaginous cap. The bony component is continuous with the underlying bone.

**ICD-O code** 9210/0

**Epidemiology**

Osteochondroma is one of the most common lesions of the long and flat bones. It may be solitary or multiple. In the facial bones, osteochondromas are very rare and almost invariably single. Osteochondromas of the facial skeleton have not been reported in the setting of multiple hereditary exostoses. The mean age at diagnosis is 40 years, which is older than that of patients with tumours occurring outside the head and neck. Females are more commonly affected than males.

### Osteoid osteoma

**ICD-O code** 9191/0

**Definition**

A rare, benign bone-forming tumour of limited growth potential, usually less than 1.5 cm, typically associated with nocturnal pain that is relieved by salicylates. It is very rare in the head and neck. It occurs in young patients (first three decades), with male predominance. On plain radiographs, dense cortical sclerosis surrounds a radiolucent nidus. Histologically, the nidus shows interconnected, ossified woven bone rimmed by osteoblasts. Fibrous tissue, vessels and multinucleated giant cells are identified in between the bony trabeculae. See WHO Classification of Tumours of Soft Tissue and Bone (775).

**Osteoblastoma**

**ICD-O code** 9200/0

**Definition**

A rare, benign, bone-forming tumour in which osteoblasts rim woven bony trabeculae, forming a mass usually over 2 cm.

**Epidemiology**

Osteoblastoma is rare, and 90% of cases occur below the age of 30 years. It is more common in males.

**Localization**

In the head and neck, the most common site of involvement is the jaws, followed by the cervical vertebrae and the skull (1570). The mandible is affected about two to three times more often than the maxilla. Most arise in the body of the mandible, rarely in the midline or coronoid process.

**Clinical features**

Osteoblastomas of the jaw cause swelling and toothache, and in the cervical spine, pain, scoliosis and nerve root compression. In contrast to osteoid osteoma, the pain is rarely nocturnal and not relieved by salicylates.

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**Fig. 1.70** A Osteoma of the right parietal bone. Mature lamellar bone with osteon-like structures. B Osteoid osteoma. Osteoblasts surround the trabeculae. C Nidus of an osteoblastoma, showing a single layer of osteoblasts lining the bony trabeculae.
On plain radiographs, osteoblastoma is a sharply circumscribed, oval-round lytic lesion. It may have a mixed lytic and sclerotic pattern, reflecting the degree of mineralization of the matrix. A reactive bony shell is detected at the periphery. Radiographic features indistinguishable from malignant lesions are reported in about one-third of cases.

**Macroscopy**
It is a red and gritty lesion often with cyst formation. The border between the tumour and the host bone is very sharp.

**Histopathology**
Woven bony trabeculae, rimmed by osteoblasts are haphazardly distributed within a richly vascularized fibrous stroma accompanied by osteoclast-like giant cells. Mitotic figures may be present, but without atypical forms. Degenerative nuclear atypia is occasionally present. When large plump osteoblasts with prominent nucleoli predominate, the tumour is often referred to as epithelioid osteoblastoma or aggressive osteoblastoma. However, these histologic features are not necessarily indicative of aggressive behaviour. Rarely, focal areas of hyaline cartilage may be identified, as well as secondary aneurysmal bone cyst-like changes. At the periphery, there is no permeative growth pattern. The histologic features are identical to cementoblastoma. Tumours showing direct continuity with the root of a tooth are preferably termed a cementoblastoma.

**Prognosis and predictive factors**
Curettage or local excision is the treatment of choice. In the few cases with recurrence, a further conservative treatment will control the disease.

**Ameloblastoma**
Ameloblastomas are very rare in the sinonasal tract and nasopharynx [1554, 2257]. See Chapter 6 on odontogenic tumours for details.

**ICD-O code**
9310/0

**Nasal chondromesenchymal hamartoma**

**Definition**
A tumefactive process arising in the nasal cavity and/or paranasal sinuses whose mixed chondroid, stromal, and cystic features are morphologically similar to the chest wall hamartoma.

**Epidemiology**
There are only 12 reported cases [45, 1140, 1284, 1311, 1678]. A pleuropulmonary blastoma was diagnosed in one of these children [1678]. One infant with the prenatal detection of hydrocephalus also had absence of the corpus callosum and hypoplasia of the cerebellar vermis. The age range is newborn to 16 years with most cases presenting in the first year of life, often before 3 months of age. There is a male predilection of approximately 3:1.

**Clinical features**

**Signs and symptoms**
Respiratory difficulty, the discovery of an intranasal mass and/or facial swelling are the most common presenting features. The respiratory distress is detected in the immediate neonatal period or develops later during feedings with accompanying cyanosis. A unilateral mass in the nasal cavity is the most consistent finding on physical examination.

**Imaging**
A mass density in the nasal cavity and/or the contiguous paranasal sinuses is noted on radiographic examination. Magnetic resonance or computed tomographic imaging discloses a dense mass with or without calcifications or a heterogeneous signal in a lesion with cystic features. Extension or involvement of the maxillary and/or ethmoid sinuses and erosion into the anterior cranial fossa are other accompanying changes.

**Macroscopy**
Multiple solid and cystic fragments of tis-
sues, some with identifiable foci of cartilage reflect the piecemeal nature of the resection in most cases. The precise site of origin of the mass has varied from the nasal septum, upper nasal cavity or floor of the anterior cranial fossa.

**Histopathology**
All tumours have had nodules of cartilage varying in size, contour and degree of differentiation. Some nodules resemble the chondromyxomatous nodules of a chondromyxoid fibroma, whereas others are well-differentiated cartilaginous nodules. At the periphery of the chondroid nodules, there is a loose spindle cell stroma or an abrupt transition to hypocellular fibrous stroma. Other areas can have a fibro-osseous appearance with a prominent cellular stromal component and small ossicles or trabeculae of immature woven bone resembling fibrous dysplasia.

Yet another common pattern is a cellular stroma with hyalinized nodules with or without perivascular stromal cells displaying a pericytomatosus pattern. Cellular myxoid foci are similar in some respects to cranial/nodular fasciitis. The aneurysmal bone cyst-like areas are surrounded by a stroma rich in multinucleated giant cells.

**Immunoprofile**
The cartilage, mature or immature, is immunoreactive for S-100 protein. The spindled stroma is immunoreactive for smooth muscle actin and vimentin.

**Differential diagnosis**
The differential diagnosis depends on the particular combination of microscopic features present in the biopsy or resection. Since cartilage is the dominant component, differential diagnoses include chondromyxoid fibroma and chondroblastoma (1858). Other differential diagnoses may include aneurysmal bone cyst, fibrous dysplasia, cranial fasciitis and osteochondromyxoma (334). Interestingly, the latter tumour may be congenital, may involve the paranasal sinuses and is associated with the Carney complex in some cases. None of the patients with nasal chondromesenchymal hamartoma are known to have the Carney complex (1678).

**Prognosis and predictive factors**
Information on the clinical behaviour is incomplete, but prognosis is apparently favourable. There is some capacity for continued local growth when the resection is incomplete.
Non-Hodgkin lymphoma

Definition
Primary non-Hodgkin lymphomas (NHL) of the nasal cavity or paranasal sinuses are defined as lymphoid cell neoplasms in which the bulk of disease occurs in these anatomic sites.

Synonyms
Most cases described in the past as polymorphic reticulosis, malignant midline reticulosis, lethal midline granuloma or angiocentric immunoproliferative lesion, are now reclassifiable as extranodal NK/T cell lymphoma of nasal-type.

Epidemiology
Malignant lymphoma is the second most common malignancy of the nasal cavity and paranasal sinuses, following squamous cell carcinoma [1013]. It accounts for 14% of all cancers in these sites [1013].

Although many different types of NHL can occur in the nasal cavity, the most common lymphoma type is extranodal NK/T cell lymphoma of nasal-type, especially in Asian populations [5,420]. The relatively high prevalence of this lymphoma type in Asians and Latin Americans also accounts for the higher overall incidence of nasal lymphomas in these populations as compared with Caucasian populations [58,2104]. Other peripheral T-cell lymphomas, such as anaplastic large cell lymphoma, can also occur in the sinonasal region.

Lymphomas presenting in the paranasal sinuses are frequently B-cell lymphomas, with diffuse large B-cell lymphoma (DLBCL) being the most common [5,551,1837]. Other B-cell lymphomas that can involve the sinonasal regions include Burkitt lymphoma, follicular lymphoma, extranodal marginal zone B-cell lymphoma of MALT type, and mantle cell lymphoma [5]. Please also refer to the section on non-Hodgkin lymphomas in Chapter 4 on tumours of the oral cavity and oropharynx.

NHL of the nasal cavity and paranasal sinus is primarily a disease of adults, with male predominance. 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 DLBCL are generally one decade older (median age 63 years), and the male to female ratio is 1.2:1 [5,420]. Children may rarely present with NHL of the nasal cavity and the paranasal sinuses, with Burkitt lymphoma being the most common type [2808].

Etiology
The etiology is unknown, but extranodal NK/T cell lymphoma of nasal-type is strongly associated with Epstein-Barr virus (EBV) irrespective of the ethnic background of the patients [68,376,1107,1126,1347,2671,2828]. There is only a weak association between B-cell lymphomas in the nasal cavity and the paranasal sinuses with EBV [376,511,2617,2740].

Immunosuppression (e.g. post-transplant, HIV infection) is associated with an increased risk of developing NHL, including in the nasal cavity and paranasal sinuses. Although the majority of the cases in immunosuppressed patients are DLBCL [511,2068], extranodal NK/T cell lymphoma of nasal-type has also been reported [328]. Most of the NHL that arise in the setting of immuno-suppression are also EBV-related [511].

Localization
Lymphomas of the nasal cavity are often locally destructive, with obliteration of the nasal passages and maxillary sinuses. In particular, extranodal NK/T cell lymphoma can involve the adjacent alveolar bone, hard palate, orbit and nasopharynx in over half of the cases [1948].

Lymphomas of the paranasal sinuses commonly show bony destruction and local extension to adjacent structures including the orbit, palate, nasal cavity, nasopharynx, and soft tissues in the cheek and infratemporal fossa [511,1836,1837]. Maxillary sinus is the most commonly involved paranasal sinus.

Clinical features
Patients may present with nasal obstruction, epistaxis, nasal discharge, pain and nasal swelling or facial swelling. Locally advanced cases can cause destruction of midline facial structures. The nasal septum or palate may be perforated. Extension to the orbits can lead to proptosis and visual disturbance. Regional lymph node involvement may occur in some patients. Occasional patients have systemic symptoms including fever and weight loss. Haemophagocytic syndrome with pancytopenia occurs at presentation in a minority of patients with extranodal NK/T cell lymphoma of nasal-type [420,2533].
Tumour spread and staging
The majority (80%) of patients with extranodal NK/T cell lymphoma of nasal-type have localized disease at presentation (Stage IE/IIE) [420,1500,1505]. Bone marrow involvement at presentation is uncommon [2810]. Although extranodal NK/T cell lymphoma often shows localized disease at presentation, spread to other sites (such as skin, gastrointestinal tract, liver, lymph node, testis) during the course of disease is common. Most of the patients (75%) with DLBCL of the nasal cavity and the paranasal sinuses present with low clinical stage (IE/IIE) [420,511]. In contrast to extranodal NK/T cell lymphoma, cervical lymph node involvement is more frequent at presentation (60%), and the common sites of relapse are lymph node, liver and lung [420].

Extranodal NK/T cell lymphoma

Immunoprofile and genetics
The lymphoma most commonly exhibits an NK-cell immunophenotype of CD2+, surface CD3(Leu4)-, cytoplasmic CD3+, CD56+ [1196]. CD43 and CD45RO are commonly positive, but other T-cell markers (including CD5) and NK-cell markers (CD16, CD57) are usually negative. The tumours commonly exhibit a cytotoxic phenotype with expression of perforin, TIA1, and granzyme B [662,1773,1878,1935]. Fas (CD95) and Fas ligand expression are frequent, and may account for the extensive necrosis [1877,1935]. Expression of the various NK cell receptors is variable. P-glycoprotein/MDR1 is often expressed (90%), and may explain the poor response to chemotherapy [2838]. The T-cell receptor genes are often in germline configuration [1196]. Practically all cases (>95%) are associated with EBV [68,376,1107,1263,1347,2671,2828]. The virus is best demonstrated in the tumour cells by in situ hybridization for EBER (EBV-encoded early RNAs) [376]. The EBV is in clonal episomal form, pro-
Tumours of the nasal cavity and paranasal sinuses

viding additional evidence of the clonal nature of the lesion (1107, 1693). Some cases are CD56 negative, but are still classified as extranodal NK/T cell lymphoma provided they express T-cell markers and cytotoxic markers, and are EBV positive. These cases may show clonally rearranged T-cell receptor genes and may represent a neoplasm of cytotoxic T-lymphocytes (426). T-cell lymphomas which lack cytotoxic markers or evidence of EBV infection are diagnosed as peripheral T-cell lymphoma unspeciﬁed. Lymphoblastic lymphoma of probable NK-cell lineage (or so-called blastic NK-cell lymphoma) with expression of CD56 and TdT and no EBV association has also been described in the nasal cavity, but this is an entity distinct from the extranodal NK/T cell lymphoma of nasal-type (1352, 1838).

Differential diagnosis

Since the tumour cells of extranodal NK/T cell lymphoma can be masked by a prominent inﬁltrative inﬁltrate, the lesion can be mistaken as an infective, inﬁltrative or granulomatous lesion (including Wegener granulomatosis). It is not uncommon that a deﬁnitive diagnosis can only be reached after repeated biopsies. While Wegener granulomatosis similarly presents with destructive nasal lesion, simultaneous pulmonary involvement may be present. There is serologic positivity for cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA), and the main histologic findings are chronic inﬁltration with microabscesses and histiocytic inﬁltrate, in the absence of atypical lymphoid cells. In those examples of extranodal NK/T cell lymphomas dominated by small cells with minimal atypia, a deﬁnitive diagnosis can be difficult to make. An angiocentric inﬁltrate with expansion of the mucosa and mucosal gland destruction, coupled with prominent necrosis, should raise suspicion for the diagnosis of extranodal NK/T cell lymphoma. Conﬁrmation of the diagnosis can be made by demonstrating sheets of CD3+, CD56+ and EBER+ cells. Some non-lymphoid CD56+ small round cell tumours (e.g. olfactory neuroblastoma, Ewing sarcoma/primitive neuroectodermal tumour, rhabdomyosarcoma) also enter in the differential diagnoses. However, these can be easily excluded by appropriate immunohistochemical stains.

Diffuse large B-cell lymphoma

ICD-O code 9680/3

In DLBCL of the nasal cavity or paranasal sinuses, the mucosa shows dense, diffuse and interstitial inﬁltration by large or medium-sized lymphoid cells. There may or may not be ulceration and necrosis. Occasional cases show angioinvasion. The tumour cells may resemble centroblasts or immunoblasts, or have a non-speciﬁc blastoid appearance. The nuclei are round, multilobated or irregularly folded, with multiple small membrane-bound nucleoli or single central prominent nucleolus. The tumour cells express pan-B markers (e.g. CD20, CD79a). Extramedullary myeloid sarcoma, plasmacytoma, undifferentiated carcinoma and amelanotic melanoma may resemble DLBCL, but these entities can be readily distinguished by appropriate immunohistochemical stains.

Histogenesis

Most cases of extranodal NK/T cell lymphoma of nasal-type are activated NK-cell neoplasms, while some appear to be neoplasms of cytotoxic T-cells (425). DLBCL are mature B-cell neoplasms at either the germinal centre or post-germinal centre stage of differentiation.

Somatic genetics

A number of cytogenetic abnormalities

Table 1.4 Non-Hodgkin lymphomas in the nasal cavity or paranasal sinuses: differences in distribution according to cell lineage.

<table>
<thead>
<tr>
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<th>Primary in nasal cavity</th>
<th>Primary in paranasal sinuses</th>
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<tbody>
<tr>
<td></td>
<td>NK/T- or T-cell lymphomas</td>
<td>B-cell lymphomas (mostly DLBCL)</td>
</tr>
<tr>
<td>Asian series (420,1837)</td>
<td>71%</td>
<td>29%</td>
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<tr>
<td>Western series (5)</td>
<td>54%</td>
<td>46%</td>
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DLBCL = diffuse large B-cell lymphoma
Haematolymphoid tumours

Haematolymphoid tumours have been reported in extranodal NK/T cell lymphoma of nasal-type, most commonly isochromosome 1q, isochromosome 6p, partial deletion of 6q, and aberration at 11q (2606,2811). Comparative genomic hybridization and loss of heterozygosity studies have suggested frequent DNA loss at 1p, 6q, 11q, 12q, 13q, 17p, whole X, and frequent gain at 1p, 2q, 6p, 10q, 11q, 12q, 13q, 17q, 19p, 20q, Xp (1346,2382,2383). Overall, the most frequent changes are del(6)(q21-25), del(17)(p12-p13), del(13)(q14-q34) and gain of 1p32-pter (422). P53 protein overexpression occurs in 45-86% of cases (1496,2104,2105), but P53 mutation is less common (24-48%) (1496,2105). TP53 mutation has been associated with large cell morphology and advanced stage (2105). FAS gene mutation is frequently observed (2331,2534). Aberrant methylation of promoter CpG region of P73 gene occurs in 94% of cases (2381), and its detection by methylation-specific polymerase chain reaction may be helpful for monitoring residual disease or early relapse (2380). There are no molecular data on DLBCL specifically occurring in the sinonasal tract.

Prognosis and predictive factors
Radiotherapy and/or systemic chemotherapy is the treatment of choice for localized disease. (420-422,1505,1550). Treatment of DLBCL follow protocols for similar tumours elsewhere in the body, as some series showed that chemotherapy might be beneficial (1550,2091). The overall survival for extranodal NK/T cell lymphoma of nasal-type is only 30-50% (420-422,1312,1838). In patients achieving complete remission, local relapse occurs in one-third to one-half of cases (421,1312), and systemic failure is also common (421). Factors associated with a worse outcome include: advanced stage, poor performance status, B symptoms, and bulky disease (422). There is no conclusive evidence to suggest that the histologic grading of NK/T cell lymphoma can predict the clinical outcome. Expression of cutaneous lymphocyte antigen (CLA) may be associated with a worse prognosis, but this finding has yet to be confirmed (2863).

Genetic susceptibility
Extranodal NK/T cell lymphoma of nasal-type has been reported in both the father and son of a family with known pesticide exposure (1354).

Extramedullary plasmacytoma

Definition
A mass-forming lesion of monoclonal plasma cells that occurs outside the bone and bone marrow. By definition, patients with primary extramedullary plasmacytoma (EMP) do not have evidence of underlying multiple myeloma.

ICD-O code 9734/3

Epidemiology
The mean age of patients with EMP of the head and neck is 60 years (range 34-78 years), with a male predominance 4:1 (1267).

Localization
Most frequent sites of involvement are nasal cavity, paranasal sinuses and nasopharynx (433,827,1267,1613,1972,2347,2656,2746).
Clinical features
EMP tends to be solitary, with multiple tumours present in only 10% of cases at diagnosis. The presenting features of head and neck EMP are: soft tissue mass (80%), airway obstruction (35%), epistaxis (35%), local pain (20%), proptosis (15%), nasal discharge (10%), regional lymphadenopathy (10%), and cranial nerve palsy (5%). The mean duration of symptoms is about 4.5 months. The tumour ranges in size from 2-5 cm. The appearance varies from grey to red, soft to firm, and sessile or pedunculated. EMP bleeds easily and is usually smooth without mucosal ulceration. Cervical lymph nodes are enlarged in only 10% of patients (2500). Occasional primary EMP may be associated with serum paraproteinaemia. An underlying multiple myeloma should always be excluded.

Macroscopy
EMP is lobulated, smooth or nodular, and has a fleshy or rubbery consistency.

Histopathology
There is a diffuse infiltrate of neoplastic plasma cells in the subepithelial tissue, accompanied by a scant vascularized stroma, and rarely blood lakes. There can be deposits of amyloid or immunoglobulin in the stroma. The tumour can be well, moderately or poorly differentiated \{18,1267\}. Well-differentiated EMP is characterized by uniform normal-looking to mildly atypical plasma cells. Intracytoplasmic crystals can be abundant in some cases. Dutcher bodies are sometimes seen. Moderately-differentiated EMP comprises moderately atypical plasma cells that vary in size. Poorly-differentiated (anaplastic) EMP comprises large cells that are often barely recognizable as being plasma cells. The nuclei often show significant variation in size, and can be round or irregularly folded. The chromatin pattern ranges from vesicular to finely granular to coarsely clumped. Nucleoli can be prominent. The cytoplasm is amphophilic and eccentrically located, and a paranuclear hof (Golgi zone) may be present. Mitotic figures are frequent. Some tumour cells can be multinucleated.

Immunohistochemistry
Immunohistochemically, the plasma cells express cytoplasmic immunoglobulin with light chain restriction. CD20 is negative in most cases, and some cases express CD79a. PAX-5 is negative, while Oct-2 and Bob.1 are frequently positive. There is usually expression of CD38, CD138 and VS38, markers characteristically positive in but not specific for plasma cells. Epithelial membrane antigen is commonly positive, and rare cases can show cytokeratin immunoreactivity (often with a dot pattern). Leukocyte common antigen, CD31 or CD56 is sometimes positive.

Differential diagnosis
Well-differentiated EMP should be distinguished from reactive plasma cell proliferations, either non-specific or associated with specific disorders, such as rhinoscleroma or Rosai-Dorfman disease. Reactive plasmacytic proliferations show a polyclonal pattern of immunoglobulin staining. Moderately or poorly-differentiated EMP can cause significant difficulties in distinction from large cell lymphoma, carcinoma, melanoma, extramedullary myeloid sarcoma and olfactory neuroblastoma. The occasional positive staining for cytokeratin can lead to a misdiagnosis of carcinoma. A high index of suspicion for EMP should be raised for any poorly differentiated neoplasm occurring in the upper aerodigestive tract. Features suggestive of the diagnosis include eccentrically placed nuclei, coarsely clumped “clock-face” chromatin in some nuclei, and amphophilic cytoplasm with a paranuclear hof. The diagnosis can be confirmed by immunohistochemistry or in-situ hybridization for immunoglobulin mRNA to look for monotypic light chain expression \{18\}.

Prognosis and predictive factors
The mainstay of treatment for primary EMP is radiotherapy. The prognosis of primary EMP is far more favourable than that associated with myeloma \{1267\}. Approximately 20% of patients with primary EMP will develop multiple myeloma, but it is not possible to predict which cases will progress.

Extramedullary myeloid sarcoma

ICD-O code 9930/3
Extramedullary myeloid sarcoma, also known as granulocytic sarcoma, is a tumour mass of myeloblasts or immature myeloid cells occurring outside the bone marrow or bone. It can precede, co-exist with or follow the presentation of acute myeloid leukaemia. It can also arise as a blastic transformation of an underlying chronic myeloproliferative disease or myelodysplastic syndrome. The most common sites for occurrence of extramedullary myeloid sarcoma are lymph node and skin, but involvement of the nasal cavity and paranasal sinuses has also been reported [1701,2204]. The tumour mass comprises diffuse sheets of blast cells, which often show a single file pattern of infiltration in some areas. The blast cells have round or ovoid nuclei, very fine chromatin, small but distinct nucleoli, and a small to moderate amount of lightly eosinophilic cytoplasm. There can be better-differentiated cells with eosinophilic cytoplasmic granules. Intermingled eosinophilic myelocytes and metamyelocytes, if present, can provide an additional clue to the diagnosis. Giemsa-stained touch preparations are excellent for identification of cytoplasmic azurophilic granules as well as Auer rods, if present. Not uncommonly, extramedullary myeloid sarcoma is misdiagnosed as malignant lymphoma.

**Immunohistochemistry**
The tumour cells show chloroacetate esterase activity in approximately 75% of cases. Immunohistochemically, they express various myeloid markers (such as myeloperoxidase, CD13, CD33, CD117, CD68/KP1, neutrophil elastase and lysozyme), with myeloperoxidase being most sensitive and specific. Myeloid sarcoma with monocytic differentiation shows a myeloperoxidase -, CD68/PGM1+ immunophenotype. The pan-T marker CD43 is commonly expressed and may lead to a misdiagnosis of T-cell lymphoma.

**Histiocytic sarcoma**

**ICD-O code**

9755/3

Histiocytic sarcoma, defined as a malignant proliferation of cells showing morphologic and immunophenotypic features of mature tissue histiocytes, is a rare tumour that can occasionally present in the nasal cavity [2043]. The large pleomorphic tumour cells have eccentrically-located round, ovoid, indented or grooved nuclei, and abundant eosinophilic cytoplasm that may show fine vacuolation. Phagocytosis is rare. Histologic distinction from large cell lymphoma is difficult, except that the cytoplasm tends to be voluminous and eosinophilic. The diagnosis depends on the demonstration of histiocytic differentiation (granular staining for CD68 and lysozyme), in the absence of expression of pan-B markers (e.g., CD19, CD20, CD22, CD79a), pan-T markers (e.g., CD3), myeloid markers (e.g., MPO), Langerhans cell marker CD1a, and follicular dendritic cell markers (e.g., CD21, CD35). Since CD68 or lysozyme per se is not totally specific for histiocytic lineage, it is preferable to demonstrate additional haematolymphoid markers such as LCA/CD45, CD4, CD43 or CD163 to confirm the diagnosis. The frequent expression of CD43 may lead to a misdiagnosis of T-cell lymphoma. A small proportion of cases can express S100 protein.

**Langerhans cell histiocytosis**

**ICD-O code**

9751/1

Langerhans cell histiocytosis may occasionally present with nasal obstruction due to facial bone involvement [1183]. For details see Chapters 4 on tumours of the oral cavity and oropharynx and 7 on tumours of the ear.

**Juvenile xanthogranuloma**

This histiocytic proliferation may mimic tumours of Langerhans cells. It commonly presents as skin nodules in infants and children, but rare extracutaneous cases involving the nasal cavity and paranasal sinuses have also been reported [568, 2245]. Some of the histiocytes have foamy cytoplasm, and frequently there are scattered Touton giant cells and spindly cells within the infiltrate of nondecript mononuclear cells. The histiocytes in juvenile xanthogranuloma express CD68 and factor XIIIa. In contrast to Langerhans cells, they are negative for S100 protein and CD1a.

**Rosai-Dorfman disease**

Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) is an uncommon reactive condition of unknown etiology, characterized by proliferation of distinctive histiocytes that usually exhibit emperipolesis of lymphocytes. The tumour masses can mimic lymphoma or other malignancies both clinically and histologically. The patients are commonly children or young adults who present with massively enlarged
cervical lymph nodes. Extranodal involvement is frequent (about 40% of cases), especially the upper aerodigestive tract [791,923,1378,2760]. The patients with upper aerodigestive tract disease present with nasal obstruction, sinusitis, epistaxis, facial pain or saddle nose deformity.

Histologically, low magnification examination reveals alternating pale and dark-staining areas. The pale areas show proliferation of a distinctive type of very large histiocytes with round nuclei, distinct nucleoli, abundant light-staining cytoplasm, and indistinct cell borders. There are typically many admixed plasma cells. The presence of spindly cells in a vague storiform growth pattern may lead to a misdiagnosis of fibrohistiocytic tumour. The characteristic histiocytes are usually much larger than the typical histiocytes with round nuclei, distinct nucleoli, abundant light-staining cytoplasm, and indistinct cell borders. There are typically many admixed plasma cells. D Immunostaining for S100 protein selectively highlights the distinctive histiocytes. Both the nuclei and cell bodies are stained, while the phagocytosed lymphocytes become much more evident because of the negative staining.

Most cases are treated by excision alone, with steroid, radiotherapy and chemotherapy having been given in a minority of cases. In general, the prognosis is excellent, most patients being free of disease or with stable disease. However, some patients may develop recurrent disease in the original site or other body sites.
Neuroectodermal tumours

Ewing sarcoma (EWS) /
Primitive neuroectodermal
tumour (PNET)

Definition
A high-grade, primitive, round cell
tumour of neuroectodermal phenotype.
EWS and PNET represent a group of
small round cell neoplasms with variable
degrees of neuroectodermal differentia-
tion, and are considered together in this
section under the rubric of EWS/PNET.

ICD-O codes
Ewing sarcoma 9260/3
PNET 9364/3

Synonyms
Peripheral neuroepithelioma, peripheral
neuroectodermal tumour, peripheral neu-
roblastoma

Epidemiology
Sinonasal Ewing sarcoma / primitive neu-
roectodermal tumour (EWS/PNET) is
rare. This is mostly a tumour of children
and young adults, with a peak in the 3rd
decade [2211]. In children, approximately
20% of EWS/PNET occur in the head
and neck, with about 20% of these aris-
ing in the sinonasal tract [2122]. On rare
occasion, older adults may be affected
[2611]. There is a very slight male pre-
dominance [2122].

Localization
Sinonasal EWS/PNET most commonly
occurs in the maxillary sinus [1518] and
nasal fossa [1424,2069].

Clinical features
Symptoms include pain, mass, and
obstruction [2069]. The tumour can be
polypoid when arising from the nasal
cavity [2069]. Bony erosion may or may
not be present [2069].

Macroscopy
EWS/PNET is a grey-white and glistening
tumour with haemorrhage and often
ulceration [2069]. It tends to be much
smaller than that arising in other sites.

Tumour spread and staging
Intranasal tumours usually spread into
the paranasal sinuses [2069]. When metastases develop, they are mainly to the lungs and bone [2122]. Staging is according to the Clinical Groups of the Intergroup Rhabdomyosarcoma Study [2122].

Histopathology
The tumour is composed of densely distributed, uniform, small to medium sized, round cells with a high nuclear to cytoplasmic ratio and fine chromatin. Mitotic activity is high, and coagulative necrosis is common. Some cases show more densely clumped chromatin or a greater degree of nuclear pleomorphism. Homer Wright rosettes are rare.

Immunoprofile
The immunophenotype includes reactivity for CD99 (MIC2, O13, HBA-71, p30/32, and 12E7), [2472] vimentin, and on occasion focally for keratins. Some cases express neural markers, such as synaptophysin, S100 protein, NSE, neurofilament protein, GFAP, and chromogranin. Fli-1 (one portion of the gene fusion product of EWS/FLI1) can be detected by immunohistochemistry.

Electron microscopy
Electron microscopy reveals, to a variable extent, interdigitating neuritic processes, neurofilaments, microtubules, neurosecretory granules and glycogen [1743,2069].

Differential diagnosis
The differential diagnoses include malignant melanoma, melanotic neuroectodermal tumour, rhabdomyosarcoma, sinonasal undifferentiated carcinoma, lymphoma, olfactory neuroblastoma, and pituitary adenoma.

Histogenesis
A pluri-potentia-l fetal neuroectodermal cell is considered the progenitor.

Somatic genetics
Most EWS/PNET have a characteristic t(11;22) with EWS/FLI1 juxtaposition or other translocations involving EWS [2646]. Molecular analysis by PCR or FISH is helpful in diagnosis.

Genetic susceptibility
Sinonasal EWS/PNET has been reported in association with retinoblastoma [627,1330].

Prognosis and predictive factors
EWS/PNET has much better prognosis in the head and neck than in other anatomical sites [2122]. Size and stage are the most important prognostic factors. Tumours demonstrating the EWS/FLI1 fusion are reported to have a better prognosis than those with less common gene fusion types [552]. With improvements in imaging techniques and multimodality treatment, a 5-year survival of 60-70% can be achieved [23].

Olfactory neuroblastoma
Definition
A malignant neuroectodermal tumour thought to originate from the olfactory membrane of the sinonasal tract.

Synonyms
Esthesioneuroblastoma, esthesioneurocytoma, esthesioneuroepithelioma, olfactory placode tumour.

ICD-O code
9522/3

Epidemiology
Olfactory neuroblastoma is an uncommon neoplasm representing approximately 2-3% of sinonasal tract tumours. The incidence has been estimated at 0.4 per million [2584]. Patients range in age from as young as 2 years to 90 years, and a bimodal age distribution has been noted in the 2nd and 6th decades of life [625,626,663,1159]. Both genders are affected equally. No racial predilection has been noted.

Etiology
There are no known etiologic agent(s) for human olfactory neuroblastoma. Injection of diethylnitrosamine in Syrian hamsters and N-nitrosopiperidine in rats has produced tumours histologically identical to human olfactory neuroblastoma [1078,2697].

Localization
The most common site of origin is in the upper nasal cavity in the region of the cribiform plate. Included in the areas of the proposed origin are Jacobson’s organ (vomeronasal organ), sphenopalatine (pterygoid palate) ganglion, olfactory placode, and the ganglion of Loci (nervus terminalis). “Ectopic” origin in lower nasal cavity or within one of the paranasal sinuses (e.g., maxillary sinus) may occur. Olfactory neuroblastoma may

Fig. 1.86 Olfactory neuroblastoma. A Tumour lobules separated by a highly vascularized stroma. B Olfactory neuroblastoma accompanied by the hyperplasia of the olfactory epithelium.
Neuroectodermal tumours

on occasion present as an intracranial (frontal lobe) mass with involvement of the superior aspect of the cribriform plate or rarely, occur intracranially with no intranasal component [987].

Clinical features

Signs and symptoms

The main presenting symptoms are unilateral nasal obstruction (70%) and epistaxis (46%); less common manifestations include anosmia, headache, pain, excessive lacrimation and ocular disturbances. Typically, these tumours are slow-growing resulting in long-standing symptomatology, the mean delay between the appearance of the first symptom and the diagnosis being 6 months [626].

Imaging

The radiologic features include the presence of a “dumbbell-shaped” mass extending across the cribriform plate. The extent of disease is best determined by pre- and postcontrast MR imaging in which there is intense signal in T2-weighted images with marked enhancement of T1-weighted images after gadolinium injection [2815]. Details of bone erosion (lamina papyracea, cribriform plate and fovea ethmoidalis) are better demonstrated by CT scan. Calcifications producing a speckled pattern on radiographic studies can be identified. Angiographic studies disclose a hypervascular neoplasm.

Macroscopy

The gross appearance includes a glistening, mucosa-covered, soft, polypoid, often highly vascularized mass varying from a small nodule measuring less than 1 cm to a large mass filling the nasal cavity and extending into paranasal sinuses, orbit and/or cranial cavity.

Histopathology

Characteristically, the tumours are localized to the submucosa, growing in circumscribed lobules or nests separated by a richly vascularized fibrous stroma. Less often the tumour shows a diffuse growth pattern. The overwhelming majority of tumours are not associated with an in-situ component. The neoplastic cells have uniform, small round nuclei with scant cytoplasm, dispersed (“salt and pepper”) coarse to fine nuclear chromatin and inconspicuous nucleoli. Nuclear pleomorphism, mitotic activity and necrosis are usually absent. However, in higher-grade tumours, nuclear pleomorphism with prominent nucleoli, increased mitotic activity and necrosis may be present. The cells do not have distinct borders and are surrounded by a neurofibrillary matrix, which corresponds to tangles of neuronal cell processes. Rosettes of the Homer

Fig. 1.87 Olfactory neuroblastoma. A Lobules of tumour separated by fibrovascular septa. B The lobules of tumour are separated by dense fibrovascular tissue. A large pseudorosette (Homer Wright) shows a central area of neurofibrillary matrix. C A high grade olfactory neuroblastoma showing a true Flexner-Wintersteiner rosette and increased mitotic figures. D The "small blue round cell" neoplasm has scant cytoplasm surrounding variably hyperchromatic nuclei. Granular nuclear chromatin can be seen. Mitotic figures are noted in higher grade lesions.
Wright type (pseudorosettes) and Flexner-Wintersteiner type (true neural rosettes) can be identified in up to 30% and less than 5% of tumours, respectively. The Homer Wright pseudorosettes represent the presence of cells in an annular arrangement surrounding central neurofibrillary matrix; distinct cell membranes are not present. Flexner-Wintersteiner rosettes are gland-like structures in which the annular arrangement of cells includes the presence of a distinct cell membrane. Perivascular pseudorosettes can be seen but are of no diagnostic utility. Uncommon findings include stromal calcifications, ganglion cells, melanin-containing cells and divergent differentiation. The latter may include the presence of glandular (adenocarcinoma-like), squamous, teratoma- tous and rhabdomyoblastic differentiation [1096,1734,2404].

**Grading**

The microscopic grading [1159] includes four grades: Grade I is the most differentiated and includes lobular architecture with intercommunication of the neoplasm between lobules. The neoplastic cells are well-differentiated with uniform, small round nuclei with scant cytoplasm, dispersed (“salt and pepper”) nuclear chromatin and inconspicuous nucleoli. The cells do not have distinct borders; rather, the nuclei are surrounded by a neurofibrillary material suggesting cytoplasmic extension. Homer Wright rosettes are frequently seen. Varying amounts of calcification may be noted. Interlobular fibrous stroma is often extremely vascular. Mitotic activity and necrosis are absent. Grade II tumours share many of the histologic features described for Grade I lesions but the neurofibrillary element is less well defined, and the neoplastic nuclei show increased pleomorphism. Scattered mitoses can be seen. Grade III tumours may retain a lobular architecture with a vascular stroma. These hypercellular tumours are characterized by cells that are more anaplastic, hyperchromatic, and have increased mitotic activity as compared to Grade I or II tumours. Necrosis is seen. The neurofibrillary component may be focally present, but is much less conspicuous as compared to Grades I or II tumours. Flexner-Wintersteiner rosettes are uncommon. Calcification is absent. Grade IV tumours may also retain the overall lobular architecture, but the neoplastic element is the most undifferentiated and anaplastic of all the histologic grades. The cellular infiltrate is characterized by pleomorphic nuclei often with prominent eosinophilic nucleoli and an indistinct cytoplasm. Necrosis is commonly seen and there is increased mitotic activity, including atypical mitoses. Rosettes are uncommon. The neurofibrillary component is generally absent. Calcification is absent. Of note is that in any given tumour there may be histologic diversity with mixed (overlapping) features.

In general, the lower grade olfactory neuroblastomas are readily recognizable and diagnostic by light microscopy. Adjunct studies, particularly in the higher histologic grade tumours, may assist in the diagnosis. The advent of immunohistochemistry has diminished the role of histochemical stains, but silver stains such as Bodian, Grimelius and Churukian-Schenk may still be of assistance.

**Immunoprofile**

The most consistently expressed marker is neuron specific enolase (NSE). Reactivity is also present in a majority of cases for synaptophysin, neurofilament protein (NFP), class III beta-tubulin, and microtubule-associated protein. S-100

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**Table 1.6 Hyams’ histologic grading system for olfactory neuroblastoma**

<table>
<thead>
<tr>
<th>Microscopic Features</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Lobular</td>
<td>≥Lobular</td>
<td>≤Lobular</td>
</tr>
<tr>
<td>Pleomorphism</td>
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<td>Present</td>
<td>Prominent</td>
<td>Marked</td>
</tr>
<tr>
<td>Neurofibrillary matrix</td>
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<td>Present</td>
<td>May be present</td>
<td>Absent</td>
</tr>
<tr>
<td>Rosettes</td>
<td>Present*</td>
<td>Present*</td>
<td>May be present**</td>
<td>May be present**</td>
</tr>
<tr>
<td>Mitoses</td>
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<td>Present</td>
<td>Prominent</td>
<td>Marked</td>
</tr>
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<td>Absent</td>
<td>Prominent</td>
<td>Prominent</td>
</tr>
<tr>
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<td>May be present</td>
<td>May be present</td>
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</tr>
<tr>
<td>Calcification</td>
<td>Variable</td>
<td>Variable</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

NF-neurofibrillary; *Homer Wright rosettes (pseudorosettes); **Flexner-Wintersteiner rosettes (true neural rosettes)

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**Fig. 1.88 Olfactory neuroblastoma.** **A** A true Flexner-Wintersteiner rosette is surrounded by intermediate sized cells with scant cytoplasm and prominent nucleoli. A mitotic figure is present. **B** Immunostaining shows strong staining for synaptophysin. **C** Immunostaining shows the characteristic S100 protein+ sustentacular cells wrapping around the tumour islands.
protein staining typically is limited to the sustentacular cells situated along the periphery of the neoplastic lobules, although such cells may be sparse in the higher-grade tumours. In addition, immunoreactivity may be present for chromogranin, glial fibrillary acidic protein (GFAP), and Leu-7.

Cytokeratin is usually negative, but some cases can show some positive cells. Epithelial markers, including epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) are absent. Leucocyte common antigen (LCA), HMB-45, desmin and CD99 are absent. Proliferation marker studies using Ki-67 and MIB-1 have shown a high proliferative index of 10-50% and flow cytometric analysis shows frequent polyploidy/aneuploidy (2560,2682).

**Electron microscopy**

Electron microscopy evaluation is a useful adjunct in the diagnosis and includes the presence of dense core neurosecretory granules measuring 50-250 nm in diameter and neurite-like cell processes containing neurofilaments and neurotubules (1096,2567,2682). In addition, Schwann-like cells and junctional complexes may be identified. When identified, olfactory rosettes show apical cilia with a 9 + 2 microtubule pattern, microvilli, and junctional complexes.

**Differential diagnosis**

The differential diagnosis of olfactory neuroblastoma includes the group of small round cell malignant neoplasms that can occur in the sinonasal tract, i.e., sinonasal undifferentiated carcinoma, lymphoma, rhabdomyosarcoma, mucosal malignant melanoma and neuroendocrine carcinomas. This discussion will be limited to neuroendocrine carcinomas; for the others the reader may refer to the specific sections detailing these specific tumour types.

Neuroendocrine carcinomas (NEC) include, among different tumour types, the carcinoid tumour, atypical carcinoid tumour and small cell carcinoma. NEC of the sinonasal tract are extraordinarily rare, and in contrast to the larynx, the most common subtype is small cell carcinoma. By light microscopy, small cell carcinoma typically is a submucosal hypercellular proliferation growing in sheets, cords and ribbons; the distinct lobular pattern of olfactory neuroblastoma is absent. The cells are small and hyperchromatic with oval to spindle-shaped nuclei, absent nucleoli and minimal cytoplasm. Cellular pleomorphism, high nuclear to cytoplasmic ratio, high mitotic activity, confluent necrotic areas and individual cell necrosis are readily apparent as well as lymphovascular and perineural invasion. Characteristically, crush artifacts of the neoplastic cells are seen. Squamous cell foci may occasionally be present; glandular or ductal differentiation is rarely seen. Although uncommon, neural-type rosettes similar to those seen in olfactory neuroblastoma can be seen in association with small cell carcinoma. The overall light microscopic findings should allow for differentiating small cell carcinoma from olfactory neuroblastoma in most cases, but immunohistochemical evaluation may be required in some cases. The immunohistochemical profile of small cell carcinoma includes variable reactivity for cytokeratin, chromogranin, synaptophysin, neuron specific enolase (NSE), S-100 protein and thyroid transcription factor-1 (TTF-1). Cytokeratin reactivity may include a punctate paranuclear or globoid pattern. The tumour usually is negative for cytokeratin, and the positive cases do not show a punctate paranuclear or globoid pattern. In contrast to olfactory neuroblastoma, NSE reactivity in small cell carcinoma is more likely to be focal than diffusely positive, and the S100 protein staining, if present, is dispersed throughout the cellular proliferation and not limited to sustentacular cells. Olfactory neuroblastoma is also negative for TTF-1.

**Genetics**

Studies on cytogenetic aberrations in olfactory neuroblastoma are sparse (2612,2521). Studies have found partial gains of chromosome material on 8q, while the other findings are conflicting. Inclusion of olfactory neuroblastoma within the Ewing sarcoma family of tumours (2428) or the primitive neuroectodermal tumours (PNET) (1865) has been proposed (2467) because of the identification, in certain cases, of translocation t(11;22), which is regarded as specific molecular abnormality for Ewing sarcoma (575). Recent studies using immunohistochemistry, fluorescent in situ hybridization and reverse transcriptase PCR have failed to confirm this translocation in olfactory neuroblastoma (72, 1384,1709,2001). Therefore, olfactory neuroblastoma should be considered an entity distinct from PNET and the Ewing sarcoma family of tumours.
Histogenesis
Proposed sources of origin of olfactory neuroblastoma include Jacobson’s vomero-nasal organ, the sphenopalatine ganglion, the ectodermal olfactory placode, Loc’s ganglion, autonomic ganglia in the nasal mucosa, and the olfactory epithelium. While a neuronal – neural crest origin is supported by the presence of neurofilaments in olfactory neuroblastoma [2634], until recently [335], few arguments linked olfactory neuroblastoma directly to the olfactory epithelium. The olfactory neuroepithelium is a unique neurosensory organ because olfactory neurons are continuously replaced throughout adult life by new ones [941,942]. Three types of cells are classically recognized in the olfactory epithelium: the basal cells, located against the basement membrane, the olfactory neurosensory cells, and the sustentacular supporting cells, the processes of which extend on the luminal surface. The globose basal cells constitute a stem cell compartment, which confers to this tissue its peculiar ability to regenerate not only physiologically but also when injured by trauma or environmental insults [1631,2690]. The globose basal cells express (1747) neural cell adhesion molecule (NCAM) [513] and mammalian homologue of Drosophilaachaete-scute (MASH) gene (958). These progenitor cells differentiate into olfactory neurosensory cells, which exhibit a progressive maturation from the basal membrane to the epithelial surface [1631,1884]. Each layer can be characterized by specific olfactory- and neuron specific markers. Immature olfactory cells express (1631,2690) GAP43, a 24 kD membrane-associated protein kinase C involved in polyphosphoinositide turnover (197). As these cells mature, they send axons to the olfactory bulb and migrate towards the surface, they express olfactory marker protein (OMP) [1630] and NCAM, but not GAP43 [1631,1884,2690].
Recently, olfactory neuroblastomas were found to express HASH, the human homologue of the MASH gene (335), while staining negative for OMP. So far, HASH has only been demonstrated in medullary thyroid carcinoma and certain small cell lung carcinoma [111]. Further indirect evidence that olfactory neuroblastoma originates from olfactory stem cells can be derived from transgenic mice in which the SV40T oncogene was inserted under the OMP gene promoter region [2307]; these mice did not develop olfactory neuroblastoma but adrenal and sympathetic ganglia neuroblastoma. Therefore, the currently available evidence links olfactory neuroblastoma with the basal progenitor cells of the olfactory epithelium.

Prognosis and predictive factors
Complete surgical eradication (craniofacial resection that includes removal of the cribiform plate) followed by full course radiotherapy is the treatment of choice [625,626,1777]. Limited success using chemotherapeutic modalities have been achieved for advanced unresectable tumours and/or for disseminated disease [2705]. High-dose chemotherapy, including platinum-based protocols and autologous bone marrow transplantation have resulted in long-term survival [634,1919,2064]. The overall 5-, 10- and 15-year survival rates have been reported to be 78%, 71% and 68%, respectively [634]. Initial multimodality therapy is associated with 5-year survival of 80% for low-grade tumours and 40% for high-grade tumours [1777]. The majority of the recurrences occur within the first two years [625]. The most frequent recurrence is local, with rates around 30%. Prognosis has traditionally been correlated to clinical staging with 5-year survival of 75-91%, 68-71% and 41-47% for Stage A, B and C tumours, respectively [663,1243]. More recently, complete tumour resection was found to be of more prognostic importance than clinical staging [1740]. Other factors purportedly implicated in prognosis include histologic grading, proliferation rate and ploidy. Histologically lower grade tumours (Grades I and II) have been reported to have a better 5-year survival than higher grade tumours (Grades III, IV) [1159]. High proliferation indices and high rate of ploidy/aneuploidy have been correlated with increased morbidity (i.e., tumour recurrence, metastasis) and mortality (i.e., decreased survival) [2560,2682].

The majority of tumours behave as locally aggressive lesions mainly involving adjacent structures (orbit and cranial cavity). Local recurrence and distant metastasis may occur years following the initial diagnosis. Approximately 15-70% of patients will experience local recurrence, 10-25% will have cervical lymph node metastasis, and approximately 10-60% will experience distant metastasis [131,663]. The more common sites of metastases include lymph nodes, lungs, and bone. All histologic grades have the capacity to metastasize.

**Melanotic neuroectodermal tumour of infancy**

**Definition**
Melanotic neuroectodermal tumour of infancy (MNTI) is a rare neoplasm of infants with a biphasic population of neuroblastic cells and pigmented epithelial cells.

**ICD-O code**
9363/0

**Synonyms**
Melanotic progonoma, retinal anlage tumour, melanotic ameloblastoma

**Epidemiology**
The tumour is very rare. It characteristically occurs in infants, with 80% of cases <6 months of age and 95% <1 year of age, with a 2:1 female predominance [1269].

**Localization**
More than 85% of patients have a mass involving craniofacial sites: maxilla (70%), mandible (10%), skull (10%), neurocranial dura or brain (1%). Occasionally other sites, such as the epi-

---

**Table 1.7 Clinical staging for olfactory neuroblastoma (663,1243)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent of Tumour</th>
<th>5-Year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Tumour confined to the nasal cavity</td>
<td>75-91%</td>
</tr>
<tr>
<td>B</td>
<td>Tumour involves the nasal cavity plus one or more paranasal sinuses</td>
<td>68-71%</td>
</tr>
<tr>
<td>C</td>
<td>Extension of tumour beyond the sinonasal cavities</td>
<td>41-47%</td>
</tr>
</tbody>
</table>
Neuroectodermal tumours
didymis (4%), skin (3%), uterus (1%), and mediastinum (1%) may be involved [1269,2026].

Clinical features
Patients present with a rapidly growing pigmented mass, which is usually located in the anterior alveolar ridge of the maxilla. The duration of symptoms ranges from 2 weeks to 5 months (mean 2 months) [1269]. Infrequently, there are elevated levels of vanilmandelic acid, which normalize following adequate therapy.

Macroscopy
The tumours range from 1-10 cm (mean, 3.5 cm), and are smooth, firm to hard, and grey to blue-black [1269].

Histopathology
This is a nonencapsulated mass composed of a dual population of small neuroblastic cells and larger melanin-containing epithelial cells in a vascularized dense fibrous stroma [1269,2026]. The epithelial cells show alveolar or tubular arrangement, and often surround nests of smaller neuroblastic cells. The latter possess small, round hyperchromatic nuclei and scant or fibrillary cytoplasm. The epithelial cells have larger, vesicular nuclei and abundant cytoplasm, most containing melanin granules. Mitoses and necrosis are rare or absent.

Immunoprofile
MNTI shows polyphenotypic expression of neural, melanocytic and epithelial markers, but without photoreceptor differentiation. Occasionally glial and rhabdomyoblastic differentiation may be seen. The larger cell (epithelial) component is immunoreactive for cytokeratin, HMB-45, vimentin, and sometimes epithelial membrane antigen [1269,2026]. Neuron-specific enolase, CD57/Leu-7 and dopamine-beta-hydroxylase are often positive in both the small neuroblastic cells and large cells. The tumour cells are negative for chromogranin, desmin, CEA, retinol-binding protein, neurofilaments, alpha-fetoprotein, and S100 protein.

Electron microscopy
The small cells demonstrate neurosecretory granules and neuritic processes, and the large cells contain melanosomes and premelanosomes [517,571,1269].

Differential diagnosis
The differential diagnoses include alveolar rhabdomyosarcoma, malignant lymphoma, EWS/PNET, metastatic neuroblastoma, immature teratoma and malignant melanoma. Primary melanoma, especially mucosal, is extremely rare in infants, should show S100 protein immunoreactivity, and lacks epithelial markers. Neuroblastomas may rarely be pigmented, but lack the dual cell population and usually show diffuse immunoreactivity for neuroendocrine markers.

Histogenesis
A neural crest origin is proposed [145, 517,571,1232,1269,2026].

Prognosis and predictive factors
The treatment of choice is complete local excision [1269,1657,2092]. Radiotherapy and chemotherapy are to be avoided.

Fig. 1.90 Melanotic neuroectodermal tumour. A Section of maxilla shows tumour infiltration of bone. Note fibrous stroma containing neoplastic cellular infiltrate. B Dual population of neoplastic cells, including smaller blue neuroblastic cells and larger pigmented epithelial cells. C There is a trabecular, tubular, or alveolar arrangement of the biphasic cell population, with the larger pigmented cells surrounding groups of the smaller round, "blue" neuroectodermal cells. The trabeculae are separated by a dense collagenous stroma. D Note spatial relationship of larger pigmented epithelial cells surrounding smaller neuroblastic cells.
unless there is evidence of metastasis.

Despite its rapid growth and tendency to destroy bone, MNTI pursues a benign clinical course in most cases [1269,2026]. However, if not totally excised, local recurrences occur frequently. About 7% of cases develop metastases to sites such as the lymph nodes, liver, bone, adrenal glands or soft tissue [2026]. The potential for recurrence or metastasis, however, cannot be predicted from the clinical or pathologic features.

**Mucosal malignant melanoma**

**Definition**

A malignant neoplasm derived from the melanocytes in the mucosa.

**ICD-O code**

8720/3

**Synonyms**

Melanosarcoma; melanoma

**Epidemiology**

Sinonasal mucosal malignant melanomas are rare, accounting for less than 1% of all melanomas [112,165], and <5% of all sinonasal tract neoplasms [205,2603]. Both genders are equally affected, without a race predilection, although an increased incidence has been suggested in Japanese patients. Malignant melanomas typically affect older individuals in the 5-8th decade with a peak incidence in the 7th decade [165,260,273,386,484,500,560,807,930,1076,2603].

**Etiology**

Formaldehyde exposure and tobacco smoking have been suggested as possible etiologic factors [260,273,1318,2603].

**Localization**

The nasal cavity is affected most frequently, followed by a combination of the nasal cavity and paranasal sinuses. Large tumours may involve multiple paranasal sinuses and present as extensive skull base tumours [260,273,386,484,500,560,807,930,1324,2603].

**Tumour spread and staging**

At presentation, 70-80% of cases are localized, 10-20% have regional lymph node and <10% have distant metastasis [112,273,386,1324,2603]. However, dur-
ing the course of disease, an additional 20% may develop nodal metastasis and 40-50% may develop distant metastasis to lungs, brain, bone and/or liver [273,386,484,500,1324,2603]. There is currently no universally accepted staging system. However, the most common and prognostically significant staging system in use is: stage I- localized tumours, stage II- tumours with lymph node metastases, and stage III- tumours with distant metastasis [1076]. Tumour thickness or depth of invasion cannot be accurately assessed due to the lack of a well-defined reference point for the surface in the respiratory mucosa, frequent ulceration, tissue fragmentation and poorly oriented specimen [273,386,2603].

Histopathology
The tumours are comprised of epithelioid, spindled, plasmacytoid, rhabdoid, and/or multinucleated tumour cells. The cells are generally medium to large-sized [260,273,386,484,1472,2603]. They have a high nuclear to cytoplasmic ratio with pleomorphic nuclei containing prominent eosinophilic nucleoli and intranuclear cytoplasmic inclusions. Nuclear molding can be present. The cytoplasm is usually densely eosinophilic, and variably contains melanin pigment. Mitoses, including atypical forms, are frequent and easily identifiable. Vascular invasion and neurotropism may be identified in up to 40% of cases. An inflammatory infiltrate admixed with pigment-laden histiocytes is commonly identified within or adjacent to the tumour. Tumour cell necrosis is common, particularly in tumours displaying a peritheliomatous or pseudopapillary growth pattern. Other growth patterns include solid, alveolar or sarcomatoid. Intraepithelial melanocytic atypia (melanoma in-situ) is sometimes seen in the overlying epithelium [260,273,386,1472,1624,2603]. The tumours usually invade the subepithelial tissue and frequently extend into the bone, cartilage or skeletal muscle.

Immunoprofile
Malignant melanoma expresses S100 protein and vimentin [1472,1661], and variably HMB45, tyrosinase, melan-A and microphthalmia transcription factor. Neuron specific enolase, CD117, CD99, synaptophysin, CD56, and CD57 have been reported to be occasionally positive, but epithelial membrane antigen, cytokeratins, and muscle markers are not expressed [260,273,484,1472,1661,2603].

Differential diagnosis
Sinonasal mucosal malignant melanoma may morphologically masquerade as a variety of benign and malignant neoplasms, such as “small blue round cell” neoplasms, pleomorphic neoplasms
Tumours of the nasal cavity and paranasal sinuses (sinonasal undifferentiated carcinoma, anaplastic large cell lymphoma, angiosarcoma), or various sarcomas \( \{260, 273, 386, 1472, 1661, 2603\} \). Metastatic melanoma to the sinonasal tract, although highly uncommon, must always be excluded, as the prognosis is even poorer. Presence of intraepithelial atypical melanocytes favours primary melanoma \( \{386, 1624, 2603\} \).

Histogenesis
Melanocytes, distributed throughout the upper respiratory tract are considered the progenitor of primary sinonasal mucosal malignant melanoma.

Genetic susceptibility
Patients with sinonasal mucosal malignant melanoma do not seem to be part of dysplastic nevus syndrome or xeroderma pigmentosum kindreds \( \{273, 2603\} \).

Prognosis and predictive factors
Surgery is the cornerstone of therapy, although wide free margins of resection are difficult to achieve. Radiation therapy has a palliative role \( \{500, 2078, 2603\} \). Local recurrence is frequent (67%-92%), may be repeated, and is a harbinger of adverse prognosis \( \{273, 386, 560, 1324, 2603\} \). Most tumours progress to regional and distant metastasis resulting in poor 5-year disease-specific survival that may range from 17-47% \( \{165, 260, 273, 386, 560, 1076, 1324, 2310, 2603\} \). Other poor prognostic factors include advanced age, obstructive symptoms, tumour size >3 cm, location in paranasal sinuses and nasopharynx, vascular invasion into skeletal muscle and bone, high mitotic count, marked cellular pleomorphism and distant metastasis \( \{165, 273, 500, 1324, 2081, 2310, 2603\} \).

Epidemiology
Most patients present at birth, and 90% of cases are diagnosed by age of 2 years. There is no gender predilection.

Localization
The lesion is situated externally on or near the bridge of the nose in 60% of cases, within the nasal cavity in 30% of cases, and in both sites in 10% of cases. In the latter cases, communication of the intra- and extranasal components is through a defect in the nasal bone.

Clinical features
Extranasal heterotopic CNS tissue presents as a smooth noncompressible subcutaneous mass over the dorsum of the nose. The intranasal lesions usually present with nasal obstruction or nasal deformity. Heterotopic CNS tissue may occur at other sites, such as the paranasal sinuses, nasopharynx \( \{2289\} \), pharynx, tongue, palate, tonsil and orbit, and may be referred to as “facial glioma”. One-third of pharyngeal heterotopic CNS tissues are associated with cleft palate or choanal stenosis.

**Heterotopic central nervous system tissue (nasal glioma)**

**Definition**
A mass of heterotopic neuroglial tissue presenting in and around the nose.

**Synonyms**
Nasal glioma, nasal glial heterotopia

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Fig. 1.94 Heterotopic central nervous system tissue. **A** Mucosal glands are subtended by reactive glial tissue composed of neuropil separated by dense, more brightly eosinophilic fibrous connective tissue. Astrocytes are not seen. **B** S-100 positivity in nuclei and cytoplasm of subepithelial glial cells. **C** The left side demonstrates a number of “gemistocytic-type” astrocytes within glial tissue, the right image shows classic neuroglial tissue without significant fibrosis or inflammatory cells. **D** Trichrome stain highlights the neural tissue red, while the reactive background fibrosis is blue (left). GFAP immunoreactivity is present in glial tissue, but not in the surrounding soft tissues (right).
A helpful clinical sign is the absence of expansion or pulsation of the mass following compression of the ipsilateral jugular vein (negative Furstenberg test), due to lack of connection of the mass with the CSF pathway. Importantly, radiographic imaging scans (CT and MRI) reveal a soft tissue mass without an intracranial component or bony defect in the floor of the anterior cranial fossa.

**Macroscopy**
The lesion appears as a polyloid, smooth, soft, grey tan, non-translucent mass with encephaloid features. It usually measures 1-3 cm.

**Histopathology**
The lesion is non-encapsulated, composed of large or small islands of glial tissue with evenly spaced astrocytes and interlacing bands of vascularized fibrous connective tissue. The glial tissue merges with the collagen of the stroma or dermis. Mitoses are absent. At times, the astrocyte nuclei may appear enlarged or multinucleated. Long-standing or recurrent lesions tend to contain a considerable amount of fibrous tissue. Neurons are rare or absent. Rarely, choroid plexus, ependyma-lined clefts and pigmented retinal epithelium are seen, especially those of the palate and nasopharynx.

The glial tissue can be confirmed by immunoreactivity for glial fibrillary acidic protein (GFAP) or S100 protein [607,1273,1323,1991,2851].

**Differential diagnosis**
The histologic differential diagnoses mainly include nasal encephalocele and, less frequently, a fibrosed nasal polyp. In contrast to heterotopic CNS tissue, encephaloceles are herniations of meningeal lined brain tissue that communicate with the intracranial ventricular system and subarachnoid space through a bony defect in the skull [1134]. Nasal encephalocele is composed of CNS tissue with easily found neurons. However, in nasal encephalocele of long-standing and in recurrences, the excessive fibrous tissue relative to the amount of glial cells and absence of neurons may make it impossible to distinguish from heterotopic CNS tissue.

Long-standing heterotopic CNS tissue may be mistaken for a fibrosed nasal polyp [1258]. The absence of glial tissue differentiates the latter from the former.

**Histogenesis**
It is a congenital malformation in which there is anterior displacement of mature cerebral tissue that has lost connection with the intracranial contents.

**Prognosis and predictive factors**
Adequate excision offers a cure in most cases, but incomplete excision can be accompanied by recurrence (15-30%). There is no local aggressive behaviour or malignant potential.

**Ectopic pituitary adenoma**
This lesion is described in Chapter 2 on tumours of the nasopharynx.
Malignant germ cell tumours and teratocarcinosarcoma exhibiting histologic features similar to germ cell tumours of the gonads arise on rare occasions in the sinonasal tract. Immature teratomas and teratomas with malignant transformation are tumours of infancy and early childhood, whereas sinonasal yolk sac tumour and sinonasal teratocarcinosarcoma have only been documented in adults.

**Immature teratoma**

**ICD-O code** 9080/3

Immature teratomas are rare in the sinonasal tract and nasopharynx, and are composed of variable quantities of immature tissue elements, mostly neuroepithelial, that are interspersed with mature and immature tissues derived from the three embryonic germ layers. They are tumours of infancy and childhood (2317).

Immature teratomas tend to be either solid-nodular or solid-cystic, while mature teratomas are usually cystic. The tumour may contain cystic spaces lined by ciliated pseudostratified epithelium as well as primitive neuroepithelium with rosettes. Mitotic figures are frequently present in the immature areas; however, cellular atypia is not found. In infants and children, a teratoma with malignant transformation has to be excluded. In adults, thorough sampling of the specimen is mandatory to rule out teratocarcinosarcoma. Immature teratomas rarely behave in a malignant fashion (570).

**Sinonasal yolk sac tumour (endodermal sinus tumour)**

**ICD-O code** 9071/3

This is a tumour that has the histological features of embryonic yolk sac, indistinguishable from yolk sac tumour (endodermal sinus tumour) of the gonads. Only two cases have been reported to arise in the sinonasal tract (1623). Both patients were adults (aged 34 and 43 years). In one case, there was an admixed component of sinonasal nonkeratinizing carcinoma. The behaviour has been aggressive.

**Sinonasal teratocarcinosarcoma**

**Definition**

A complex malignant sinonasal neoplasm combining features of teratoma and carcinosarcoma. Benign and malignant epithelial, mesenchymal, and neural elements are typically present, including immature tissue with blastomatous features, while embryonal carcinoma, choriocarcinoma or seminoma is absent.

**Synonyms**

Malignant teratoma, blastoma, teratocarcinoma, teratoid carcinosarcoma

**Epidemiology**

Sinonasal teratocarcinosarcoma is very rare (755). Approximately 60 cases have been published (755,1042,1619,1970,2339,2578,2749). Patients are exclusively adults, with age ranging from 18-79 years (mean 60 years). There is a marked male predominance (1042).

**Localization**

It almost exclusively arises in the ethmoid sinus and maxillary antrum. One tumour has been reported to arise in the roof of the nasopharynx and another from the dorsum of the tongue (1042).

**Clinical features**

Patients present with a short history of nasal obstruction and epistaxis (1042). Imaging studies reveal a nasal mass, occasionally accompanied by opacification of the paranasal sinuses. Bone destruction may be seen.

**Macroscopy**

Tumours are usually bulky, soft to rubbery, and red-tan to purple.
Histopathology
There are multiple tissue types derived from two or three germ layers, exhibiting variable degrees of maturity. In addition, there are intermingled carcinomatous and sarcomatous components [755, 2319]. The epithelial component is usually made up of keratinizing and nonkeratinizing squamous epithelium, pseudostatified columnar ciliated epithelium, and glandular structures lined by either cuboidal or columnar cells that may show mucous differentiation. Nests of immature squamous cells containing clear cells (fetal-appearing) are a common finding and an important diagnostic clue [1042]. The carcinomatous component is usually glandular, but sometimes squamous. Neuroepithelial elements with rosettes and neuroblastoma-like areas are present in most instances. The mesenchymal areas range from immature tissues (such as cartilage) to sarcomas (such as rhabdomyosarcoma and fibrosarcoma). There may be a proliferation of small round cells that are difficult to classify.

Immunoprofile
The undifferentiated/primitive component often shows positive immunoreaction for CD99 and occasionally synaptophysin and S-100 protein [1970]. The spindle cell component is consistently positive for vimentin, and sometimes desmin, myoglobin, and glial fibrillary acidic protein. The neuroepithelial component is positive for neuron-specific enolase and occasionally chromogranin, alfa-fetoprotein, and cytokeratin. The epithelial component is positive for cytokeratins, epithelial membrane antigen, and occasionally S-100 protein and glial fibrillary acidic protein.

Differential diagnosis
Inadequate sampling may lead to erroneous diagnoses of olfactory neuroblastoma, squamous cell carcinoma, undifferentiated carcinoma, adenocarcinoma, malignant salivary gland-type tumors and adenosquamous carcinoma [1042].

Histogenesis
The tumor is unlikely to be of germ cell origin, but probably arises from a primitive cell in the olfactory/sinonasal membrane that not only reproduces the neuroectodermal features of olfactory neuroblastoma, but also has the capacity to differentiate into divergent types of somatic cells [1970].

Prognosis and predictive factors
Teratocarcinosarcomas are highly malignant. They are locally aggressive, rapidly invading soft tissue and bone as well as the orbit and cranial cavities. They also have the potential to metastasize to regional lymph nodes and distant sites, mainly the lungs. The average survival is less than 2 years, with 60% of the patients not surviving beyond 3 years [1042]. Recurrences usually appear within 3 years.

Mature teratoma
Teratoma is the principal benign germ cell tumor of the sinonasal region and shows histologic features similar to its
counterparts in the gonads and in other extragonadal locations.

**Definition**
Tumour composed of a variety of mature tissues that are foreign to the site of occurrence. There are typically tissues derived from two or three germ layers.

**ICD-O code**
9080/0

**Synonyms**
Teratoid tumour, benign teratoma.

**Epidemiology**
Teratomas of the head and neck account for only 6% of all teratomas [2558]. Mature teratomas in the sinonasal tract are even more uncommon [955]. Most cases occur in neonates and older infants, with equal sex distribution [955,1737]. Stillbirth, prematurity, fetal malpresentation, dystocia, and maternal polyhydramnios are frequent associations.

**Localization**
In the sinonasal tract, the maxillary antrum and nasal cavity are affected more often than the sphenoid sinus [1036,1408,1778,1805,2312]. The nasopharynx can also be the primary site of involvement.

**Clinical features**
Facial deformity, nasal obstruction, and a nasal mass are common manifestations. Occasional calcifications may be seen on imaging [955,1805]. Teratomas may be associated with other skull deformities, anencephaly, hemicrania, and palatal fissures [8].

**Macroscopy**
The tumours are usually cystic, but can be solid or multilocular. They are commonly encapsulated masses that measure up to 7 cm.

**Histopathology**
Teratomas are composed of variable admixtures of mature skin, skin appendages, fat, glial tissue, smooth muscle, cartilage, bone, minor salivary glands, respiratory epithelium and gastrointestinal epithelium. Neural tissues are seen more often in sinonasal teratomas than in teratomas of other sites. Although the variegated histologic appearance of mature teratomas is usu-
ally diagnostic, heterotopic CNS tissue and meningocele should be considered in the differential diagnosis. The presence of immature elements or any other germ cell tumour excludes mature teratoma.

**Histogenesis**
The most popular theories are derivation from primordial germ cells or primitive somatic cells that escaped the influence of organizers and inducers [2558].

**Prognosis and predictive factors**
Complete surgical excision is curative.

---

**Dermoid cyst**

**Definition**
A dermoid cyst is a developmental lesion histogenetically and histologically composed of ectoderm and mesoderm, but no endoderm.

**ICD-O code** 9084/0

**Synonyms**
Nasal dermoid sinus cyst, cystic dermoid.

**Epidemiology**
Dermoid cysts of the nose comprise 3% of all dermoids and about 10% of those of the head and neck region [2891]. There is a male predominance. More than half are detected in children 6 years old or less, and approximately a third are present at birth [582].

**Localisation**
Dermoid cysts of the head and neck are located more often in the subcutaneous tissue of the lateral supraorbital ridge and nose. In the nose, they occur most commonly in the bridge and always in the midline. The glabella, nasal tip, and columella are less common sites [582,2891]. A few cases have been described as originating in the paranasal sinuses [2622].

**Clinical features**
Nasal dermoid cysts manifest as a midline nasal pit, fistula, or subcutaneous infected mass. They may cause broadening of the nasal bridge and occasionally cellulitis or purulent discharge. On palpation, the cysts are soft to fluctuant with a pale yellowish-pink colour noted beneath the thinned but intact epithelium; when keratin debris and sebum fill the lumen, they may have a doughy consistency [99,582,822,2891]. Most patients do not have other congenital malformations, but some do [2058]. Imaging studies are valuable in detecting a potential intracranial component and excluding an encephalocele [582,2622,2891].

**Macroscopy**
The cysts range up to 12 cm. The lumen contains cheesy, yellow-white material.

**Histopathology**
Dermoid cysts are lined with mature keratinizing squamous epithelium and frequently contain cutaneous appendages in the cyst wall. This lesion is differentiated from a teratoma by the limited variety of tissue types and the absence of endodermal components. Epidermal inclusion cysts may resemble dermoid cysts but do not contain adnexa and occur predominantly in adults [99,582,2622].

**Histogenesis**
The most likely explanation for the ontogeny of dermoid cysts is the retention of ectodermal tissue along the lines of closure at junctions of bones, soft tissues, and embryonic membranes.

**Prognosis and predictive factors**
Dermoid cysts are treated by complete surgical excision. Recurrence is uncommon (<7%) [582,2891].
Tumours of the nasal cavity and paranasal sinuses

Definition
Tumours that involve the nasal cavity and paranasal sinuses that originate from, but are not in continuity with, primary malignant neoplasms of other sites. Leukaemias and lymphomas are excluded.

Epidemiology
Metastases to the nasal cavity and paranasal sinuses are rare (1300,2085) and may occur in any age group. In a review of 82 cases, the median age of patients with metastatic tumours at diagnosis was 57 years (range 3 months to 76 years), and about 60% were males (202).

Localization
The distribution of tumour among the paranasal sinuses and the most frequent tumour types to metastasize to these sites are shown in the Table 1.8 and 1.9. In 10-15% of cases, the metastases are limited to the nasal cavity.

Clinical features
Metastases to the sinonasal tract are haematogenous. They may be solitary or multifocal and ordinarily produce symptoms indistinguishable from those of a primary tumour. These include nasal obstruction, headache, facial pain, visual disturbances, exophthalmos, facial swelling, cranial nerve deficits and epis-taxis (especially metastatic renal and thyroid carcinomas). In some instances, the metastasis may be the first manifestation of an otherwise clinically occult carcinoma, usually renal cell carcinoma.

Prognosis and predictive factors
Although the eventual outcome is usually poor, prognosis depends, in part, on whether the sinonasal metastasis is isolated or part of widespread disseminated disease. If the metastasis to the nasal cavity and sinuses is localized and treated aggressively, the average survival following discovery of the metastasis may be as long as 20-30 months (1300).

<table>
<thead>
<tr>
<th>Table 1.8</th>
<th>Most frequent sites of primary tumours that metastasize to the paranasal sinuses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Tumour</td>
<td>Frequency</td>
</tr>
<tr>
<td>Kidney</td>
<td>40%</td>
</tr>
<tr>
<td>Lung</td>
<td>9%</td>
</tr>
<tr>
<td>Breast</td>
<td>8%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>8%</td>
</tr>
<tr>
<td>Prostate</td>
<td>7%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>28%</td>
</tr>
<tr>
<td>*Data derived from reference (2085)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 1.9</th>
<th>Distribution of 168 tumours metastatic to paranasal sinuses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus</td>
<td>Frequency</td>
</tr>
<tr>
<td>Maxillary</td>
<td>33%</td>
</tr>
<tr>
<td>Sphenoid</td>
<td>22%</td>
</tr>
<tr>
<td>Ethmoid</td>
<td>14%</td>
</tr>
<tr>
<td>Frontal</td>
<td>9%</td>
</tr>
<tr>
<td>Multiple sinuses</td>
<td>22%</td>
</tr>
<tr>
<td>*Data based on reference (2085)</td>
<td></td>
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</tbody>
</table>

Fig. 1.99 Metastatic carcinoma. A Renal cell carcinoma metastatic to the maxillary sinus showing clear cells (due to accumulation of glycogen in the cytoplasm) and prominent sinusoidal vascularity. B Secondary prostatic adenocarcinoma. A malignant epithelial proliferation is identified within the large, patulous vessels in the sinonasal tract mucosa. C (Same case as B). The metastatic nature of the tumour (left) was confirmed when the prostate specific antigen (PSA) was strongly and diffusely immunoreactive in the cytoplasm of tumour cells within vascular spaces (right).