Tumours of the Hypopharynx, Larynx and Trachea

Squamous cell carcinoma is, by far, the most important tumour of the hypopharynx, larynx and trachea. It is clearly related to the abuse of tobacco and alcohol and, as such, could be drastically reduced if individuals would only alter their lifestyles. Precursor lesions have been identified and the genetic-molecular events underlying their origin and progression into clinically apparent carcinomas are gradually being elucidated. The terminology of these precursor lesions, however, is still evolving and no single classification has been universally accepted. The three most commonly used classifications and their equivalent terms are presented.
### WHO histological classification of tumours of the hypopharynx, larynx and trachea

<table>
<thead>
<tr>
<th>Malignant epithelial tumours</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
</tr>
<tr>
<td>Verrucous carcinoma</td>
<td>8051/3</td>
</tr>
<tr>
<td>Basaloid squamous cell carcinoma</td>
<td>8083/3</td>
</tr>
<tr>
<td>Papillary squamous cell carcinoma</td>
<td>8052/3</td>
</tr>
<tr>
<td>Spindle cell carcinoma</td>
<td>8074/3</td>
</tr>
<tr>
<td>Acantholytic squamous cell carcinoma</td>
<td>8075/3</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>8560/3</td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma</td>
<td>8082/3</td>
</tr>
<tr>
<td>Giant cell carcinoma</td>
<td>8031/3</td>
</tr>
<tr>
<td>Malignant salivary gland-type tumours</td>
<td></td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>8430/3</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>8200/3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Malignant epithelial tumours</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyosarcoma</td>
<td>8900/3</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>9120/3</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>9140/3</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumour</td>
<td>9040/3</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>9040/3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Borderline tumours / LMP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory myofibroblastic tumour</td>
<td>8825/1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benign tumours</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwannoma</td>
<td>9560/0</td>
</tr>
<tr>
<td>Neurofibroma</td>
<td>9540/0</td>
</tr>
<tr>
<td>Lipoma</td>
<td>8850/0</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>8890/0</td>
</tr>
<tr>
<td>Rhabdomyoma</td>
<td>8900/0</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>9120/0</td>
</tr>
<tr>
<td>Lymphangioma</td>
<td>9170/0</td>
</tr>
<tr>
<td>Granular cell tumour</td>
<td>9580/0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neuroendocrine tumours</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical carcinoid</td>
<td>8240/3</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>8249/3</td>
</tr>
<tr>
<td>Small cell carcinoma, neuroendocrine type</td>
<td>8041/3</td>
</tr>
<tr>
<td>Combined small cell carcinoma, neuroendocrine type</td>
<td>8045/3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neuroendocrine tumours</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical carcinoid</td>
<td>8240/3</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>8249/3</td>
</tr>
<tr>
<td>Small cell carcinoma, neuroendocrine type</td>
<td>8041/3</td>
</tr>
<tr>
<td>Combined small cell carcinoma, neuroendocrine type</td>
<td>8045/3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benign epithelial tumours</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Papilloma</td>
<td>8050/0</td>
</tr>
<tr>
<td>Papillomatosis</td>
<td>8060/0</td>
</tr>
<tr>
<td>Salivary gland-type adenomas</td>
<td></td>
</tr>
<tr>
<td>Pleomorphic adenoma</td>
<td>8940/0</td>
</tr>
<tr>
<td>Oncocytic papillary cystadenoma</td>
<td>8290/0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benign epithelial tumours</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Papilloma</td>
<td>8050/0</td>
</tr>
<tr>
<td>Papillomatosis</td>
<td>8060/0</td>
</tr>
<tr>
<td>Salivary gland-type adenomas</td>
<td></td>
</tr>
<tr>
<td>Pleomorphic adenoma</td>
<td>8940/0</td>
</tr>
<tr>
<td>Oncocytic papillary cystadenoma</td>
<td>8290/0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Soft tissue tumours</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant tumours</td>
<td></td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>8810/3</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>8830/3</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>8850/3</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>8890/3</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>TNM classification</th>
<th>Subglottis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong> – Primary tumour</td>
<td>T1 Tumour limited to subglottis</td>
</tr>
<tr>
<td><strong>TX</strong> Primary tumour cannot be assessed</td>
<td>T2 Tumour extends to vocal cord(s) with normal or impaired mobility</td>
</tr>
<tr>
<td><strong>T0</strong> No evidence of primary tumour</td>
<td>T3 Tumour limited to larynx with vocal cord fixation</td>
</tr>
<tr>
<td><strong>Tis</strong> Carcinoma in situ</td>
<td>T4a Tumour invades through cricoid or thyroid cartilage and/or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hypoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, oesophagus</td>
</tr>
<tr>
<td><strong>Supraglottis</strong></td>
<td>T4b Tumour invades prevertebral space, mediastinal structures, or encases carotid artery</td>
</tr>
<tr>
<td><strong>T1</strong> Tumour limited to one subsite of supraglottis with normal vocal cord mobility</td>
<td></td>
</tr>
<tr>
<td><strong>T2</strong> Tumour invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx</td>
<td></td>
</tr>
<tr>
<td><strong>T3</strong> Tumour limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or with minor thyroid cartilage erosion (e.g., inner cortex)</td>
<td></td>
</tr>
<tr>
<td><strong>T4a</strong> Tumour invades through the thyroid cartilage and/or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hypoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, oesophagus</td>
<td></td>
</tr>
<tr>
<td><strong>T4b</strong> Tumour invades prevertebral space, mediastinal structures, or encases carotid artery</td>
<td></td>
</tr>
<tr>
<td><strong>Glottis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>T1</strong> Tumour limited to vocal cord(s) (may involve anterior or posterior commissure) with normal mobility</td>
<td></td>
</tr>
<tr>
<td><strong>T1a</strong> Tumour limited to one vocal cord</td>
<td></td>
</tr>
<tr>
<td><strong>T1b</strong> Tumour involves both vocal cords</td>
<td></td>
</tr>
<tr>
<td><strong>T2</strong> Tumour extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility</td>
<td></td>
</tr>
<tr>
<td><strong>T3</strong> Tumour limited to larynx with vocal cord fixation and/or invades paraglottic space, and/or with minor thyroid cartilage erosion (e.g., inner cortex)</td>
<td></td>
</tr>
<tr>
<td><strong>T4a</strong> Tumour invades through the thyroid cartilage, or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hypoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, oesophagus</td>
<td></td>
</tr>
<tr>
<td><strong>T4b</strong> Tumour invades prevertebral space, mediastinal structures, or encases carotid artery</td>
<td></td>
</tr>
<tr>
<td><strong>Subglottis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>T1</strong> Tumour limited to subglottis</td>
<td></td>
</tr>
<tr>
<td><strong>T2</strong> Tumour extends to vocal cord(s) with normal or impaired mobility</td>
<td></td>
</tr>
<tr>
<td><strong>T3</strong> Tumour limited to larynx with vocal cord fixation</td>
<td></td>
</tr>
<tr>
<td><strong>T4a</strong> Tumour invades through cricoid or thyroid cartilage and/or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hypoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, oesophagus</td>
<td></td>
</tr>
<tr>
<td><strong>T4b</strong> Tumour invades prevertebral space, mediastinal structures, or encases carotid artery</td>
<td></td>
</tr>
</tbody>
</table>

---

1 (847,2418).
2 A help desk for specific questions about the TNM classification is available at www.uicc.org/index.php?id=508
3 The regional lymph nodes are the cervical nodes.
# TNM classification of carcinomas of the hypopharynx

<table>
<thead>
<tr>
<th>TNM classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T – Primary tumour</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour limited to one subsite of hypopharynx and 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension, without fixation of hemilarynx</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour more than 4 cm in greatest dimension, or with fixation of hemilarynx</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour invades any of the following: thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus, central compartment soft tissue*</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades prevertebral fascia, encases carotid artery, or invades mediastinal structures.</td>
</tr>
</tbody>
</table>

*Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

<table>
<thead>
<tr>
<th>N – Regional lymph nodes</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis as specified in N2a, 2b, 2c</td>
</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>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node more than 6 cm in greatest dimension</td>
</tr>
</tbody>
</table>

Note: Midline nodes are considered ipsilateral nodes.

<table>
<thead>
<tr>
<th>M – Distant metastasis</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

## Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>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>IVA</td>
<td>T1, T2, T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>T4a</td>
<td>N0, N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>IVC</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
</tbody>
</table>

1 (947,2418).
2 A help desk for specific questions about the TNM classification is available at www.uicc.org/index.php?id=508
3 ## The regional lymph nodes are the cervical nodes.
With emphasis now on accurate staging and conservative surgery to retain as many functions as possible, especially in the larynx, the pathologist has emerged as an invaluable member of the health care team. Precise and detailed examination of resected head and neck specimens regarding the site of origin of the tumour, structures involved, tumour grade, adequacy of resection margins, and the presence of lymph node metastasis, extranodal spread of tumour, perineural involvement, and vascular invasion are just a few of many features that are important to the clinician who must decide on the total therapeutic regimen for the patient.

Definitions / anatomy

**Larynx**
The larynx extends from the tip of the epiglottis to the inferior border of the cricoid cartilage. Anteriorly, its boundaries are the lingual epiglottis, the thyrohyoid membrane, the anterior commissure, thyroid cartilage, cricothyroid membrane and the anterior arch of the cricoid cartilage. The posterior boundaries include the posterior commissure mucosa (which covers the cricoid cartilage) the arytenoid region, and the interarytenoid space.

The larynx is divided into three compartments - supraglottis, glottis, and subglottis. The supraglottis is composed of the epiglottis, aryepiglottic folds, false vocal cords (vestibular folds), ventricles and saccules. The tip of the epiglottis and the aryepiglottic folds form the superior and lateral supraglottic margins. The inferior limit is a horizontal plane passing through the lateral margin of the ventricle at its junction with the superior surface of the true vocal cord (vocal fold) (947). The ventricle is the “pocket” between the true and false vocal cords. The lateral superior ventricular extension, or “cul-de-sac”, is variably sized, and referred to as the saccule. The epiglottis is further divided into suprahypopharyngeal and infrahypopharyngeal components by a plane at the level of the hyoid bone.

The glottis extends, superiorly, from a horizontal plane passing through the lateral margin of the ventricle, at its junction with the superior true vocal cord, to an imaginary horizontal plane 10 mm inferiorly from the lateral margin of the ventricle (947). The glottis consists of the true vocal cords, plus their undersurfaces, and the anterior and posterior commissures. The subglottis extends from 10 mm below the true vocal cords to the inferior margin of the cricoid cartilage. Most tumours that clinically appear as “subglottic”, actually arise from the undersurface of the true vocal cord and are still considered glottic. The term “transglottic” does not refer to a specific anatomic site. It designates those tumours that cross the ventricle vertically, to involve both the supraglottis and glottis, and occasionally subglottis (1679).

The growth and spread of laryngeal tumours is determined by the site of origin and the anatomic barriers of the different laryngeal compartments (1941). Three of these are especially important: anterior commissure tendon (Broyles’ ligament), paraglottic space and the preepiglottic space.

The anterior commissure tendon is a band of fibrous tissue 1 mm in width and 10 mm in length that extends from the vocal ligaments to the midline of the inner surface of the upper thyroid cartilage (286). It is significant not only because it contains lymphatic and blood vessels, but also because it is devoid of perichondrium at the attachment to the thyroid cartilage, thereby acting as a conduit for tumour spread into the adjacent soft tissue or the paralaryngeal (Delphian) lymph node.

The paraglottic space is a potential space deep to the ventricles and saccules filled with adipose and loose connective tissue. It is bounded by the

---

**Fig. 3.1** A Diagram of the larynx showing the various components and subdivisions. B Diagram of the larynx showing the paraglottic space and surrounding landmarks. Reprinted from Ref. (131). Courtesy of Marcel Dekker Inc.
conus elasticus inferiorly, the thyroid cartilage laterally, the quadrangular membrane medially and the pyriform sinus posteriorly. The pre-epiglottic space, also filled with adipose and connective tissue, is triangular shaped. It is bounded anteriorly by the thyroid cartilage and thyrohyoid membrane, posteriorly by the epiglottis and thyroepiglottic ligament, and superiorly by the hyoepiglottic ligament which forms its base. Both paraglottic and pre-epiglottic spaces contain lymphatics and blood vessels, but no lymph nodes. Suprahyoid epiglottic tumours are distinct from the more common infrahyoid tumours in that they are superior to the pre-epiglottic space, and often spread to the base of the tongue. Tumours that invade the pre-epiglottic and paraglottic spaces may spread without impedance through the loose connective tissue and eventually invade the extralaryngeal tissues. The supraglottic larynx is well endowed with lymphatics draining primarily into the upper, middle and lower jugular lymph nodes (levels II, III and IV, respectively). The glottis, in contrast, has a limited lymphatic supply, but also drains to the same group of lymph nodes. If a glottic carcinoma extends more than one centimeter inferi orly, the paratracheal lymph nodes are at risk for metastasis. The lymphatic drainage of the subglottis is mainly to the paratracheal lymph nodes and, only infrequently, to the middle and lower jugular lymph nodes (levels III and IV). Early in life, the larynx is entirely lined by ciliated respiratory epithelium. With time, this epithelium is gradually replaced by non-keratinizing stratified squamous epithelium. The adult larynx is lined entirely by squamous epithelium, with the exception of the ventricles and the subglottis – which continue to be lined by respiratory epithelium. Infrequently, one may see small patches of persistent ciliated respiratory epithelium in an otherwise typical adult supraglottis. The nonkeratinized squamous mucosa of the true vocal cords is normally about 5-10 cells thick. Although mucoserous glands are abundant in the supraglottis and subglottis, they are essentially absent in the true vocal cords.

**Hypopharynx**

The pharynx is a hollow muscular tube extending from the skull base to the lower border of the cricoid cartilage. It is arbitrarily divided into three regions: nasopharynx, oropharynx, and hypopharynx. The hypopharynx (also known as laryngopharynx) lies behind the larynx and partially surrounds it on either side, commencing from a plane of the superior border of the hyoid bone (or floor of the vallecula) to the inferior border of the cricoid cartilage. It is continuous with the oropharynx above and with the cervical esophagus below. The junction of hypopharynx with the cervical esophagus corresponds to the sixth cervical vertebra. The lumen of the hypopharynx is cone-shaped, wide superiorly and rapidly narrowing in the postcricoid and cervical esophageal areas. The hypopharynx has three components: right and left pyriform sinuses, postcricoid area, and lateral and posterior pharyngeal walls. The pyriform sinuses are extralaryngeal gutters nestled against the thyroid lamina. Each pyriform sinus is shaped like an inverted pyramid with the apex pointed toward the lower limit of the cricoid cartilage. The superior border corresponds to the pharyngoepiglottic fold. Each sinus has three walls, medial, lateral and anterior. The postcricoid area forms the anterior wall of the hypopharynx and connects the two pyriform sinuses. It extends from the level of the arytenoid cartilages to the inferior border of the cricoid cartilage (947). The lateral pharyngeal wall merges with the pyriform sinus. The posterior pharyngeal wall extends from the level of the superior surface of the hyoid bone to the inferior border of the cricoid cartilage.

The hypopharynx is richly supplied with lymphatics. The major drainage is along the jugular chain (levels II, III and IV), retropharyngeal lymph nodes and the node of Rouvière at the skull base. The hypopharynx is typically lined by nonkeratinizing squamous epithelium, although areas of parakeratin or orthokeratin can be seen secondary to chronic irritation. The lamina propria contains scattered lymphoid aggregates as well as mucoserous glands.

**Trachea**

The trachea extends from the lower border of the cricoid cartilage to the carina and averages 11 cm long in adults, varying roughly in proportion to an individual’s height (1660). It is 20-27 mm transversely and 16-20 mm sagitally (64). There are approximately two tracheal cartilaginous rings per centimeter of trachea, with a total of about 18-22.
Although usually referred to as rings, the cartilages are incomplete posteriorly, and form about two-thirds of a circle. The tracheal cartilages are connected to each other by fibroelastic annular ligaments. Sometimes the first tracheal ring may be fused to the cricoid cartilage. The trachea is continuous with the larynx superiorly and the bronchi inferiorly. Anteriorly, it is intimately associated with the thyroid gland and posteriorly with the esophagus. The trachea is lined entirely by ciliated respiratory epithelium and contains abundant mucouserous glands in the lamina propria. Posteriorly, the non-cartilaginous or membranous portion of the trachea contains smooth muscle. The submucosal lymphatics drain toward the posterior part of the trachea and connect with the paratracheal lymph nodes. They also anastomose with subcarinal, peribronchial and esophageal lymph nodes [64].

**Neck dissections**

A neck dissection is a tissue mass containing the cervical lymphatics. In its classical form, it extends from the submandibular soft tissues to the supraclavicular fatty tissue, laterally bordered by the platysma, and medially by the internal jugular vein. The lymph nodes in this area are divided into 6 different compartments, referred to as levels [2183]. Level I is subdivided in two compartments, the submental area (level IA) that lies between both anterior bellies of the digastric muscle and the hyoid bone dorsally, and the submandibular area (level 1B) that lies between the anterior belly of the digastric muscle medially and the mandibular bone laterally. Dorsally, this area is bordered by the tendon between the anterior and posterior belly of the digastric muscle that is attached to the hyoid bone, and the stylohyoid muscle. Thus, the triangle of soft tissue enclosed anteriorly and laterally by the mandible and dorsally by the hyoid is subdivided into one median compartment, the submental area and 2 lateral compartments, the submandibular areas. Level II represents the upper jugular (cervical) group of lymph nodes. This area extends from the base of the skull superiorly to the level of the inferior border of the hyoid bone inferiorly. The lymph nodes in this area mainly cluster in the vicinity of the internal jugular vein and are laterally covered by the body of the sternocleidomastoid muscle. Level III represents the middle jugular (cervical) group of lymph nodes. These lymph nodes are located around the middle third of the internal jugular vein that superiorly begins where the upper jugular compartment ends; the lower border lies at the inferior border of the cricoid cartilage. Level IV comprises the lymph nodes located around the lower third of the internal jugular vein extending from the inferior border of the cricoid cartilage superiorly to the clavicle inferiorly. Level V is the lymph nodes collectively taken together as the posterior triangle group. This is a triangular area lying between the anterior border of the trapezius muscle posteriorly, the posterior border of the sternocleidomastoid muscle anteriorly and the clavicle caudally. It is subdivided into a superior compartment, level VA that contains the spinal accessory lymph nodes and a lower compartment (level VB) that contains the transverse cervical and the supraclavicular lymph nodes. A horizontal plane through the inferior border of the anterior cricoid arch separates both sublevels. Level VI is the anterior compartment. This compartment has the hyoid bone as its cranial and the suprasternal notch as its caudal border. Both lateral borders are the common carotid arteries. This area is rectangular and lies between the area defined as level I above and the sternum below. Four different types of neck dissections are recognized [2183]. A radical neck dissection consists of lymph nodes from level I through V. The internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve also form part of it. A modified radical neck dissection comprises all lymph nodes from levels I-V while preserving one or more of the non-lymphoid structures that should be specified, e.g. modified radical neck dissection with preservation of spinal accessory nerve. If less than level I-V is removed, the neck dissection is referred to as selective, while specifying the levels that are included. The use of terms such as supra-omohyoid neck dissection is less preferable due to ambiguities about the extent of the surgical procedure. Extended radical neck dissection is the fourth type. This term refers to any type of neck dissection that consists of a radical neck dissection together with additional structures either lymphatic or non-lymphatic that have to be identified specifically. These structures may be additional lymph node compartments, nerves, or blood vessels. Examination of a neck dissection should be done with the following questions in mind: (1) does the specimen contain lymph nodes with metastatic deposits, (2) if so, how many lymph nodes with metastases are present, specified for each level (3) what is the size of the largest positive lymph node, necessary for staging, and (4) is there extracapsular tumour spread? Dissection of the specimen starts with determination of the type of neck dissection and identification of the various lymph nodes levels and any additional non-lymphoid structures that may have been removed. As the anatomical boundaries that are used by the surgeons to identify the lymph node levels are not present in the specimen, these cannot be used by the pathologist. Optimal processing of a neck dissection therefore requires that the surgeon submit the specimen with all lymph node levels properly labelled.

**Epidemiology**

**Age and sex distribution**

Laryngeal and hypopharyngeal squamous cell carcinoma (SCC) occur most frequently in the sixth and seventh decades, but some cases have been described in children [123,1934]. They are more common in men [344,2113] though the male:female ratio is decreasing in some countries; women are becoming increasingly affected because of increased prevalence of smoking over the last two decades [584]. Tracheal SCC occurs predominantly

---

Fig. 3.3 Schematic drawing to show the various lymph node levels in the neck. Drawing by John A.M. de Groot.
between 40 and 60 years of age, men are affected at least twice as often as women [1040].

Incidence
SCC comprises about 95% of laryngeal malignancies. The majority originate from the supraglottic and glottic regions, although there are geographic variations in the relative ratio between these two sites. The incidence in men is high (10/100,000 pa or more) in southern and central Europe, southern Brazil, Uruguay and Argentina and among Blacks in the United States. The lowest rates (<1/100,000 pa) are recorded in South-East Asia and central Africa. The incidence in women is below 1/100,000 pa in most populations. An estimated 140,000 new cases occurred worldwide in 1990, 86% of these patients were men [1980,1981]. The incidence is slightly more common in urban than in rural areas [344,2113].

There are also geographic differences in the topographic distribution of the laryngeal SCC [126]. In France, Spain, Italy, Finland and the Netherlands, supraglottic SCC predominates, while in the United States, Canada, England and Sweden glottic SCC is more common. In Japan, SCC is approximately equally distributed between the two sites.

Interpretation of incidence rates of hypopharyngeal cancer is probably complicated by absence or misclassification within subsites of the pharynx. Recorded incidence is highest among men (>2.5/100,000 pa) in India, Brazil and Central and Western Europe, and is lowest (<0.5/100,000 pa) in East Asia, Africa and Northern Europe. Incidence among women is low (<0.2/100,000 pa) in most populations except India, where rates up to 1/100,000 pa are recorded [1981]. This is probably due to the fact that tobacco is more often chewed than smoked in India.

Tracheal carcinoma is rare with approximately one tracheal carcinoma per 75 laryngeal carcinomas. It accounts for less than 0.1% of cancer deaths [1040]. SCC is the most frequent malignant tumour of the trachea representing 56-73% of all tracheal carcinomas [1040].

Trends
The incidence of laryngeal and hypopharyngeal SCC is increasing in much of the world, both in men and in women. This increase is related to changes in tobacco and alcohol consumption [344]. Primary prevention of laryngeal and hypopharyngeal SCC could be achieved by cessation of smoking and reduction of alcohol consumption [344].

Etiology
Tobacco and alcohol - Larynx
Most cases of laryngeal cancer in Western countries are related to smoking and alcohol abuse [90]. The combined effect follows a multiplicative rather than additive model [285,772,1607,1608,1800,1943,2647,2885]. The increased relative risk (RR) for alcohol consumption differs by site, and is higher for the supraglottis and hypopharynx and lower for the glottis and subglottis [2647]. The impact of increased RR (10x) for smoking is stronger for glottic than supraglottic SCC [2647]. Studies in several populations have shown a direct dose-related response between smoking and SCC and the benefits of cessation. Smoking black tobacco cigarettes entails a stronger risk than smoking blond tobacco [2235]. Other smoking habits that increase the RR of laryngeal SCC include: smoking at a young age, long duration, high number of cigarettes per day, and deep smoke inhalation [195,1035]. The influence of tobacco on RR of laryngeal SCC is confirmed even for non-drinkers [308,2833]. Case-controlled studies from Italy and Switzerland show an increased RR of 2.46 for heavy drinkers and laryngeal SCC. The RR for current smokers who do not drink is 9.38 [238]. Avoiding cigarettes and alcohol could prevent about 90% of laryngeal and hypopharyngeal SCC [718].

Tobacco and alcohol - Hypopharynx
Studies from India have also reported an association between chewing tobacco-containing products [968] and hypopharyngeal SCC. Tobacco and alcohol are also the main risk factors for hypopharyngeal SCC. The effect of alcohol is stronger and the impact of tobacco is weaker than for laryngeal SCC.

Asbestos and occupational exposure
There is controversy regarding occupational asbestos exposure and increased risk for developing laryngeal SCC [247,1255,1982,2484]. A recent review has not supported a causative role for asbestos exposure [283]. However, there is evidence supporting other occupational exposures and increased risk of laryngeal SCC, such as polycyclic aromatic hydrocarbons, metal dust, cement dust, varnish, lacquer, etc [1608]. After adjustment for alcohol and tobacco consumption, the increased risk ranged from 1.8 for cement dust to 2.7 for polycyclic aromatic hydrocarbons. Significant associations are also found with ionizing radiation, diesel exhausts, sulphuric acid mists and mustard gas [1608,2821].

Fig. 3.5 Global incidence rates of cancer of the larynx (all ages) in males. Age-standardized rates (ASR, world standard population) per 100,000 population and year. From: Globocan 2000 (730).
**Human papillomavirus (HPV)**

There is conflicting evidence implicating HPV16, in 3-85% of laryngeal SCC (1523). The prevailing opinion is that HPV has a minor causative role, if any, in laryngeal carcinogenesis (853,1253, 1510,1523,1999,2330). Additionally, HPV DNA has been detected in 12-25% of individuals with clinically and histologically normal larynges (1912,2172), suggesting that the occasional demonstration of HPV in laryngeal SCC may be incidental.

**Diet and nutritional factors**

A protective effect is probably exerted by high intake of fruits and vegetables (238, 565,1405,1910,1951,2003,2885,2901). Specific evidence regarding carotenoids and vitamin C, is inadequate for a conclusion (2821). Maté drinking has been suggested to be a risk factor in studies from Brazil and Uruguay (90).

**Gastroesophageal reflux**

Gastroesophageal reflux has been related to increased risk of laryngeal SCC, especially among patients who lack other major risk factors (80,812,1782, 2724). Gastroesophageal reflux may act as a promoter in the presence of tobacco and alcohol (812).

**Genetic susceptibility**

There is no evidence of strong genetic factors in laryngeal carcinogenesis; however, polymorphisms for enzymes implicated in the detoxification of alcohol and tobacco, such as alcohol and aldehyde dehydrogenases, are likely to represent weak susceptibility factors, with relative risks in the order of 1.5-2 (200,1590). Bloom syndrome is an inheritable condition with a predisposition towards laryngeal and hypopharyngeal SCC.

**Pathology overview and principles**

Compartmentally, the supraglottis is distinct from the glottis and subglottis. The supraglottis is embryologically derived from the buccopharyngeal anlage (branchial arches V and VI). The fascial compartmentalization, as well as the lymphatic drainage is distinct for the supraglottis and glottis and is the oncologic basis for the supraglottic horizontal laryngectomy. Dye injected into the supraglottis remains confined and does not travel to the ventricular or glottic tissues. Likewise, glottic dye injections do not pass superiorly to the ventricle or inferiorly to the mucosa overlying the cricoid cartilage. In fact, the mucosa overlying the lamina propria of the glottis (Reinke’s space or laryngeal bursa) may burst from fluid distention rather than allowing injected dye to extend into the ventricle or cross the anterior commissure. These studies also confirm that the larynx is divided into right and left compartments (2087).

The anatomic site of occurrence of tumour within the larynx can influence 1) the type of presenting symptoms, 2) stage at presentation, 3) treatment, and 4) prognosis. The vast majority of malignancies of the supraglottis and glottis are SCC. However the relative distribution of SCC per laryngeal compartment varies worldwide. Non-squamous tumours comprise a small subset of laryngeal malignancies, and are more likely encountered in the supraglottis and infraglottis than the glottis. Glottic tumours present with hoarseness and are typically small when detected. In contrast, the supraglottis is a clinically silent area and, as such, tumours in this site are often large at the time of diagnosis. Epiglottic tumours may present with a change in vocal quality (a muffled or “hot potato voice”), airway obstruction, dysphagia and/or cervical metastasis. Tumours at the base of the epiglottis may escape visualization at indirect laryngoscopy (“Winkelkarzinom” or “cancer in the corner”). Primary ventricular tumours are rare and often remain obscured on laryngeal examination, merely forming a bulge beneath the false vocal cord. Tumours of the pyriform sinus are usually large when discovered and typically present as odynophagia or referred otalgia. If the tumour involves the medial wall or the apex of the pyriform sinus, vocal cord dysfunction may result.

**Content of surgical pathology report, including cervical lymph nodes**

The surgical pathology report of a laryngectomy specimen should indicate the type of procedure (hemilaryngectomy, or total laryngectomy), and whether any additional tissues are attached (neck dissection, thyroid gland, parathyroid gland). Additional features that should be addressed include 1) site of origin, size and extent of the tumour; 2) histologic type and grade; 3) presence of perineural, lymphovascular, cartilaginous and/or extralaryngeal invasion and 4) status of the resection margins (3,290). The neck dissection should include the details as stated above (see ‘Anatomy - Neck dissections’). Surgical pathology report of a hypopharyngectomy specimen should indicate whether the tumour is arising from the
A detailed history and physical examination is necessary to determine whether the tumour is intra- or extraluminal. Clinical features and diagnostic procedures include endoscopy, which is not only necessary to obtain a biopsy but also important to further evaluate the extent of the disease and rule out additional primary tumours.

Imaging studies should always precede endoscopy since the latter procedure often results in edema and a decrease in the accuracy of image studies. Direct endoscopy is not only necessary to obtain a biopsy but also important to further evaluate the extent of the disease and rule out additional primary tumours. Distant metastasis frequently distinguishes surgical from non-surgical candidates. Accordingly, tests for hepatic function and imaging studies of lung and bones are invaluable.

### Table 3.1 Histologic diagnoses for 479 patients with laryngeal malignancies*

<table>
<thead>
<tr>
<th>Histology</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma-in-situ</td>
<td>46</td>
<td>9.6%</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>383</td>
<td>79.9%</td>
</tr>
<tr>
<td>Verrucous carcinoma</td>
<td>5</td>
<td>1.0%</td>
</tr>
<tr>
<td>Spindle cell carcinoma</td>
<td>8</td>
<td>1.7%</td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>Subtotal</td>
<td>443</td>
<td>92.5%</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma</td>
<td>4</td>
<td>0.8%</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>2</td>
<td>0.4%</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>3</td>
<td>0.6%</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>8</td>
<td>1.7%</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>3</td>
<td>0.6%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>6</td>
<td>1.2%</td>
</tr>
<tr>
<td>Plasmacytoma</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>Malignant granular cell tumour</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>Secondary papillary thyroid carcinoma</td>
<td>7</td>
<td>1.5%</td>
</tr>
<tr>
<td>Fibrosarcoma, low-grade</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>479</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

*Mount Sinai Medical Center, 1994-2003

Second primary tumours

Second primary tumours (SPT) are defined as additional primary malignancies that are distinctly separate from the index tumour (IT). Synchronous SPT are diagnosed at the same time, or within six months of the IT. If the SPT is discovered after six months, it is classified as metachronous. The median prevalence of synchronous SPT for the upper aerodigestive tract (UADT) is 9% (1027). The annual risk for SPT, is rather constant and varies between 1.5% (453) and 5.1% (1309) among patients with UADT SCC. The definition of SPT has been further expanded based on molecular markers of clonality or genetic profiling. This includes comparing patterns of loss of heterozygosity (LOH) and specific p53 mutations at various hotspots among IT, SPT and adjacent mucosa. There are drawbacks to comparing only LOH patterns: 1) LOH at various loci can be so frequent, as to be coincidentally present in two tumours, and 2) Progression in genomic loss can be seen with tumour recurrence. This issue is addressed to some extent by p53 mutational analysis, however, identical mutations can occur at various hotspots in 5% of tumours. Some studies have revealed both similarities and discordances in genetic profiling between paired IT and SPT (248). Concordant genetic profiles of IT and adjacent mucosa support the concept of mucosal field cancerization as a clonal expansion phenomenon in proximity to the IT. So SPT can arise either as related (clonal) events via lateral mucosal spread of premalignant cells, or as genetically unrelated events. Furthermore, there appears to be an indirect relationship between the distance from the IT to SPT, and the time interval between both, and genetic clonality. Thus synchronous multicentric tumours may be explained by the migration or the distant settling of tumoral cells, whereas distant SPT or metachronous tumours would be better explained by the concept of field cancerization. Newly proposed definitions for “true” SPT, local recurrence, second field tumour and metastasis have been proposed based on molecular profiling (248). “True” SPT are genetically distinct with discordant genetic profiles compared with the IT. If two metachronous carcinomas yield concordant genetic profiles, then the latter tumour is a locoregional recurrence of the former. A second field tumour (SFT) distinguishes a second, genetically discordant neoplasm adjacent to the IT, not as a local recurrence but due to the second tumour arising within the same “condemned mucosa” of the IT.

The likelihood and site for developing SPT are influenced by the site of the IT. For UADT IT, the most frequent site for SPT is within the UADT (453,1027,1309,1473,1898); usually an oral SPT associated with intraoral IT. With respect to the larynx, the risk of developing SPT is higher in patients with supraglottic tumours than in those with glottic tumours (1473,1898). Patients with glottic carcinomas are more likely to develop SPT along the respiratory axis (usually lung carcinoma), whereas patients with supraglottic carcinomas are more likely to develop SPT along the aerodigestive axis. No doubt this relates to the specific environmental promoters. The risk of developing SPT clearly correlates with tobacco and alcohol abuse. This risk is more than doubled in patients using tobacco and alcohol, as compared to those patients without exposure (1473). There is a direct dose-dependent relationship between tobacco and alcohol exposure and risk of SPT development (453,1473). The risk of developing a SPT after laryngeal IT increased proportionally to the number of cigarettes smoked per day at the time of the diagnosis (1106). Susceptibility towards the development
of SPT can be demonstrated via mutagen sensitivity tests, such as bleomycin-induced chromatid breaks of cultivated lymphocytes [461,462]. Increased mutagen sensitivity is significantly associated with an increased risk of SPT, with higher risk for both smoking-related and all SPTs (relative risks 2.62 and 2.77, respectively) [2450]. A significantly higher number of chromatid breaks are seen in patients with multiple cancers (mean 1.20) than in patients with a single cancer (mean 0.96) [461,462]. Radiation exposure is also carcinogenic, yet might also have a protective effect on the development of SPT. For patients with laryngeal IT, the latency period for SPT development in irradiated regions was significantly longer than that in non-irradiated patients, suggesting that radiotherapy (RT) may delay the development of SPT [1898]. In patients with laryngeal IT treated by primary RT, the incidence of laryngeal SPT was lower (4.3%) as compared to those patients with laryngeal IT treated primarily surgically (9.2%), again implying a protective effect [1684].

Prognosis and predictive factors
Small glottic or supraglottic SCC can be treated conservatively by laser excision, limited resection, or primary radiotherapy (RT), with curative potential, and overall good survival [1605]. RT failures can be salvaged by conservative, potentially curative voice-sparing surgery. Glottic or supraglottic carcinomas that fix the vocal cord(s) can be treated either by primary resection, with possible adjuvant RT, or organ sparing protocols (neoadjuvant chemotherapy with curative RT). If the carcinoma persists or recurs, overall survival is not compromised by delayed, salvage, total laryngectomy. The TNM tumour classification consistently correlates, on multivariate survival analyses, with disease-free and overall survival. Among TNM stage IV patients, extensive cartilage invasion and/or bulky tumour volume are predictors of poor response to chemoradiotherapy; these patients are best treated with primary resection and possible adjuvant RT [1883]. Clinical comorbidities have been demonstrated to significantly affect survival over TNM prognosticators [2041]. The Washington University Head and Neck Comorbidity Index incorporates seven conditions (congestive heart disease, cardiac arrhythmia, peripheral vascular disease, pulmonary disease, renal disease, cancer controlled, and cancer uncontrolled) weighted according to severity, and is a significant predictor of survival. Generally, histological grading has limited impact on survival. By contrast, the pattern of tumour invasion at the advancing host/tumour interface has been demonstrated, by itself or in combination with other histological variables, to have predictive value for laryngeal carcinoma [290]. Thus within T1/T2 laryngeal SCC, biopsy assessment of the pattern of invasion, may be utilized to predict which patients may respond to primary RT, versus which patients are better treated by primary resection. In multivariate analysis, overexpression of p53 is predictive of improved overall survival [1103]. p53 overexpression and elevated PCNA (proliferating cell nuclear antigen) index have been demonstrated to be significant independent predictors of successful organ preservation [249].

Hypopharynx
SCC is optimally treated with surgery and adjuvant RT. Prognosis is inversely related to TNM stage and extracapsular spread [148,1370].

Trachea
SCC is the most common primary tracheal malignancy, which is usually treated with RT. Poor prognosticators include mediastinal and distant metastases and poor patient performance status [393,1217].
Squamous cell carcinoma

Definition
Squamous cell carcinoma (SCC) is the most common malignancy of the larynx, pharynx and trachea. It occurs mainly in adult males who abuse tobacco and alcohol, and is characterized by squamous differentiation.

ICD-O code 8070/3

Synonym
Epidermoid carcinoma

Epidemiology
See Introduction page 113-114.

Etiology

Localization
The most common sites for laryngeal SCC vary according to geography, with the supraglottic and glottic regions being the most common locations. Hypopharyngeal SCC originates most frequently in the pyriform sinus, followed by the posterior pharyngeal wall, and the postcricoid area (1053,2661). Tracheal SCC occurs frequently in the lower third, and less frequently in the upper and middle thirds (1040).

Clinical features
Signs and symptoms
Clinical features depend on the localization of SCC. The most common early symptom in glottic carcinoma is hoarseness. Symptoms of supraglottic, and hypopharyngeal tumours include dysphagia, change in quality of voice, foreign body sensation in the throat, haemoptysis, odynophagia and neck mass. Dyspnoea, and stridor are especially common in subglottic tumours (749). Tracheal SCC usually presents clinically with dyspnoea, wheezing or stridor, acute respiratory failure, cough, haemoptysis, and/or hoarseness (2143).

Macroscopy
Laryngeal and hypopharyngeal SCC may present as a flat plaque with a well-defined, raised edge, or exhibits a polypoid exophytic appearance, which may relate to prognosis. The surface of the tumour is sometimes ulcerated (1711). Tracheal SCC usually presents as a polypoid mass projecting into the lumen, rarely does it grow as a circumferential or an annular mass (1040).

Tumour spread and staging
SCC may spread directly to contiguous structures, or via lymphatic and blood vessels to lymph nodes and more distant sites.

Direct spread to contiguous structures
Supraglottic SCC tends to spread into the pre-epiglottic space, pyriform sinus or towards the base of the tongue, but it rarely invades the glottis and thyroid cartilage. Glottic SCC tends to remain localized for a long period; in late stages of the disease, it may extend to the opposite true vocal cord, to the supraglottis and subglottis; it may also extend through the thyroid cartilage and invade the soft tissue of the neck. The subglottic SCC may spread to the thyroid gland, hypopharynx, cervical esophagus and tracheal wall. SCC that crosses the ventricles and involves the supraglottis and glottis, is termed transglottic SCC (1679). Hypopharyngeal SCC frequently involves the larynx.

Stomal recurrence
Stomal recurrence, defined as recurrent SCC at the mucocutaneous junction of
the tracheostoma, is a well recognized, but infrequent complication after total laryngectomy. Patients with subglottic and postcricoid involvement and advanced stage of the primary SCC are at risk to develop this complication.

**Local and distant metastases**

Laryngeal, hypopharyngeal and tracheal SCC are likely to metastasize to the regional lymph nodes. The location and frequency of lymph node metastases depends upon the site of the primary tumour. Extracapsular spread (ECS) refers to carcinoma penetrating the lymph node capsule and infiltrating extracapsular tissue. Extracapsular spread is further divided into macroscopic and microscopic ECS [337]; macroscopic ECS is evident to the naked eye and appears as matted lymph nodes. Microscopic ECS is only evident on histologic examination and is usually limited to the adjacent perinodal fibrolipidose tissue.

Clinically relevant haematogenous metastases are infrequent but may occur in late stages of the disease. The most common site for spread is the lung, and less commonly, liver and bones [2435]. In patients with blood-borne metastases, regional lymph node metastases are usually also present or have been treated.

**Staging**

Tumours of the larynx and hypopharynx are staged by the TNM system (AJCC and UICC) [947,2418]. Tracheal tumours are not included in the TNM system. In the definition of the N classification, the specified 3.0 cm and 6.0 cm measurements include the total tumour mass in the area (lymph node mass) and not just the individual lymph node size [2801].

**Histopathology**

Squamous differentiation, often seen as keratinization with variable “pearl” formation, and invasive growth are the prerequisite features of SCC. Invasion is manifested by disruption of the basement membrane, and extension into the underlying tissue, often accompanied by stromal reaction. Angiolympathic and perineural invasion are additional signs of malignancy.

The tumours are traditionally graded into well-, moderately-, and poorly differentiated SCC. Well differentiated SCC resembles closely normal squamous epithelium. Moderately differentiated SCC contains distinct nuclear pleomorphism and mitotic activity, including abnormal mitoses; there is usually less keratinization. In poorly differentiated SCC, immature cells predominate, with numerous typical and atypical mitoses, and minimal keratinization. Although keratinization is more likely to be present in well- or moderately-differentiated SCC, it should not be considered an important histological criterion in grading SCC. Most SCC are moderately differentiated, so grading by differentiation is really of limited prognostic value, as compared to pattern of invasion.

**Invasive front**

Tumour growth at the invasive front can show an expansive pattern, an infiltrative pattern, or both. Expansive growth pattern is characterised by scattered small irregular cords or single tumour cells, with poorly defined infiltrating margins and is associated with a more aggressive course [290]. Some guidelines recommend categorizing tumours into cohesive, and non-cohesive fronts, (Reporting Guideline for the Royal College of Pathologists).

**Stromal reaction**

Invasive SCC is almost always accompanied by stromal reaction that consists of desmoplasia with deposition of extracellular matrix and proliferation of myofibroblasts [2907]. Neovascularization is frequently seen.

**Immunoprofile**

SCC expresses epithelial markers such as cytokeratins. The patterns of expression of cytokeratin subtypes may change during malignant transformation and relate to the histologic grade, degree of keratinization, and the likelihood of metastases. Low-grade SCC expresses medium-high molecular weight (MW) cytokeratins, but not low MW cytokeratins [1617]. High-grade SCC may express vimentin [2668].

**Electron microscopy**

SCC exhibits desmosomes and attached tonofilaments [880].

**Differential diagnosis**

The diagnosis of SCC is usually not prob-
Tumours of the hypopharynx, larynx and trachea also includes other malignant tumours, types of SCC. The differential diagnosis must be distinguished from various sub-

differentiation.

Further, moderately or poorly differentiated SCC lacks prominent branched fibrovascular cores [171,2602]. Verrucous SCC is composed of papillary projections and bulbous invaginations, lacking cytological atypia. Well-differentiated SCC must also be distin-
guished from pseudoepitheliomatous hyperplasia, a benign hyperplastic epithelial condition composed of irregular elongated rete pegs extending deeply into the stroma. It typically occurs in association with chronic infections (tuberculosis, mycosis), trauma, and classically, granular cell tumours. The cytological features of malignancy are not found in pseudoepitheliomatous hyperplasia.

Distinguishing SCC from radiation changes can be difficult. Radiation can result in ulceration, epithelial and stromal atypia, inflammation and vascular changes. The seromucinous glands may be atrophic. Squamous metaplasia and hyperplasia of ducts, can mimic SCC. Preservation of ductal lumens and lobu-

lar architecture aid in making this distinc-
tion.

Moderately or poorly differentiated SCC must be distinguished from various sub-
types of SCC. The differential diagnosis also includes other malignant tumours, such as adenocarcinoma, neuroen-
docrine carcinoma, melanoma and lymphoma. The correct diagnosis is best achieved by the use of appropriate immunohistochemistry.

**Precursor lesions**

Precursor lesions are defined as altered epithelium with an increased likelihood for progression to SCC [847,852,1253, 1581]. Epithelial dysplasia is the term used traditionally to describe these microscopic alterations, although other terms have been proposed (see section on epithelial precursor lesions). Pathologists are frequently asked to assess epithelial dysplasia, because it is believed to be an important indicator of malignant potential. The likelihood of malignant change directly relates to the severity of dysplasia. However, it is clear that malignancy can develop from any grade of dysplasia or even from morpho-

tically normal epithelium.

**Histogenesis**

SCC originates from the squamous mucosa or from ciliated respiratory epithelium that has undergone squa-

mous metaplasia.

**Somatic genetics**

*Cytogenetics and comparative genomic hybridization (CGH)*

The most frequent chromosomal alterations detected by CGH are +3q, +5p, +8q, +11q13, +17q, and −3p. Additional alterations, such as +1q, +7p, +7q +9q, +14q, +18p, and −4p, −5q, −11qter, and −18q are also frequent [1074,1145]. These alterations are very similar to those reported with conventional karyotyping analysis of early passage cells from laryngeal carcinomas [1219]. Predictive models based on hierarchical branching and distance-based trees indicate +3q21-29 as the most important early chromosomal alteration, followed in importance and chronology by −3p [1145]. High-level amplifications are found at 3q24-pter and, less frequently 11q13, 18p, 18q11.2, 8q23-24, and 11q14-22. Some of these amplifications are at loci containing known oncogenes (CCND1 for 11q13) [1074]. Metastasizing tumours show a higher number of DNA copy losses than non-

metastasizing tumours. Losses at 8p, 9q, and 13 are more frequent in metastatic than in primary tumours [1381].

**Molecular genetic alterations**

Neoplastic transformation implies modula-
tion of a large number of genes [1810] as well as telomerase re-activation as indicated by hTERT expression [1588]. CCND1 is amplified and overexpressed mostly in advanced cases [811,1207]. MYC and EGFR are amplified in 6-25% of cases although amplification is not relat-
ed to overexpression [612,794,811]. Loss of RB1 expression is seen in less than 20% of tumours [1208,2546] although LOH at 13q14 is present in 60% or more of tumours, suggesting the existence of other(s) tumour suppressor gene(s) neighbouring RB1 [2857]. TP53 mutations are found in 13-50% of laryngeal tumours. The excess of G to T transversions and the codons more frequently affected are both attributed to the carcinogenic effect of tobacco smok-
ing [1939,2027]. TP53 alterations are found in premalignant lesions indicating participation early in the neoplastic transformation process [847,1809]. However, neither TP53 overexpression nor CDKN1A expression are reliable markers for TP53 mutations. Instead, CDKN1A expression is clearly related to squa-
mous differentiation [1811]. TP73L, a TP53 homologue with oncogenic poten-
tial, maps to 3q27-28, a region with fre-
quent gains. In primary carcinoma, low-

copy number TP73L amplification has been detected by fluorescent in-situ
hybridization (FISH) [2837].

The role of HPV infection in laryngeal carcinoma may be overestimated [1810]. The use of PCR-based techniques for the detection of HPV-DNA has yielded variable results (for a review see [1523]). In fact, the virus has even been demonstrated in more than 12-25% of non-neoplastic samples examined [2008].

CDKN2A can be inactivated by mutation, homozygous deletion, and promoter hypermethylation [1208,2168]. CDKN2A mutations can occur in cases with mRNA and/or protein overexpression [1209]. Significant levels of MMP13 mRNA are detectable in some laryngeal tumours, restricted to those that retain features of squamous differentiation. MMP13 expression is coordinated with MMP2 and MMP14 overexpression, two molecules that can efficiently activate MMP13. Both MMP13 expression and MMP14 overexpression are associated with advanced tumours, indicating a more aggressive behaviour [348]. CDH1 expression is lower in metastatic tumours [798]. In addition, gene expression silencing of CDH1 by promoter hypermethylation is more frequent in metastatic (77%) than in primary laryngeal tumours (40%) [95].

Prognosis and predictive factors

The overall 5-year survival rate is 80-85% in glottic SCC, 65-75% in supraglottic SCC, about 40% in subglottic SCC [126], 62.5% in hypopharyngeal SCC [2434], and 47% in tracheal SCC [2143].

Clinical predictive factors

Stage

TNM remains the most significant predictor of survival.

Localization

Tumour localization is important [754]. The best prognosis has been reported for glottic SCC, and the worst prognosis for hypopharyngeal, subglottic and tracheal SCC.

Other factors that can have an impact on the presentation and outcome of SCC include age, [428,2374], comorbidity (concurrent diseases) [402] and performance status [428].

Histopathological predictive factors

Resection margins

The complete excision of tumour is the most important principle of oncologic surgery. Negative resection margins are generally associated with decreased recurrence and improved survival [1557, 2403]. Although controversial, a distance of a few millimeters may be adequate in selected glottic SCC [2462,2738]. For supraglottic, advanced glottic, and hypopharyngeal SCC, resection margins have not been precisely defined but distances of at least 5 mm or greater are desired [841].

Proliferation

Proliferation fraction determined immunohistochemically with antibodies against Ki67 and proliferating cell nuclear antigen (PCNA) have been reported to correlate strongly with the degree of differentiation in SCC [1372,2906] and the presence of lymph node metastases [798]. However, proliferation fraction is not an independent prognostic factor [1372].

Lymphovascular and perineural invasion

The penetration of tumour cells into lymphatic and/or blood vessels is associated with an increased propensity for lymph node and/or distant metastases. It tends to occur in aggressive SCC and is associated with recurrence and poor survival [2853]. Similarly, perineural invasion is associated with increase local recurrence, regional lymph node metastases and decrease survival [708,2853].

Extracapsular spread in lymph node metastases

Lymph node metastasis is the single most adverse prognostic factor in head and neck SCC [750]. Recent studies have shown that the presence of extracapsular spread in lymph nodes is strongly associated with both regional recurrence and distant metastases, resulting in decreased survival [750, 1094,2507].

DNA ploidy

The prognostic significance of DNA ploidy has been studied extensively and the results are controversial. Some studies have shown that aneuploid tumours are associated with a higher rate of lymph node metastases and decreased survival [652,2545,2805] while others have not confirmed this [139,574]. Conflicting results have also been reported regarding the predictive value of DNA ploidy and treatment response [2645, 2774].

Genetic predictive criteria

The prognostic value of p53 abnormalities is generally inconclusive for laryngeal carcinoma [79,1809,1914]. CCND1 amplification is related to poor prognosis independent of stage [192]. Simultaneous CDK4 and CCND1 overexpression is associated with poor prognosis [615]. In patients with locally advanced laryngeal cancer, CDKN2A mutations have prognostic significance in predicting adverse outcome [183].
**Definition**
Verrucous carcinoma (VC) is a non-metastasizing variant of well-differentiated squamous cell carcinoma (SCC) characterized by an exophytic, warty, slowly growing neoplasm with pushing margins.

**ICD-O code**
8051/3

**Synonym**
Ackerman tumour [12]

**Epidemiology**
VC occurs predominantly in men in the 6th and 7th decades of life [1671].

**Etiology**
VC has been related to tobacco smoking. Human Papillomavirus (HPV) genotypes 16 and 18, and rarely 6 and 11, have been identified in some, but not all, VC [250,289,777,1233,1283].

**Localization**
Larynx is the second most common site of VC in the head and neck (after oral cavity) and accounts for 15-35% of all VC [1350] and 1-4% of all laryngeal carcinomas [777,1671,1956]. Most arise from the anterior true vocal cords, though it may occur in the supraglottis, subglottis, hypopharynx and trachea [1350,1671].

**Clinical features**
Hoarseness is the most common presenting symptom; other symptoms include airway obstruction, weight loss, dysphagia, and throat pain [1671,1956]. Enlarged lymph nodes are common and reactive rather than neoplastic [978].

**Macroscopy**
VC presents as a sharply circumscribed, broad based exophytic warty tumour which is usually firm, and tan to white.

**Histopathology**
VC consists of thickened club-shaped papillae and blunt intrastromal invaginations of well-differentiated squamous epithelium with marked keratinization and thin fibrovascular cores. The squamous epithelium lacks cytologic criteria of malignancy, and by morphometry, the cells are larger than those seen in SCC [489]. Mitoses are rare, and observed in the basal layers. DNA synthesis (S-phase) is also limited primarily to the basal layers [737]. VC invades the stroma with a pushing, rather than infiltrating border. Dense lymphoplasmacytic host response is common. Intraepithelial microabscesses are seen, and the abundant keratin may evoke a foreign body reaction. The surrounding mucosa shows progressive transition from hyperplasia to VC. A downward dipping of epithelium often “cups” the VC periphery, and is the ideal site for deep biopsy [174,1192].

Hybrid tumours are VC containing foci of conventional SCC. The incidence of hybrid tumours in the larynx is approximately 10% [1956]. It is important to recognize this variant of VC, as it has the potential to metastasize [131,174].

**Differential diagnosis**
The differential diagnosis of VC includes exophytic SCC, hybrid VC, papillary SCC, keratinizing squamous cell papilloma and verruca vulgaris. VC lacks cytological atypia, this distinguishes it from exophytic SCC, hybrid VC and papillary SCC. The pushing margins of VC are smooth, in distinction to the irregular shaped invasive islands of SCC. Papillomas have thin, well-formed papillary fronds, with limited keratinization, as compared to the markedly keratinized papillae of VC. Verruca vulgaris of the larynx [722] characteristically contains layers of parakeratotic squamous cells with large keratohyaline granules, identical to their counterpart on the skin.
Prognosis and predictive factors

VC is characterized by a slow, locally invasive growth causing extensive local destruction if left untreated. Pure VC does not metastasize (746,1956). In contrast, hybrid VC has the potential for metastasis and, accordingly these patients should be managed as similarly staged patients with SCC (1956). VC has an excellent prognosis; the reported five-year survival rate for laryngeal VC is 85-95% (751,1350). Patients with VC may be treated by excision (by laser or surgery), or by radiotherapy. Although surgery is more effective, radiotherapy is an acceptable alternative for patients who are poor surgical candidates (978,1350, 1671,1956,2582). Some reports have suggested that VC may undergo anaplastic transformation following radiotherapy. Critical review of these cases however has shown many to be unrecognized hybrid VC or other carcinomas that were inappropriately labelled as VC.

Fig. 3.14 Larynx verrucous carcinoma. Increased number of cell layers (left), with a broad pushing border of infiltration without cytologically atypical cells (right upper). Keratosis, including parakeratotic crypting is present (right lower).
Definition
Basaloid squamous cell carcinoma (BSCC) is an aggressive, high-grade, variant of SCC composed of both basaloid and squamous components.

ICD-O code 8083/3

Synonyms
Basaloid carcinoma, adenoid cystic-like carcinoma.

Epidemiology
BSCC occurs in both sexes, but predominantly in men 60-80 years of age (132, 1578, 2128, 2709).

Localization
The piriform sinus and supraglottic larynx are the usual sites of involvement (684, 688, 1337, 1578, 1774, 2128, 2709). It has also been described in the trachea (1992, 1997, 2232).

Clinical features
BSCC may present with neck mass, hoarseness, pain, sore throat, dysphagia, cough, otalgia, bleeding, and/or weight loss (117, 1997, 2128).

Etiology
Tobacco and alcohol abuse have been proven to be strong risk factors (117, 132, 1997, 2128).

Macroscopy
BSCC appears as a centrally ulcerated mass with extensive submucosal induration that may be confused with a minor salivary or soft tissue tumour (132, 1578, 1997, 2128).

Histopathology
BSCC has two components, i.e. basaloid and squamous cells. Basaloid cells are small, with hyperchromatic nuclei without nucleoli, and scant cytoplasm. They are closely packed, growing in a solid pattern with a lobular configuration, and in some cases, there is prominent peripheral palisading. Comedo-type necrosis is frequent. Distinctive features of BSCC, not found in SCC, are small cystic spaces containing PAS- and Alcian blue-positive material, and stromal hyalinization (117, 2709). BSCC is always associated with a SCC component which can be either in-situ carcinoma, or invasive keratinizing SCC. The latter is usually located superficially; it may also present as a focal squamous differentiation within the basaloid tumour islands. The junction between the squamous and basaloid cells may be abrupt (117, 132). Rarely, BSCC is associated with a spindle cell component (1791). Metastases may demonstrate basaloid carcinoma, squamous carcinoma, or both (688, 1578, 2128).

Immunoprofile
BSCC expresses cytokeratins and epithelial membrane antigen but the percentage of positive cells is highly variable. To avoid false-negative results, a cocktail of cytokeratin antibodies (i.e. CAM 5.2, AE1/3) is recommended (132). The antibody 34βE12, directed against high MW cytokeratins is most sensitive for the detection of basaloid cells (117, 1774). In the distinction between BSCC and adenoid cystic carcinoma, absence of myoepithelial cells and the presence of dot-like vimentin expression in BSCC can be helpful. S-100 protein reactivity is not helpful in the differential diagnosis, and if observed, usually corresponds to intermingled dendritic cells. BSCC is negative for chromogranin, synaptophysin, and glial-fibrillary acid protein (117, 132, 1337).

Electron microscopy
Desmosomes and tonofilaments have been observed in basaloid and squamous cells. There are no neurosecretory

Fig. 3.15 Basaloid squamous cell carcinoma of the larynx. 
A Polypoid tumour with an intact squamous epithelium, subtended by lobules of basaloid cells with areas of central comedonecrosis. 
B Panoramic view of a tumour that arises from the surface epithelium and is composed of basaloid and squamous nests of cells situated above the epiglottic cartilage.
granules, myofilaments, or secretory granules in BSCC [1082,2709].

**Differential diagnosis**
This includes neuroendocrine carcinoma, adenoid cystic carcinoma, and adenosquamous carcinoma. Neuroendocrine carcinoma typically lacks squamous differentiation, and is strongly positive for neuroendocrine markers. Adenoid cystic carcinoma, especially the solid variant, may resemble BSCC but adenoid cystic carcinoma has a myoepithelial component [132, 1337] and lacks in most instances squamous differentiation. Furthermore, palpable metastatic cervical lymph nodes, quite common in BSCC, are very rare in adenoid cystic carcinoma [2128]. Adenocarcinoma and adenosquamous carcinoma can be distinguished from BSCC by the presence of true ductoglandular differentiation, and intracellular mucin.

**Histogenesis**
The suggested precursor of the BSCC is a totipotent primitive cell located in the basal cell layer of the surface epithelium, or in the proximal ducts of minor salivary glands [2128,2709].

**Prognosis and predictive factors**
BSCC is an aggressive, rapidly growing tumour characterised by an advanced stage at the time of diagnosis and a poor prognosis. Metastases to the regional lymph nodes have been reported in two thirds of patients [117,1337,1997,2128], and distant metastases involving lungs, bone, skin and brain, in 35-50% of patients [117,1337,2128]. Although controversial, it is generally believed that BSCC is more aggressive than SCC when matched stage for stage [117,736,1337,1578,2709,2787,2798].

---

**Fig. 3.16** Basaloid squamous cell carcinoma (BSCC). **A** Abundant intercellular hyaline globules conferring a cribriform-like pattern. **B** Nest of basaloid cells with peripheral palisading of the nuclei and a central keratin pearl. **C** Peripheral palisading of hyperchromatic columnar nuclei and areas of central necrosis. **D** Hyaline stromal deposits between nests of basaloid and squamous cells. **E** Central comedo-type of necrosis in a basaloid nest. **F** Peripherally palisaded nuclei with hyperchromatic nuclei in cells with high nuclear to cytoplasmic ratio. Abrupt keratinization is noted in the centre of this lobule.

**Fig. 3.17** Metastatic basaloid squamous cell carcinoma in a regional lymph node, displaying both basaloid (left) and squamous (right) components.
Papillary squamous cell carcinoma

Definition
Papillary squamous cell carcinoma (PSCC) is a distinct variant of SCC characterized by an exophytic, papillary growth, and a favourable prognosis.

ICD-O code 8052/3

Epidemiology
PSCC occurs predominantly in males in the 6th and 7th decades [501,743,2602].

Etiology
Smoking and alcohol abuse are etiologic factors [501,2602]. Although HPV has been suggested as an etiologic factor, (929) reported prevalence of HPV has varied from 0-48% [171,501,2488]. Its role in the etiology of PSCC is therefore unsettled.

Localization
The larynx and the hypopharynx are among the most common sites of involvement [501,687,743,2488,2602]. Laryngeal PSCC is most often found in the supraglottis, slightly less often in the glottis, and rarely in the subglottis [131, 687,1187,2602].

Clinical features
Hoarseness and airway obstruction are the most common presenting symptoms. Other features include dysphagia, sore throat, cough, and haemoptysis.

Macroscopy
PSCC presents as a soft, friable, polypoid, exophytic, papillary tumour. It frequently arises from a thin stalk, but broad-based lesions have also been described.

Tumour spread and staging
Metastases to the regional lymph nodes may be present, but distant metastases are rare [743]. Lung metastases have been observed in a few patients with laryngeal PSCC [2488].

Histopathology
The tumour is characterized by a predominant papillary growth pattern [2602]. These papillae have thin fibrovascular cores covered by neoplastic, immature basaloid cells or more pleomorphic cells. Commonly, there is minimal keratosis. Foci of necrosis and haemorrhage are frequent. Multiple PSCC or precursor lesions may occur. Stromal invasion consists of a single or multiple nests of tumour cells with dense lymphoplasmacytic inflammation at the tumour-stromal interface. If no stromal invasion is found, the lesion should be called atypical papillary hyperplasia or PSCC in-situ.

Differential diagnosis
This includes squamous papilloma, verrucous carcinoma, and exophytic SCC. Though squamous papilloma and verrucous carcinoma share similar architecture with PSCC, the latter is easily recognized by atypia of the squamous epithelium [743]. Most PSCC strongly express p53 immunohistochemically [2488]. The distinction between exophytic and papillary SCC can be difficult as the criteria for diagnosing exophytic SCC are not clearly delineated [171,2602]. In general, the papillary stalks of PSCC are much better defined than in exophytic SCC.

Precursor lesions
PSCC may evolve from pre-existing papillary mucosal hyperplasia or squamous cell papilloma. Precursor lesions may be solitary or multiple [171,2488].

Prognosis and predictive factors
Patients with PSCC are generally believed to have a better prognosis than those with SCC though reports in the literature are controversial [131,171,1187, 2488,2602]. The better prognosis is probably related to limited invasion.

Fig. 3.18 Papillary squamous cell carcinoma (PSCC). Exuberant papillary neoplastic outgrowth in the glottic-supraglottic region.

Fig. 3.19 PSCC. A Low power view of the tumour revealing the characteristic papillary finger-like pattern of growth. B Markedly pleomorphic cells showing focal intercellular bridge formation. C Strong nuclear immunoreactivity for p53.
Spindle cell carcinoma

Definition
Spindle cell carcinoma (SPCC) is a biphasic tumour composed of a squamous cell carcinoma, either in-situ and/or invasive, and a malignant spindle cell component with a mesenchymal appearance, but of epithelial origin.

ICD-O code
8074/3

Synonyms
Sarcomatoid carcinoma, carcinosarcoma, collision tumour, pseudosarcoma.

Epidemiology
SPCC occurs predominantly in males in the 7th decade of life (1490, 2604).

Etiology
SPCC has been linked to cigarette smoking and alcohol consumption (1490, 2604) and may develop after radiation exposure (1482, 1490, 2604).

Localization
Larynx is among the most common sites in the head and neck (204). Less frequently it arises in the hypopharynx (62). In the larynx, the glottis is most frequently involved (1490).

Clinical features
Patients usually present with hoarseness, dysphagia, and/or airway obstruction (1490).

Macroscopy
It usually exhibits a polypoid appearance of variable size. The surface is frequently ulcerated. It may rarely appear as an ulcerative infiltrative lesion.

Tumour spread and staging
SPCC metastasizes to the regional lymph nodes in up to 25% of cases; but distant dissemination is less common (5-15 %) (1420, 1490, 2604).

Histopathology
The spindle cell component usually forms the bulk of the tumour, which can assume several patterns. Resemblance to fibrosarcoma or malignant fibrous histiocytoma is most common (1490, 2604). Occasional cases can appear less malignant and resemble a reactive fibroblastic proliferation or radiation-induced stromal atypia (62). Foci of osteosarcomatous, chondrosarcomatous, or rhabdosarcomatous differentiation may be present, particularly in patients with previous radiotherapy (RT) (1420, 1490, 2604). Evidence for squamous epithelial derivation can be seen as either in-situ carcinoma or as invasive SCC. Carcinoma-in-situ can be obscured by extensive ulceration. Infiltrating SCC may be focal, requiring multiple sections for demonstration (1482). Sometimes, only spindle cells are present; in such cases, SPCC can be mistaken for a true sarcoma. Metastases usually contain SCC alone or both SCC and spindle cell component, and rarely, only the spindle cell component (2457, 2604).

Immunoprofile
Tumour cells can express both epithelial and mesenchymal markers (1700, 2535, 2610, 2882). The most useful epithelial markers are AE1AE3, CK1, CK18, and epithelial membrane antigen (EMA) (2604). Spindle cells express vimentin and often other mesenchymal filaments, such as smooth muscle actin, muscle specific actin, and desmin.

Electron microscopy
SPCC often displays features of epithelial differentiation in spindle cells, such as desmosomes and tonofilaments (175, 1056, 2535, 2882).

Differential diagnosis
The diagnosis of SPCC generally requires the demonstration of both malignant spindle cells and squamous cell carcinoma, either in-situ or invasive. When a SCC component is inconspicuous, then the spindle cells should be investigated for evidence of epithelial differentiation. However, even in the absence of SCC and negative epithelial markers, SPCC cannot be entirely ruled out. In the larynx and hypopharynx sarcomas are very rare, and SPCC is still more likely. SPCC can also be confused...
with reactive or benign spindle cell proliferations, such as nodular fasciitis, and inflammatory myofibroblastic sarcoma, and low-grade myofibroblastic sarcoma, and myoepithelial carcinoma.

**Histogenesis**

There is mounting molecular evidence that SPCC is a monoclonal epithelial neoplasm (954,2596,2620), with a divergent (mesenchymal) differentiation (172, 954, 1490,2596,2620), rather than a collision tumour, or biphasic derivation, or “pseudosarcoma” (126).

**Prognosis and predictive factors**

Favourable prognostic features are: low-stage, polypoid rather than endophytic growth, a glottic site of origin, relatively shallow depth of sarcomatoid process, and absence of prior radiation (172). Although controversial, limited immunoreactivity for polyclonal cytokeratin has been associated with significantly improved survival rates (1944,2604). The reported 5-year survival is between 65 and 95% (168,2604).

![Fig. 3.21 Spindle cell carcinoma. A The ulcerated surface is subtended by a highly pleomorphic spindle cell population with atypical mitotic figures. B Transition between squamous cell carcinoma and spindle cell component. C Pure spindle cell component with marked cellular atypia mimicking a leiomyosarcoma. D Spindle cell component surrounding small nests of squamous cells mimicking synovial sarcoma.](image)

![Fig. 3.22 Spindle cell carcinoma. A The surface epithelium blends imperceptibly with the spindle cell component. B Abrupt areas of squamous differentiation within a spindle cell carcinoma. C Metaplastic cartilage, including malignant transformation (left) and metaplastic osteoid, including malignant transformation (right) can be seen in spindle cell carcinoma. D Strong and diffuse immunoreactivity for keratin is seen in a majority of spindle cell carcinomas.](image)
Acantholytic squamous cell carcinoma

Definition
This is an uncommon histopathologic variant of squamous cell carcinoma (SCC), characterised by acantholysis of the tumour cells, creating pseudolumina and false appearance of glandular differentiation.

ICD-O code 8075/3

Synonyms
Adenoid squamous cell carcinoma, pseudoglandular SCC, SCC with gland-like features, angiosarcoma-like SCC, pseudovascular adenoid squamous cell carcinoma.

Etiology
No special etiological factor has been discovered for the mucosal acantholytic SCC [2876].

Localization
It rarely arises in the supraglottic larynx [1079] and hypopharynx [157], but is more frequent in sun-exposed areas of the head and neck [1847].

Clinical features
There are no special clinical features.

Macroscopy
There are no special gross features.

Tumour spread and staging
As with SCC

Histopathology
This neoplasm is composed of SCC, but with foci of acantholysis in tumour nests, creating the appearance of glandular differentiation. The pseudolumina usually contain acantholytic and dyskeratotic cells, or cellular debris, but they may be empty [157,742]. They are more frequent in the deeper portions of the tumour. There is no evidence of true glandular differentiation or mucin production. The SCC component predominates, and is usually moderately differentiated. Clear and spindle cells may also be present. The stroma is usually desmoplastic, with a lymphoplasmacytic response [157,742]. The acantholysis may also form anastomosing spaces and channels mimicking angiosarcoma.

Immunoprofile
Acantholytic SCC expresses epithelial markers, such as cytokeratins, and epithelial membrane antigen [742].

Electron microscopy
The tumour cells exhibit hemidesmosomes and attached tonofilaments, and no glandular features thus supporting the squamous origin [2876].

Differential diagnosis
Acantholytic SCC must be differentiated from adenosquamous carcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma. This is achieved by demonstrating a lack of true gland formation, absence of myoepithelial cells and negative mucin staining. Vascular markers can be used to distinguish it from angiosarcoma. Cytokeratin, however, might be positive also in some angiosarcomas [939].

Histogenesis
Acantholytic SCC is derived from the surface squamous epithelium.

Prognosis and predictive factors
Prognosis is similar to SCC, however some reports suggest a more aggressive behaviour [157,742,899,2876].

Fig. 3.23 Acantholytic squamous cell carcinoma. A Marked acantholysis of squamous cells giving rise to anastomosing empty spaces with pseudoglandular appearance. B Acantholytic channels, interningled with dilated capillary blood vessels, mimicking angiosarcoma.
Adenosquamous carcinoma

Definition
This rare aggressive neoplasm originates from the surface epithelium and is characterized by both squamous cell carcinoma (SCC) and true adenocarcinoma.

ICD-O code 8560/3

Epidemiology
There is a male predisposition, with a tendency to develop in the 6th and 7th decades.

Etiology
Cigarette smoking and alcohol consumption have been implicated {1294}. The role of gastroesophageal reflux has not been well established.

Localization
The larynx is the most frequent site, {15,43,831,876,1294}; the hypopharynx is occasionally involved {1646,2237}.

Clinical features
Patients present with hoarseness, sore throat, dysphagia, and/or haemoptysis {1294}.

Macroscopy
It can present as an exophytic or polypoid mass, or as a poorly defined mucosal induration, frequently with ulceration {876,1294}.

Histopathology
The main feature is both true adenocarcinoma and SCC. The two components occur in close proximity, but they tend to be distinct and separate, not intermingled as in mucoepidermoid carcinoma. The SCC component can present either as in-situ or as an invasive SCC {43}. The adenocarcinomatous component tends to occur in the deeper parts of the tumour. It consists of tubular structures that give rise to “glands within glands”. Mucin production is typically present, either intraluminal or intracellular, and can appear as signet ring cells. However, mucin is not a requirement for the diagnosis in the presence of true glanduloductal formation. Metastases may display both components; one usually predominates.

Immunoprofile
There is positive staining for high-molecular weight cytokeratin in both components. The glandular component expresses CEA and low MW cytokeratins: specifically, CK7 is positive, and CK20, is negative {43,1646}.

Electron microscopy
Features of both squamous and adenocarcinomatous differentiation are found {231,1190}.

DNA ploidy
A high prevalence of aneuploidy has been demonstrated {43}.

Differential diagnosis
This includes mucoepidermoid carcinoma.

Table 3.2 Differential diagnosis between adenosquamous carcinoma and mucoepidermoid carcinoma of the head and neck

<table>
<thead>
<tr>
<th>Adenosquamous carcinoma</th>
<th>Mucoepidermoid carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous carcinoma in-situ</td>
<td>No squamous carcinoma in-situ</td>
</tr>
<tr>
<td>Origin from squamous epithelium</td>
<td>Origin from seromucinous ducts</td>
</tr>
<tr>
<td>Keratin pearls</td>
<td>Limited keratin pearls</td>
</tr>
<tr>
<td>Glands at lower invasive parts</td>
<td>Glands widely intermingled</td>
</tr>
<tr>
<td>No lobular arrangement</td>
<td>Lobular arrangement</td>
</tr>
<tr>
<td>No intermediate cells</td>
<td>Large, clear “Intermediate cells”</td>
</tr>
</tbody>
</table>

Fig. 3.24 Adenosquamous carcinoma. A squamous cell carcinoma in-situ (upper-left) appears in continuity with gland-like formations (bottom-right).
ma, acantholytic SCC, and SCC invading seromucinous glands, and necrotizing sialometaplasia. The most important differential diagnosis is from mucoepidermoid carcinoma as adenosquamous carcinoma has a poorer prognosis (see Table 3.02) [231]. The presence of mucin in true glandular spaces helps to distinguish adenosquamous carcinoma from acantholytic carcinoma. SCC invading or entrapping mucoserous glands can mimic adenosquamous carcinoma, especially in biopsy specimens. In such cases, preservation of lobular gland architecture, and lack of significant atypia can distinguish SCC from adenosquamous carcinoma. Adenosquamous carcinoma is distinguished from necrotizing sialometaplasia, a benign condition that lacks the cytological features of malignancy.

Adenosquamous carcinoma will always have a surface (mucosal) component (dysplasia, in-situ carcinoma), whereas this feature is not seen in mucoepidermoid carcinoma.

**Histogenesis**
Adenosquamous carcinoma originates from basal cells of surface epithelium that are capable of divergent differentiation [1844,1873,2285,2677].

**Prognosis and predictive factors**
Adenosquamous carcinoma is reported as being more aggressive than SCC [876,1844,2237,2611]. Many present as high stage tumours. However, stage for stage comparison with SCC has not been well established. In a recent review, 75% of patients had regional lymph node metastases, and 25% of patients had distant metastases [1294], most commonly to the lungs [731,1294]. The reported 5-year survival rate is 15-25% [831,876,1294]. Half of the patients die of disease after a mean of 23 months (range 12-35 months) [43].

---

**Fig. 3.25** Adenosquamous carcinoma of the larynx. A Blended adenocarcinoma and squamous cell carcinoma within a single tumour mass. B Mucin-filled epithelial cells are part of areas of squamous differentiation.

**Fig. 3.26** Adenosquamous carcinoma. A Positive immunohistochemical reaction for CK7 in areas with glandular differentiation. B Mucicarmine positive secretion in the cytoplasm of a single signet ring cell showing a markedly atypical nucleus.
Lymphoepithelial carcinoma

**Definition**
Lymphoepithelial carcinoma (LEC) is an undifferentiated carcinoma with a prominent, reactive lymphoplasmacytic infiltrate, morphological indistinguishable from nasopharyngeal carcinoma.

**ICD-O code** 8082/3

**Synonyms**
Lymphoepithelioma {2317}; undifferentiated carcinoma of the nasopharyngeal type {2317}; lymphoepithelioma-like carcinoma {2741}; undifferentiated carcinoma with lymphoid stroma

**Epidemiology**
LEC of the larynx, hypopharynx and trachea are very rare, and account for less than 0.5% of all cancers in these sites {1722}. There is a male predominance of 4:1, and the mean age is 60 years. In contrast to nasopharyngeal carcinoma, almost all reported cases have occurred in Caucasians {621,1601}.

**Etiology**
Smoking and alcohol abuse are noted {621}. Epstein-Barr virus (EBV) is uncommonly demonstrated {621,1601,1637,2741}.

**Localization**
They occur with equal incidence in the larynx and hypopharynx. About two-thirds of the laryngeal tumours are found in the supraglottic region {1601,1637}.

**Clinical features**
Patients present with hoarseness, neck mass, sore throat, cough, otalgia, dysphagia or haemoptysis.

**Macroscopy**
The tumour forms a mass that may show deep or superficial ulceration.

**Tumour spread and staging**
Many patients have cervical lymph node metastasis at presentation or early in the course. Distant metastasis (liver, lung, mediastinum, and skin) develops in about one-third of patients {1601,1637}.

**Histopathology**
Some LEC show a pure growth pattern, indistinguishable from LEC of other sites. (see Chapter 2 on Tumours of the Nasopharynx). In about half of the cases, there is a component of squamous cell carcinoma that accounts for 10-75% of the entire tumour {1601}. The overlying epithelium can show carcinoma-in-situ.

**Prognosis and predictive factors**
LEC of the larynx and hypopharynx are aggressive, with a propensity for regional lymph node and distant metastasis. A mortality rate of 30% at median follow up of 21 months has been reported {1601}.

---

**Fig. 3.27** Lymphoepithelial carcinoma. Islands of undifferentiated carcinoma cells intimately admixed with numerous small lymphocytes and plasma cells.
Giant cell carcinoma

**Definition**

An undifferentiated carcinoma composed of many bizarre multinucleated giant cells, often containing neutrophils or cellular debris in the cytoplasm. It is similar to giant cell carcinoma of the lung (474,768,890,989,2722).

**ICD-O code**

8031/3

**Synonyms**

Large cell carcinoma, pleomorphic carcinoma, undifferentiated carcinoma, anaplastic carcinoma.

**Epidemiology**

Giant cell carcinomas of the larynx are extremely rare (744).

**Etiology**

Smoking and alcoholic consumption have been implicated.

**Localization**

The tumours have all occurred in the larynx, with no site of predilection (744).

**Clinical features**

Progressive dysphonia and dyspnoea are the most common complaints.

**Macroscopy**

The tumours are indistinguishable from squamous cell carcinoma (SCC).

**Histopathology**

The hallmark is the presence of numerous, non-cohesive, bizarre giant cells that contain prominent, frequently multiple nuclei with coarse chromatin and large nucleoli. The cytoplasm is abundant, eosinophilic, sometimes vacuolated, and often contains neutrophils or cellular debris. Additionally, the tumour contains a background population of smaller anaplastic tumour cells. Giant cell carcinoma may exist in a pure or mixed form, in association with SCC, adenocarcinoma, or spindle cell carcinoma (474,768).

**Histogenesis**

The histogenesis remains uncertain, and it has been questioned whether giant cell carcinoma is a specific entity (768).

**Prognosis and predictive factors**

The reported cases have shown a poor prognosis (744).
In a large series of laryngeal tumours from one institution, 72% of salivary gland-type neoplasms were malignant (1039). The majority were mucoepidermoid and adenoid cystic carcinomas.

ICD-O codes
Mucoepidermoid carcinoma 8430/3
Adenoid cystic carcinoma 8200/3

Mucoepidermoid carcinomas
Laryngeal mucoepidermoid carcinomas (MEC) are rare, only about 100 cases have been reported (1573). They comprise one third of malignant laryngeal salivary-type tumours (1606). They are much more common in men and most cases present between the ages of 45 and 75 years (peak incidence in the 6th decade) but cases have been reported in children (1750). The most common site is the supraglottis (1937). They present with progressive hoarseness and dysphagia or dysphonia. Nearly half of the cases present with, or develop, cervical lymph node metastases (217,533).

Tumours size is variable. Microscopically they are similar to MEC elsewhere. The behaviour tends to be unpredictable. However, it is acknowledged that a significant number of tumours originally diagnosed as high-grade MEC may have been adenosquamous carcinomas that generally have a poorer prognosis.

Adenoid cystic carcinoma
Adenoid cystic carcinoma (ACC) is very uncommon in the larynx and forms only 0.07-0.25% of all laryngeal carcinomas (732,2475), accounting for 1% of all ACC (2446). Only 120 reported cases were identified in a literature review (642). Most occur between the fourth and sixth decades (1039). The majority are subglottic (60%) or supraglottic (35%) and the true cords are involved in only 6% of cases (1573). The microscopic features and outcome of laryngeal ACC are the same as in other sites (469,1942).

Other salivary-type tumours
A variety of other carcinomas have been reported in the seromucous glands of the larynx. However, they are very rare and are usually presented as single case reports: acinic cell carcinoma (734,1250, 2146,2454), malignant myoepithelioma (1167), carcinoma ex pleomorphic adenoma (180,232,1729,2220), epithelial myoepithelial carcinoma (1726), salivary duct carcinoma (745,910), papillary adenocarcinoma (2182), mucinous adenocarcinoma (2640) and clear cell carcinoma (1855,2020,2306).

Table 3.3 Salivary gland-type neoplasms of the larynx*

<table>
<thead>
<tr>
<th>Tumour types</th>
<th>No of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleomorphic adenoma</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Oncocytic tumours</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Cystadenoma</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

*Modified from Heffner (1039)
Neuroendocrine neoplasms of the larynx are a heterogeneous group of tumours that vary from benign to highly malignant. Similar to the lung, they can be divided into several types. As a group, they are uncommon with only about 500 cases recorded in the literature as of 1998 (738). The atypical carcinoid is the most frequent, constituting 54% of all neuroendocrine tumours in this site, followed by the small cell carcinoma, neuroendocrine type (34%), paraganglioma (9%) and the typical carcinoid (3%) (125,648,897, 2420,2816).

Cells similar if not identical with Kulchitsky cells of the bronchi are found in the larynx. These, as well as pluripotential endobronchial stem cells, are the putative cells of origin of the typical carcinoid, atypical carcinoid, and small cell carcinoma, neuroendocrine type. Paragangliomas of the larynx are derived from paraganglia normally found in the larynx and are discussed in chapter 8.

**Typical carcinoid**

**Definition**
An epithelial tumour of low-grade malignancy composed of round to spindle cells with histologic, immunohistochemical and ultrastructural evidence of neuroendocrine differentiation.

**ICD-O Code** 8240/3

**Synonyms**
Carcinoid, mature carcinoid, well differentiated (Grade I) neuroendocrine carcinoma.

**Epidemiology**
The typical carcinoid (TC) is the least common of the neuroendocrine neoplasms of the larynx with only 42 cases recorded as of 2005 (2420). It is three times more common in men and most patients are between 45-80 years of age (average 64 years) at diagnosis (738, 2419).

Table 3.4 Classification of neuroendocrine tumours of the larynx.

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Synonyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Typical carcinoid</td>
<td>Carcinoid, well differentiated (Grade I) neuroendocrine carcinoma</td>
</tr>
<tr>
<td>B. Atypical carcinoid¹</td>
<td>Malignant carcinoid, moderately differentiated (Grade II) neuroendocrine carcinoma¹</td>
</tr>
<tr>
<td>C. Small cell carcinoma, neuroendocrine type²</td>
<td>Small cell neuroendocrine carcinoma, poorly differentiated (Grade III) neuroendocrine carcinoma</td>
</tr>
<tr>
<td>D. Combined small cell carcinoma, neuroendocrine type, with non-small cell carcinoma, adenocarcinoma, etc.)</td>
<td>Combined small cell carcinoma, composite small cell carcinoma</td>
</tr>
<tr>
<td>E. Paraganglioma</td>
<td>Non-chromaffin paraganglioma</td>
</tr>
</tbody>
</table>

¹Some atypical carcinomas may fulfill the diagnostic criteria of large cell neuroendocrine carcinoma of lung
²Not all small cell carcinomas of the larynx will show neuroendocrine differentiation

Fig. 3.30 Typical carcinoid. Typical carcinoid of epiglottis composed of small trabeculae and clusters of cells lying in the lamina propria. The overlying squamous mucosa is intact and free of atypia and/or dysplasia.
 Localization
Most occur in the supraglottic larynx in the vicinity of the aryepiglottic fold, arytenoid or false vocal cord.

 Clinical features
Symptoms, ranging from three weeks to four years in duration, include dysphagia, hoarseness and a sore throat. At least one patient developed the carcinoid syndrome after the tumour metastasized to the liver (738).

 Macroscopy
The tumours have ranged from 0.5 – 3.0 cm. (average 1.6 cm.) in greatest dimension and present as a submucosal or polypoid mass (738).

 Histopathology
TCs are composed of round and/or spindle cells that grow in small nests, trabeculae, large sheets, glands and/or rosettes. The cytoplasm is pink and the nuclei have finally stippled or dense chromatin. Nucleoli and mitoses are sparse to absent (less than 2 mitoses/10 HPFs). Necrosis and pleomorphism are not seen. The stroma is highly vascular and often focally fibrotic or hyalinized.

 Rarely, carcinoids, either typical or atypical, may be oncocytic or oncocytoid. The distinction depends on the presence (oncocytic) or absence (oncocytoid) of mitochondria on ultrastructural examination. A few may contain mucin and, exceptionally, even amyloid.

 Immunohistochemistry
TCs are positive for cytokeratin, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), synaptophysin, chromogranin, neuron specific enolase (NSE), and protein gene product 9.5. They are also variably positive for a variety of peptides, including serotonin, calcitonin, bombesin and somatostatin.

 Electron microscopy
TCs contain abundant membrane-bound, electron-dense neurosecretory granules varying in size from 90-230 nm (2762). Cellular junctional complexes are observed as well as numerous mitochondria if the TC is of the oncocytic type.

 Differential diagnosis
See under atypical carcinoid.

 Prognosis and Predictive factors
Since radiation and chemotherapy are ineffective, surgery is the treatment of choice. The extent of resection should be as conservative as possible, as long as complete removal is achieved. A neck dissection is not warranted.

 Although the series is small, data indicate that 33% of patients with TCs of the larynx have experienced distant metastases (liver, bones) (648,2419). At least one patient developed the carcinoid syndrome and another died of disease five years after treatment. While this suggests that TCs of the larynx may be more aggressive than those of the lung, some of these tumours on critical review are probably best classified as atypical carcinoids.
Atypical carcinoid

**Definition**
An epithelial tumour composed of round to spindle cells with histologic, immunohistochemical and ultrastructural evidence of neuroendocrine differentiation exhibiting more mitoses and cellular atypia than a typical carcinoid.

**ICD-O code**
8249/3

**Synonyms**
Malignant carcinoid, moderately differentiated (Grade II) neuroendocrine carcinoma, large cell neuroendocrine carcinoma.

**Epidemiology**
The atypical carcinoid (AC) is 15 times more common than the TC and is the most frequent neuroendocrine neoplasm of the larynx. It is 2-3 times more common in men and has been described in patients from 36-83 years of age (average 61 years) [2769,2816]. Most are heavy smokers.

**Localization**
Over 90% arise in the supraglottic larynx in the vicinity of the aryepiglottic fold, arytenoid or false vocal cord.

**Clinical features**
Hoarseness, dysphagia, pain in the throat and a neck mass are the usual symptoms. An associated paraneoplastic syndrome is exceptional.

**Macroscopy**
The tumours present as a tan, gray, pink or haemorrhagic submucosal or polypoid mass 0.2 – 4.0 cm. in greatest dimension (average 1.6 cm) [2769, 2816].

**Histopathology**
ACs are infiltrative tumours that grow in a variety of patterns, including small nests, sheets, trabeculae, glands and/or a combination of these patterns. Cysts with intracystic papillary-like projections of tumour cells may also be seen. In contrast to TCs, the cells are larger and the nuclei are often vesicular and contain prominent nucleoli. Mitoses (usually 2-10/10 HPFs) necrosis, cellular pleomorphism and angiolymphatic invasion are common. Some tumours may even fulfill the diagnostic criteria of large cell neuroendocrine carcinoma of the lung (10 or more mitoses per 10 high power fields and prominent necrosis). Mucinous changes, amyloid, spindle cells and oncocytic-oncocytoid cells may also be observed.

**Immunohistochemistry**
The tumours may stain for synaptophysin (100%), cytokeratin (96%), chromogranin A (94%), calcitonin (80%), CEA (75%), somatostatin (50%), serotonin (21%), and adrenocorticotropic hormone (17%) [2816].

**Electron microscopy**
Membrane-bound, electron-dense neurosecretory granules ranging from 70-420 nm are prominent [2769]. Cellular junctional complexes, rough endoplasmic reticulum, mitochondria, Golgi complexes and infrequent bundles of tonofilaments may also be seen.

**Differential diagnosis**
AC may be confused for a TC, paraganglioma, malignant melanoma, and medullary thyroid carcinoma. The AC is distinguished from the TC by the presence of larger cells, prominence of nucleoli, mitoses, necrosis, pleomorphism and angiolymphatic invasion. AC is positive for cytokeratin, CEA and calcitonin, whereas the paraganglioma is negative for these markers. Malignant melanoma is positive for HMB-45 and tyrosinase and negative for synaptophysin and cytokeratin. Separating AC from metastatic medullary thyroid carcinoma (MTC) may be more problematic since both tumours are positive for synaptophysin, calcitonin and CEA. Clinical and imaging studies to detect the presence or absence of a mass in the larynx or thyroid may offer some assistance. Although the serum calcitonin level is almost invariably elevated in metastatic MTC and usually negative in AC, rare cases of laryngeal AC associated with elevated levels of serum calcitonin have been reported [2409]. Reliance on this test to distinguish between these two tumours is, therefore, not absolute. Knowledge of the serum CEA level (especially if markedly elevated), however, may be helpful. This test is almost universally elevated in MTC, but thus far, has not been reported in association with AC. More recently, thyroid transcription factor – 1 (TTF) has been useful in separating these two tumours. MTC is strongly and diffusely positive for this marker while the AC is typically negative or only focally, weakly positive.

Fig. 3.34 Atypical carcinoid. A Same case as shown in Figure 3.33. Higher magnification shows large cells with prominent nucleoli and mitoses. B Tumour cells are strongly positive for calcitonin.
Tumours of the hypopharynx, larynx and trachea

Prognosis and Predictive factors
ACs are aggressive tumours, with 5- and 10-year accumulative survival rates of 48% and 30%, respectively. Metastases to cervical lymph nodes have observed in 43% of patients, to skin and subcutaneous tissues in 22%, and to other distant sites in 44% (particularly lungs, liver, and bones {2816}).

Factors adversely affecting prognosis include metastatic disease at presentation, positive tumour margins, angiolymphatic invasion, and tumours larger than one centimeter {2769,2816}. Determination of DNA ploidy has no prognostic significance {1097}.

Small cell carcinoma, neuroendocrine type

Definition
A highly malignant epithelial tumour composed of small round, oval or spindle cells with evidence of neuroendocrine differentiation.

Synonyms
Small cell carcinoma, small cell neuroendocrine carcinoma, poorly differentiated (Grade III) neuroendocrine carcinoma, oat cell carcinoma, anaplastic small cell carcinoma, small cell neuroendocrine carcinoma of intermediate type.

ICD-O Code 8041/3

Epidemiology
Although the second most common neuroendocrine tumour of the larynx, small cell carcinoma, neuroendocrine type (SCCNET), is still an unusual neoplasm accounting for only 0.5% of all laryngeal carcinomas. It is three times more common in men and is distinctly unusual in patients below 40 years of age {897}. Most are heavy smokers.

Localization
Although the tumour may arise in any region of the larynx, the supraglottis is, by far, the most common site.

Clinical features
Symptoms and signs are those associated with other laryngeal neoplasms and depend on the site of origin. Hoarseness and dysphagia are the usual complaints. Almost half of patients have cervical lymph node metastases at presentation. Exceptionally the tumour may be associated with a paraneoplastic syndrome. Among these include Cushing, Eaton-Lambert, and Schwartz-Bartter syndromes {752}.

Macroscopy
The tumours often present as ulcerated submucosal lesions and, as a consequence, may be indistinguishable from ordinary squamous cell carcinoma.

Histopathology
The tumour is composed of sheets or rib-
bons of closely packed cells with inconspicuous cytoplasm and round, oval and/or spindle nuclei with dense chromatin and absent nucleoli. Mitoses, necrosis, apoptosis, and lymphatic, vascular, and perineural invasion are common as well as nuclear molding and DNA-coating of the walls of blood vessels. Rare rosettes may be seen. The mucosa is often ulcerated but the marginal epithelium is free of dysplasia. Exceptionally, SCCNET may be associated with a squamous or adenocarcinoma (see “Combined carcinoma” below).

**Immunophenotype**
The immunoprofile is essentially similar to that of the TC and AC. Some may also express thyroid transcription factor – 1.

**Ultrastructure**
Membrane-bound, electron-dense neurosecretory granules ranging from 50-200 nm are scant compared to the TC and AC [2762].

**Differential diagnosis**
The differential diagnosis includes TC, AC, basaloid squamous cell carcinoma, malignant lymphoma, and a metastasis from a primary SCCNET of the lung. Compared to TC and AC, SCCNET is composed primarily of short spindle cells without nucleoli and exhibits more nuclear molding, necrosis and mitotic activity. In addition, SCCNET may be positive for thyroid transcription factor – 1 while the AC is usually negative [1097]. Basaloid squamous cell carcinoma (BSCC) is a biphasic tumour composed of basal and squamous cell components that characteristically grow in a lobular pattern with central comedonecrosis. In addition, BSCCs often exhibit prominent nucleoli, cyst-like areas and hyalinosis and are negative for neuroendocrine markers and TTF. Malignant lymphomas are positive for leukocyte common antigen and negative for neuroendocrine markers. A metastasis from a primary SCCNET of the lung is based primarily on negative imaging studies of the lung.

**Prognosis and predictive factors**
SCCNET is an aggressive tumour with early regional and distant metastasis. Almost half of patients will present with positive cervical lymph nodes and about 60-90% will develop distant metastases, especially to the lungs, liver and bones. The 2- and 5-year survival rates are 16% and 5%, respectively [897]. Because many patients have disseminated disease at the time of diagnosis, radical surgery (laryngectomy with neck dissection) is rarely indicated. Instead a therapeutic protocol using a combination of local radiation and chemotherapy, similar to that for pulmonary SCCNET, is advocated.

**Combined small cell carcinoma, neuroendocrine type**
Small cell carcinoma, neuroendocrine type (SCCNET) associated with a squamous or adenocarcinomatous compo-
Epithelial precursor lesions

Definition
Precursor lesions are defined as altered epithelium with an increased likelihood for progression to squamous cell carcinoma (SCC). The altered epithelium shows a variety of cytological and architectural changes that have traditionally been grouped under the term dysplasia. However, other classifications, e.g. squamous intraepithelial neoplasia (SIN) and squamous intraepithelial lesions (SIL, Ljubljana classification) have also proven to be useful [222,504,846,1054,1055,1253,1254,1711,2317]. Rarely, malignant transformation can develop even from morphologically normal epithelium. Atypia is not considered synonymous with dysplasia. Atypia has been used in the context of inflammatory and regenerative changes, particularly referring to cytologic features. In this text, the term atypia refers to cytological change that may or may not be pre-malignant. Various classifications have evolved to describe the spectrum of histological changes in relation to their malignant potential [222,504,846,1054,1055,1253,1254,1711,2317].

Epidemiology
The entire spectrum of laryngeal and hypopharyngeal precursor lesions are mostly seen in the adult population and affect men more often than women. This gender disparity is especially pronounced after the sixth decade [245]. Mean ages for the first precursor lesion diagnosis are reported from 48.0-56.5 years [243,1253]. The incidence varies worldwide with the magnitude and manner of carcinogen exposure.

Etiology
Precursor lesions are strongly associated with tobacco smoking and alcohol abuse, and especially a combination of these two [221,566,766,1607,1608,1800,2564]. The risk of developing these lesions increases with duration of smoking, the type of tobacco and the practice of deep inhalation. Additional etiological factors are: industrial pollution, specific occupational exposures, nutritional deficiency, and hormonal disturbance [766,1253,1255,1256,1608,1982].

The role of human papillomavirus (HPV) infection in laryngeal carcinogenesis remains unsolved [2412]. The prevalence of HPV in laryngeal carcinoma varies significantly among various studies, ranging from 0% to 54.1% [2517]. Although the overall prevalence of HPV infection found in 9 studies of precursor lesions [97,276,793,853,927,928,1522,2065,2172] was 12.4%, HPV DNA was detected in a clinically and histologically normal larynx in 12-25% of individuals [1912,2172]. Thus, definite evidence of an etiologic role of HPV in precursor lesions, at least at present, is lacking, and HPV infection in precursor lesions may represent an incidental HPV colonization rather than true infection of the laryngeal mucosa.

Localization
Precursor lesions appear mainly along the true vocal cords. Two thirds of vocal cord lesions are bilateral [243]. They can extend over the free edge of the vocal cord to the subglottic surface. An origin in, or extension along the upper surface

| Table 3.5 Classification schemas that histologically categorize precursor and related lesions |
|-----------------------------------------------|-----------------------------------------------|
| **2005 WHO Classification** | **Squamous Intraepithelial Neoplasia (SIN)** | **Ljubljana Classification Squamous Intraepithelial Lesions (SIL)** |
| Squamous cell hyperplasia | | Squamous cell (simple) hyperplasia |
| Mild dysplasia | SIN 1 | Basal/parabasal cell hyperplasia* |
| Moderate dysplasia | SIN 2 | Atypical hyperplasia** |
| Severe dysplasia | SIN 3*** | Atypical hyperplasia** |
| Carcinoma in-situ | SIN 3*** | Carcinoma in-situ |

* Basal/parabasal cell hyperplasia may histologically resemble mild dysplasia, but the former is conceptually benign lesion and the latter the lower grade of precursor lesion.
** ‘Risky epithelium’. The analogy to moderate and severe dysplasia is approximate.
*** The advocates of SIN combine severe dysplasia and carcinoma in-situ.

Fig. 3.38 Microlaryngoscopic view of laryngeal leukoplakia. Both vocal cords are moderately thickened; an exophytic, well-circumscribed, white plaque is seen in the left vocal cord.

Fig. 3.39 Squamous cell hyperplasia (simple hyperplasia). There is an increased number of ordinary-arranged, otherwise normal cells in the spinous layer. A keratin layer is present on the surface.
of the vocal cord is less common \{1253,1332\}. The commissures are rarely involved \{243\}. Hypopharyngeal precursor lesions are rarely identified as the common presentation is established malignancy \{2661\}. No good data exist regarding tracheal precursor lesions.

**Clinical features**
Most patients with precursor lesions give a history of a few months or more of symptoms, but may be asymptomatic \{243\}. Symptoms depend on the location and severity of the disease and include fluctuating hoarseness, throat irritation, sore throat, and/or chronic cough. Precursor lesions can be either sharply circumscribed and grow exophytically, or be predominantly flat and diffuse, related in part to the amount of keratin present.

**Macroscopy**
Precursor lesions have a clinically diverse appearance, variously described as leukoplakia (white patch), chronic hyperplastic laryngitis or rarely erythroplasia/erythroplakia (red patch). A circumscribed thickening of the mucosa covered by whitish patches, or an irregularly growing, well-defined warty plaque may be seen. A speckled appearance of lesions can also be present, caused by unequal thickness of the keratin layer. However, the lesions are commonly more diffuse, with a thickened appearance, occupying a large part of one or both vocal cords. Their surface is rough, may be muddy brown to red (erythroplasia), perhaps with increased visible vascularity, or coated with diffuse or dispersed circumscribed whitish plaques (speckled leukoplakia) \{1253,1332\}. Few white patches are ulcerated (6.5%) or combined with erythroplasia (15%) \{243\}. Leukoplakia, in contrast to erythroplasia, tends to be well demarcated. In general, leukoplakia has a lower risk of malignant transformation than mixed white and red lesions, or speckled leukoplakia, which has an intermediate risk, and pure erythroplasia which has the highest risk of cancer development \{2759\}. However, no one clinical appearance is reliably diagnostic of any histologic grade of precursor lesion. Occasionally precursor lesions may appear clinically normal.

**Histopathology**
The epithelium of all precursor lesions is generally thickened. However, in a minority of cases patchy atrophy, thinning of the viable cellular layers, may be present. By definition there is no evidence of invasion. The magnitude of surface keratinization is of no importance. Allocation to categories within each of the classifications requires consideration firstly of architectural features and then of cytology.

1. **Hyperplasia**
Definition: Hyperplasia describes increased cell numbers. This may be in the spinous layer (acanthosis) and/or in the basal/parabasal cell layers (progenitor compartment), termed basal cell hyperplasia. The architecture shows regular stratification and there is no cellular atypia.

<table>
<thead>
<tr>
<th>Table 3.6 Criteria used for diagnosing dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Architecture</strong></td>
</tr>
<tr>
<td>Irregular epithelial stratification</td>
</tr>
<tr>
<td>Loss of polarity of basal cells</td>
</tr>
<tr>
<td>Drop-shaped rete ridges</td>
</tr>
<tr>
<td>Increased number of mitotic figures</td>
</tr>
<tr>
<td>Abnormal superficial mitoses</td>
</tr>
<tr>
<td>Premature keratinization in single cells</td>
</tr>
<tr>
<td>Keratin pearls within rete pegs</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

![Fig. 3.40 Mild dysplasia (basal-parabasal cell hyperplasia, SIN1). A Note the increased number of basal-parabasal cells with hyperchromatic, uniform nuclei, perpendicularly oriented to the basement membrane. The upper part of the epithelium shows a regular spinous layer and thin parakeratotic layer on the surface. B Increased number of uniform, slightly enlarged basal and parabasal cells, perpendicularly oriented to the basement membrane. Increased number of regular mitoses are evident. At the right corner (lower half) the epithelial cells show minimal cytologic atypia. The upper half of the epithelium is composed of regular spinnous cells, which become flattened toward the surface. A thin parakeratotic layer is present on the surface.](bb9_2a_126-150.ps)
142 Tumours of the hypopharynx, larynx and trachea

2. Dysplasia (intraepithelial neoplasia, atypical epithelial hyperplasia potentially malignant lesions)
Definition: When architectural disturbance is accompanied by cytologic atypia the term dysplasia applies. There is a challenge in the recognition of the earliest manifestations of dysplasia, and no single combination of the above features allows for consistent distinction between hyperplasia and the earliest stages of dysplasia as well as in attempting to rigidly divide the spectrum of dysplasias into mild, moderate and severe categories.

Mild dysplasia
In general architectural disturbance limited to the lower third of the epithelium accompanied by cytological atypia define the minimum criteria of dysplasia.

Moderate dysplasia
Architectural disturbance extending into the middle third of the epithelium is the initial criterion for recognizing this category. However, consideration of the degree of cytologic atypia may require upgrading.

Severe dysplasia
Recognition of severe dysplasia starts with greater than two thirds of the epithelium showing architectural disturbance with associated cytologic atypia. However, as noted in the previous paragraph, architectural disturbance extending into the middle third of the epithelium with sufficient cytologic atypia may be upgraded from moderate to severe dysplasia.

Carcinoma in-situ
The theoretical concept of carcinoma in-situ is that malignant transformation has occurred but invasion is not present. It is not always possible to recognize this morphologically. The following is recommended for the diagnosis of carcinoma in-situ: full thickness or almost full thickness architectural abnormalities in the viable cellular layers accompanied by pronounced cytologic atypia. Atypical mitotic figures and abnormal superficial mitoses are commonly seen in carcinoma in-situ.

Differential diagnosis
Reactive, regenerative or reparative squamous epithelium (for example in response to trauma, inflammation, irradiation or ulceration) may manifest atypical cytology or architectural disturbance. Nutritional deficiencies such as iron, folate, and vitamin B12, can also simulate dysplasia. Such lesions are not considered precursor lesions and should be distinguished from them. Clinical history is helpful, and morphologic changes suggestive of the inciting event (e.g. ulceration, inflammation, haemorrhage, radiation-induced mesenchymal and/or endothelial nuclear enlargement and hyperchromasia) may be present. The epithelial changes in these cases are generally less pronounced than in severe dysplasia/atypical hyperplasia or CIS, atypical mitoses are almost never present, and the epithelium may be thinned, or, if thickened, stratification and maturation often develop as the regenerative/reparative process matures.

Somatic genetics
In studies addressing the genetic changes underlying pre-malignant lesions of the head and neck, the larynx and hypopharynx are often dealt with in a broader anatomic context including the oral cavity. True to current models of carcinogenesis, malignant transformation of the mucosa lining the larynx and other
regions of the head and neck is fundamentally a genetic process that involves activation of key oncogenes and inactivation of critical tumour suppressor genes. These genetic alterations generally occur in order of progression; however, it is fundamentally the net accumulation of multiple genetic alterations that dictates the frequency and pace of progression to invasive carcinoma [318, 319]. Genetic progression does not imply a uniform orderly progression through various stages of histologic progression. By some estimates, progression from normal mucosa to invasive squamous cell carcinoma requires as many as ten independent genetic events [2156]. Loss of heterozygosity studies indicate that the earliest alterations appear to target specific genes located on chromosomes 3p, 9p21, and 17p13 [318]. These alterations, particularly LOH at 9p21, may precede histopathologic evidence of dysplasia [317,2667]. Hyperplasia without any histologic evidence of dysplasia has been found to represent clonal populations of cells sharing the same genetic alterations found in SCC. Alterations that tend to occur in association with higher grades of dysplasia and SCC can include cyclin D1 amplification, pTEN inactivation, and LOH at 13q21, 14q32, 6p, 8, 4q27 and 10q23 [318,787]. Advanced precursor lesions of the head and neck demonstrate a spectrum of genetic alterations that is qualitatively and quantitatively similar to SCC [230, 294,2436]. For some of the chromosomal regions commonly lost or amplified in precursor lesions of the head and neck, the targeted genes have been identified. Two tumour suppressor genes residing at 9p21: p16 (CDKN2/MTS1) inhibit cell cycling via the Rb pathway, and p14(ARF) inhibits cell cycling via the p53 pathway [1022]. The p53 tumour suppressor gene resides at chromosome 17p13. p53 is involved in several cellular regulatory pathways including DNA repair, cell cycle control, and apoptosis [1115]. The cyclin D1 oncogene resides on chromosome 11q13 and is amplified in about a third of SCC [321,811]. However, for most regions of common chromosomal loss such as loss at chromosome 3p, the targeted gene(s) have not yet been well characterized. Retrospective studies examining the prognostic value of molecular markers, including LOH of chromosomes 3p, 9p21, and 17q13 as well as general aneuploidy, have demonstrated that genetic alterations confer significant risk of malignant progression of precursor lesions. These precursor lesions include clinically defined leukoplakia, with corresponding histologic diagnoses varying along the spectrum of benign to precursor lesions mentioned above. In some cases, retrospective genetic analysis was able to define risk of malignant progression in hyperplastic lesions [1627,2201,2492].

Prognosis and predictive factors
Some precursor lesions are self-limiting and reversible, others persist and some progress to SCC [503]. The histopathologic degree of severity of these lesions can be a predictive factor [222,846, 1054,1689]. Simple and basal/parabasal cell hyperplasias have a minimal likelihood of malignant progression (0.9%). These patients do not require close clinical follow-up. Lesions classified as atypical hyperplasia (moderate to severe dysplasia) have a 11% rate of malignant transformation [1054]. Diagnosis of precursor lesions implies a need for close follow-up and complete excision depending on the clinical situation [846,1054]. Patients with carcinoma in-situ require more extensive management, depending on the clinical circumstance [504,1253, 1808,2151,2432].

Fig. 3.42 Severe dysplasia (SIN 3, atypical hyperplasia). A The atypical epithelial cells occupy two thirds of the epithelial thickness. Note partially preserved epithelial stratification, expressed cytologic atypia and increased mitotic activity. Keratin layer is present on the surface. B Carcinoma in-situ (SIN 3). Prominent architectural disarray, marked cytologic atypia and increased mitotic figures with pathologic forms.
Papilloma / papillomatosis

Definition
Squamous cell papillomas are the most common benign epithelial tumours of the larynx, caused by HPV infection. The tumours can be multiple and often recur.

ICD-O codes
- Papilloma 8050/0
- Papillomatosis 8060/0

Synonyms
Recurrent respiratory papillomatosis (RRP), laryngeal papillomatosis, juvenile papillomatosis, adult papillomatosis.

Epidemiology
They rarely appear as solitary lesions, more frequently, especially in children, as recurrent respiratory papillomatosis (RRP). It is characterized by multiple contiguous lesions with great propensity for local recurrences. There is a bimodal age of distribution; the first peak is before the age of 5 (juvenile form), with no gender predominance. The second peak occurs between the ages of 20-40 years (adult form) with a 3:2 male predominance {178,586,618,1282,1519}. Its true incidence and prevalence are uncertain. A wide range in incidence, 0.4-4.3/100,000, has been recorded for various regions worldwide {73,585,1253,1520}.

Etiology
HPV-6 and 11 are the most frequent genotypes associated with RRP as well as solitary papillomas {10,848,1484,1788,2074,2173,2461}. Rarely, HPV 16, 18, 31, 33, 35 and 39 have been identified in RRP {389,2004,2074,2173,2461}. The mode of HPV infection in children is perinatal vertical transmission related to maternal genital infection {178,586,2311}. An epidemiological triad has been identified: the first-born child, vaginal delivery and teen-aged mother correlating with juvenile RRP {1282}. Caesarean delivery has not been found to be entirely protective against the disease {2357}. Factors that influence the conversion of HPV exposure to active HPV infection resulting in epithelial proliferation are not known {944}. The mode of HPV infection in adults remains unclear. The reactivation of a latent infection acquired perinatally or adult acquired infection with orogenital contacts have been suggested {10,1281}.

Localization
The disease almost invariably involves the larynx, especially true and false vocal cords, subglottic areas and ventricles {10,126}. Papillomas may spread to other laryngeal sites; the most frequent sites of extralaryngeal spread are the oral cavity, followed by trachea and bronchi. Extralaryngeal extension of RRP has been identified in 30% of children and in 16% of adult patients {240}. Endobronchial and pulmonary dissemination occurs in 5% of patients with RRP {585}. Rare cases of isolated tracheal lesions without laryngeal involvement have been reported {2662}. The distribution of RRP follows a predictable pattern, occurring mainly at anatomic sites in which ciliated and squamous epithelia are juxtaposed. An injury of ciliated mucosa after surgical procedures may result in squamous metaplasia creating an iatrogenic squamous-ciliary junction, thereby inducing a new background for additional tumours {1280}.

Clinical features
Squamous papillomas have been traditionally divided into juvenile and adult groups {586,1282,1519,2579} and additionally into multiple or solitary groups {1519,1524}. Although caused by the same viruses, they follow distinctly diverse and variable clinical courses. For children, extensive growth with rapid recurrences is characteristic. In some patients, RRP becomes indolent as the patient reaches adulthood. Disease progression is more frequent in the juvenile form, usually associated with subglottic papillomas and prior tracheotomy {2743}. Tracheobronchial extension of RRP is associated with morbidities such as pneumatoceles, lung abscesses, tracheal stenosis and rarely malignant transformation {219}. The relatively small airway in children predisposes to airway obstruction. The clinical course in adults is usually not so dramatic, the development of respiratory distress and other complications are rare, although RRP can be aggressive with multiple recurrences {240,2074}.

Signs and symptoms
Adult laryngeal papillomas cause hoarseness {240,1253}. The disease is usually self-limiting. Most children with laryngeal RRP present with dysphonia and stridor, less commonly with chronic cough, recurrent pneumonia, dyspnoea, and acute life-threatening events {178,240,587}. Delay, due to mistaken diagnoses, such as bronchitis, asthma, and other allergic manifestations, may lead to gradual respiratory distress and urgent tracheotomy, which is associated with more frequent extension into the tracheobronchial tree. The overall mortality rate of patients with

**Fig. 3.43** Laryngeal papillomatosis. A Recurrent respiratory papillomatosis fills the endolaryngeal space. B Multilobulated grape like clusters of papillomas are located on the right side and anterior commissure of the larynx. (Endoscopic view)
RRP ranges from 4-14 % [126], often due to asphyxia, infection, pulmonary complications, and malignant transformation [109,126,2437].

**Macroscopy**
They are exophytic, branching, pedunculated or sessile masses, pink or red, with finely lobulated surface, disposed to bleeding with minor trauma, presenting either singly or in clusters.

**Histopathology**
Squamous papillomas are composed of finger-like or frond-like projections of squamous mucosa, containing thin fibrovascular cores. Secondary or tertiary branching of papillae may be present. Keratosis is minimal. Frequently, parabasal cell hyperplasia, usually extending up to the mid-portion with a perpendicular orientation of the cells to the basement membrane, is seen. Mitotic features may be prominent within this area. Koilocytosis is occasionally evident [2066]. Premature and abnormal keratinizing individual cells (dyskeratosis) if present, contributes to a disorganized appearance. Premalignant changes are not commonly observed, and should be reported when present [1253].

**Histogenesis**
RRP mainly originates from the squamous epithelium where ciliated and squamous epithelia are juxtaposed [1280]. HPV enters the basal cells through a microtraumatized squamous epithelium. Viral replication occurs in the spinous layer, causing a disturbance of epithelial maturation [2917].

**Prognosis and predictive factors**

**Clinical criteria**
The clinical course of RRP is unpredictable, characterised by periods of active disease and remissions. The presence of HPV in apparently normal mucosa is thought to be a virus reservoir and the source of repeated recurrences [2171,2411]. RRP in the neonatal period is associated with poor prognosis, with a greater need for tracheotomy and likelihood of mortality [587].

**Histopathological criteria**
Significant histological prognosticators of local recurrences and malignant transformation have not been identified [501, 908, 2100].

**DNA ploidy, proliferation**
DNA aneuploidy and Ki-67 proliferative index, in contrast to histologic indices, have been found to predict disease recurrence and extension for children with RRP [2470,2471].

**HPV genotype**
HPV 11 and 16 are associated with more aggressive disease, with frequent recurrence and progression in children and adults [2074,2110,2174].

**Malignant transformation**
Malignant change is not common, but occurs in the setting of smoking, irradiation, or other promoters [2112]. It is an exceptional event in the absence of predisposing factors [196,959,2144,2356]. The overall incidence of cancer development for irradiated patients is 14% and 2% for the non-irradiated [126]. Malignancies occur preferentially in the tracheobronchial tree in children, and in the larynx in adults [944]. Prognosis in children is poor [2422]. HPV 11 is most frequently associated with malignant transformation of RRP [487,1465,1521,2112], followed by HPV 16 [619] and HPV 18 [2226].

**Differential diagnosis**
Adult papillary keratosis reveals keratotic, hyperplastic squamous epithelium with keratohyaline granules, occasionally atypia, and absence of koilocytes [126]. Verrucous carcinoma exhibits thicker squamous fronds with prominent keratosis, bulbous rete pegs, that infiltrate in a blunt, pushing manner. Papillary squamous carcinoma usually presents an architecture similar to RRP, but is cytologically malignant. Laryngeal verruca vulgaris is extremely rare, and shows the same features as in the skin [138].

**Fig. 3.44** Squamous papillomas of the larynx. **A** Higher magnification of a papillary branch. **B** Pronounced koilocytosis is evident in the upper part of the squamous epithelium. **C** Positive in-situ hybridization signal for HPV genotypes 6 and 11 in the upper part of the squamous epithelium.

**Fig. 3.45** Branch of a laryngeal squamous papilloma. **A** Note atypical hyperplasia of the covering epithelium. **B** Note basal and parabasal cell hyperplasia of the covering epithelium extending up to the half of the epithelial thickness.
Benign salivary gland-type tumours

In the larynx, benign salivary gland-type tumours are rare and less frequent than the malignant varieties (1039).

**ICD-O codes**
- Pleomorphic adenoma 8940/0
- Oncocytic papillary cystadenoma 8290/0

**Pleomorphic adenoma**
Most pleomorphic adenomas arise in the epiglottis or aryepiglottic folds and can reach several centimetres before producing symptoms. Microscopically, laryngeal pleomorphic adenomas are similar to those in other minor salivary glands.

**Oncocytic papillary cystadenoma (OPC)**
Synonyms: oncocytic cyst, oncocytic papillary cystadenomatosis of the larynx, oncocytic adenomatous hyperplasia, oxyphil adenoma, oncocytoma and adenolymphoma in laryngocele (1641,2845).

Laryngeal oncocytic lesions usually consist of unilocular or multilocular cysts lined by cytologically bland oncocytic epithelium with or without intraluminal papillary ingrowths (748,1548). These lesions probably represent duct hyperplasia and metaplasia rather than true neoplasia. Most patients are older than 50 years, and present with hoarseness or other symptoms. The most frequent locations are the false vocal cords and the laryngeal ventricular areas (850). The lesions are not encapsulated, may be multicentric, and can have a Warthin-like lymphoid component (792). Solid oncytomomas of the larynx resembling those seen in major salivary glands are rare to absent. Recurrence is uncommon and they have no malignant potential.

Fig. 3.46 Focal ductal oncocytic metaplasia and adjacent area of seromucous glands.

Fig. 3.47 Extensive ductal oncocytic metaplasia and hyperplasia with cystic dilatation.
Malignant soft tissue tumours

Fibrosarcoma

ICD-O code 8810/3

In the past, the term “fibrosarcoma” was often applied indiscriminately to any malignant spindle cell tumour associated with collagen production. On critical review of these cases, supplemented with immunohistochemistry, it has become apparent that many alleged fibrosarcomas are examples of other entities (1636,2191). With the possible exception of radiation-induced tumours, de novo fibrosarcoma is now recognized as a relatively uncommon tumour (1831). The main differential diagnoses include spindle cell carcinoma and, occasionally, inflammatory myofibroblastic tumour, posttraumatic spindle cell nodule, and radiation-induced stromal atypia (2604, 2889).

Malignant fibrous histiocytoma (MFH)

Definition
An aggressive, highly controversial malignant mesenchymal neoplasm composed of primitive round to spindle-shaped cells, often with admixed inflammatory and multinucleated giant cells, that grows either focally or diffusely in a storiform pattern.

ICD-O code 8830/3

Epidemiology
MFH of the larynx is an uncommon tumour. It occurs in all age groups (6-68 years) and is more common in males by a ratio of 3:1 (1985,2283).

Etiology
Other than those related to prior radiation exposure, there are no known predisposing factors.

Localization
MFH is distinctly unusual in the hypopharynx and trachea. In the larynx, the glottis is the site of predilection.

Clinical features
Symptoms vary according to location and include hoarseness, airway compromise, dysphagia or a sensation of a foreign body in the throat.

Macroscopy
The tumours are sessile to polypoid, firm, often ulcerated and have a yellow-tan to grey-white cut surface.

Histopathology
The histomorphology is highly variable but includes several of the following features: histiocyte-like cells, spindle-shaped cells, foam cells, pleomorphic multinucleated giant cells, typical and atypical mitoses, and necrosis. The tumour characteristically grows in a storiform pattern, either focally or diffusely.

Differential diagnosis
MFH must be distinguished from spindle cell carcinoma, which may be difficult on small biopsies. In spindle cell carcinoma, the tumour cells are typically positive for cytokeratin, as opposed to MFH. The presence of dysplasia or carcinoma in situ in the overlying mucosa also indicates a carcinoma.

Prognosis and predictive factors
Surgery is the treatment of choice. The role of irradiation and chemotherapy is largely untested. In the absence of enlarged lymph nodes, a prophylactic neck dissection is not indicated (2283). The tumour is unpredictable but certainly has the potential for local recurrence, haematogenous metastasis and death from disease.

Liposarcoma

ICD-O-code 8850/3

Primary liposarcomas of the larynx are rare, comprising less than 20% of all head and neck liposarcomas and fewer than 0.5% of all laryngeal neoplasms. Patients of all ages are affected, with a median of 64 years. There is a marked male to female predominance (nearly 10:1). The tumours, which occur almost exclusively in the supraglottic larynx or hypopharynx (pyriform sinus), most commonly cause airway obstruction. Imaging, especially with MR or CT, will document the lipomatous nature and extent of the mass. The tumours are firm, polypoid pedunculated, up to 10 cm in greatest dimension and demonstrate a lobulated, glistening, translucent cut surface often traversed by bands of fibrous tissue. The mucosa is usually intact. The majority of cases are well-differentiated lipoma-like liposarcomas (grade I), similar to their histologic counterparts in other anatomic sites, with infrequent reports of myxoid and pleomorphic types. Lipoblasts may be scanty necessitating multiple sections. Atypical cells, scattered lipoblasts, and infiltrative growth pattern differentiate liposarcomas from lipomas. In spite of surgical treatment, multiple recurrences are not uncommon (80% of patients). Metastasis has not been reported and the long-term prognosis is excellent (90% 5-year survival) (733,918,1155, 1371,2765,2772).

Fig. 3.48 Liposarcoma. The marked increase in cellularity with fibrous bands along with the increased nuclear to cytoplasm ratio even at this relatively low power is highly suggestive of a liposarcoma.
Leiomyosarcoma

ICD-O-code 8890/3

Leiomyosarcomas arising in the larynx are exceedingly rare accounting for less than 0.1% of all laryngeal malignancies. They present mainly in adults with no gender predilection. Symptoms are non-specific. Tumors can occur anywhere in the larynx but supraglottic lesions have been more frequently reported. They have a histology similar to leiomyosarcomas in soft tissues and demonstrate increased cellularity, nuclear and cellular pleomorphism, cytoplasmic vacuolization, necrosis, haemorrhage, and increased mitotic activity in addition to invasive growth. The diagnosis of leiomyosarcoma requires histologic, immunophenotypic (desmin, actins), and/or ultrastructural (parallel actin filaments, dense bodies and pinocytotic vesicles) confirmation as spindle cell carcinoma must always be excluded. Primary treatment is surgical. A variable prognosis is achieved [840,1247,1530,1635,1686,1969,2208,2373,2706].

Rhabdomyosarcoma

ICD-O code 8900/3

Rhabdomyosarcomas of the hypopharynx, larynx and trachea are poorly documented and exceedingly rare, comprising no more than 2% of all rhabdomyosarcomas [25,518,1084,1293,1508,2215,2781]. They have been described in all age groups and, in the larynx, are centered around the glottic region. Possibly because of early presentation, prognosis has generally been good but death from disease has been recorded. The differential diagnosis includes a spindle cell carcinoma [915].

Angiosarcoma

ICD-O-code 9120/3

Primary angiosarcomas of the larynx are exceedingly rare, with only a few well-documented reports. Despite the fact that nearly 50% of all angiosarcomas occur in the skin and superficial soft tissues of the head and neck, angiosarcoma accounts for less than 0.1% of all head and neck malignancies. Laryngeal angiosarcoma is twice as frequent in men with a mean age at presentation in the 7th decade of life. Symptoms are non-specific; previous radiation exposure is frequently noted. The supraglottis is affected more frequently, specifically the epiglottis, where an increasing size is associated with a worse clinical outcome. Tumours demonstrate the typical histomorphologic features of angiosarcoma in other soft tissue sites. Tumour cells are consistently positive with Factor VIII-related antigen, CD34, and CD31. Contact ulcer, haemangioma, acantholytic squamous cell carcinoma and mucosal malignant melanoma are the principal differential diagnostic considerations. Surgical excision is the treatment

Fig. 3.49 Rhabdomyosarcoma. A Cells with eosinophilic and striated cytoplasm contain eccentrically placed nuclei with prominent eosinophilic nucleoli. Degeneration is noted. B The neoplastic cells are strongly immunoreactive with desmin, accentuated in both the "epithelioid" and spindled cells.

Fig. 3.50 Laryngeal angiosarcoma. A Intermediate power demonstrating the anastomosing vascular channels lined by atypical endothelial cells. B A high power showing nuclear atypia of the hobnailed endothelial cells in a laryngeal angiosarcoma. C Factor VIII R-Ag reacts strongly and diffusely with the neoplastic endothelial cells.
Malignant soft tissue tumours

149

**Kaposi sarcoma**

**ICD-O-code**  9140/3

Kaposi sarcoma (KS) of the larynx is uncommon and only a few well-documented cases have been reported since 1983, coincident with the time frame during which HIV and AIDS were beginning to be recognized. This finding lends support to the strong association of KS of the larynx with the advanced HIV disease in epidemic AIDS rather than an association with the iatrogenic immunocompromised transplant, the endemic African, or the sporadic form. Men are almost exclusively affected, usually in the middle decades of life, presenting with upper airway obstruction. A flat to raised, violaceous, plaque-like mass is usually identified in the supraglottis, although glottic lesions are also frequent. Multifocal involvement is reported. The cut surface is fleshy and demonstrates recent and old haemorrhage. The histology is identical to the various stages of cutaneous KS, although the plaque-tumour stage with its sieve-like vasoformative pattern with eosinophilic, glassy-hyaline intra- and extracellular globules (PAS positive) is most common. Human herpesvirus 8 (HHV-8) is usually positive, helping to confirm the diagnosis. Biopsy is contraindicated, as brisk haemorrhage will require emergent tracheostomy and possible death by exsanguination. Treatment is generally nonsurgical, encompassing radiotherapy or chemotherapy (systemic or intralesional). Laryngeal KS is usually non-lethal {191,499,815,1487,1753,2262,2552}.

**Peripheral nerve sheath tumours (PNST)**

**ICD-O-codes**

- Schwannoma  9560/0
- Neurofibroma  9540/0
- Malignant peripheral nerve sheath tumour (MPNST)  9540/3

Both benign (especially schwannoma and neurofibroma) and malignant peripheral nerve tumours (MPNST) can occur in the larynx, although vanishingly rare. Any age group can be affected and there is no gender predilection. Association of neurofibroma with neurofibromatosis-1 (NF1) has been reported in the larynx [385,2508].

Macroscopically, benign and malignant PNST most often involve the supraglottis in relation to the superior laryngeal nerve. The tumours are of variable size and present as smooth, round or lobulated to fusiform submucosal masses, often demonstrating cystic or mucinous degeneration. The mucosa is usually intact, although larger tumours may ulcerate. Schwannoma is encapsulated and solitary with the nerve of origin attached peripherally. In contrast, neurofibroma is non-encapsulated, occasionally multiple or plexiform, especially when it is associated with NF1 and expands the nerve in a fusiform fashion rather than pushing it aside. MPNST are infiltrative, mitotically active and often ulcerate the mucosa. The tumour cells are immunoreactive, often patchy, with S-100 protein, vimentin, epithelial membrane antigen (EMA) and Leu-7. Distinguishing benign from malignant tumours on small biopsies may be difficult {385,659,1202,1235,1974,2508,2591}.

**Synovial sarcoma**

**ICD-O-code**  9040/3

Primary synovial sarcoma of the larynx and hypopharynx is rare, while secondary involvement by direct extension from the neck is slightly more common. Although all age groups may be affected, most patients are young and there is no gender bias. Symptoms are non-specific. The tumours are often exophytic or pedunculated, and infiltrative with surface ulceration. Both monophasic and biphasic synovial sarcomas have been described and are similar to the counterpart in the soft tissue. Immunohistochemically, both epithelial and spindle cells may be reactive with cytokeratin and epithelial membrane antigen (EMA), while only the spindle cells are positive for vimentin. Molecular studies reveal a characteristic translocation t(X;18)(p11.2;q11.2). The prognosis is variable but tends to be better than those arising in soft tissue {573,740,1735,1780,2102}.
Inflammatory myofibroblastic tumour

**Definition**
Inflammatory myofibroblastic tumour (IMT) is a distinct borderline lesion composed of myofibroblastic cells with a variable admixture of inflammatory cells, including mature lymphocytes, histiocytes, plasma cells and eosinophils, and collagen. It occurs predominantly in the soft tissue and viscera but also in the head and neck (2761).

**ICD-O code** 8825/1

**Synonyms**
Inflammatory pseudotumour, plasma cell granuloma, plasma cell pseudotumour, pseudosarcomatous lesions/tumours.

**Epidemiology**
Head and neck IMTs are rare. There are very few comprehensive studies detailing their clinicopathologic features. In contrast to soft tissue and visceral IMTs, that occur predominantly in children and young adults, IMTs of the upper aerodigestive tract are more common in adults (median age of 59) and men (2761).

**Etiology**
The etiology of IMT is unknown. Previous trauma, and immunosuppression have been implicated (858,2761). Recently, human herpesvirus-8 DNA sequences and overexpression of interleukin 6 and cyclin D1 have been reported in IMTs (920).

**Localization**
In the head and neck, inflammatory myofibroblastic tumours are most common in the larynx [396,686,1648, 2761] especially in the region of true vocal cord (2761). Non-laryngeal sites include the oral cavity [632,677,1531], tonsil [858,2736] parapharyngeal space [383,1165,2739], sinonasal tract [1278, 1616,2165,2429,2739], salivary glands [1178,2739,2794] and trachea (53).

**Clinical features**
Laryngeal IMTs present with hoarseness, stridor, dysphonia, and/or a foreign body sensation in the throat (2761). Constitutional and/or systemic signs and symptoms such as fever, weight loss, pain, malaise, anaemia, thrombocytosis, polyclonal hyperglobulinemia and elevated erythrocyte sedimentation rate seen in association with soft tissue and visceral IMTs are not usually a component of upper aerodigestive tract IMTs; however, they are occasionally reported (383, 2165).

**Macroscopy**
The gross appearance of laryngeal IMT is a smooth, polypoid or nodular lesion with fleshy to firm consistency and varying dimensions.
creating a tadpole-like appearance. The myofibroblasts invariably maintain a low nuclear-to-cytoplasmic ratio. Focal nuclear pleomorphism may be present. Mitoses are common, sometimes even numerous, but never atypical. Necrosis and marked nuclear pleomorphism are not seen.

**Immunoprofile**

IMTs show strong diffuse cytoplasmic immunoreactivity for vimentin, and usually variable expression of smooth muscle actin and/or desmin. Cytokeratin staining may be seen but usually focal to absent.

**Electron microscopy**

The tumour cells show myofibroblastic and fibroblastic differentiation [707, 2761].

**Genetics**

Recent evidence reveals the presence of anaplastic lymphoma kinase (ALK) gene rearrangements and expression in IMTs [486,949,1440,2865]. These rearrangements are common in IMTs of children and young adults [949,1440,2486] and are uncommon over the age of 40 [367,486,1440]. Both the gene rearrangements and protein activation are restricted to the myofibroblastic component, while the inflammatory cell component is normal [270,466,466,486, 949,1440]. Fusion of ALK to Ran-binding protein 2 gene in IMTs expand the spectrum of ALK abnormalities seen in IMT further confirming the clonal, neoplastic nature of IMTs [1593].

**Prognosis and predictive factors**

Laryngeal IMT is usually cured by conservative resection [2761]. Corticosteroid and nonsteroidal anti-inflammatory agents have been used for treatment resulting in regression in some patients [795,2487]. A recurrence rate of approximately 25% has been reported for extrapulmonary IMTs [467]. IMT was originally believed to be a reactive non-neoplastic lesion. This has been refuted by the above genetic studies. An occasional IMT may follow an aggressive clinical course. Rarely non-head and neck visceral IMTs have metastasized [466]. It is difficult to predict on the basis of histology which IMTs will be more aggressive [1156,1363,2842].
Lipoma

ICD-O code 8850/0

Lipomas of the larynx and hypopharynx comprise less than 0.5% of benign neoplasms at these sites, occur in all ages and affect both genders equally. The symptoms are non-specific but often include airway obstruction. In the larynx, supraglottic lesions predominate. Computed tomography and magnetic resonance document the lipomatous (low attenuation values and negative densitometry) nature and the extent of the mass. A lipoma is usually solitary, soft and sessile to polypoid. Tumours are composed of mature adipose cells, occasionally with foci of myxoid stroma. Distinction from well-differentiated liposarcoma is important. Association with systemic lipomatosis has been reported [1770]. Simple but complete excision is curative [329,409,1528,2756,2765].

Rhabdomyoma

Definition

A benign mesenchymal tumour with skeletal muscle differentiation and a propensity for occurrence in the head and neck.

ICD-O code 8900/0

Epidemiology

Based on histology rather than age, rhabdomyomas are divided into three types: fetal, juvenile (intermediate), and adult.

Fetal rhabdomyoma (FRM) are 2-3 times more common in males and have been described in patients from birth to 65 years of age; about half of all patients are 15 years old or older at the time of diagnosis [597,1271].

Juvenile rhabdomyomas (JRM) are 2 times more common in males and have been observed in patients from 5 months to 58 years of age (average 18 years) [508,1271].

Adult rhabdomyomas (ARM) are 3-5 times more common in males and occur in an older population. About 80-90% of patients are over the age of 40 years (median 55-60 years, range 15 months to 82 years) [597,1272].

Etiology

Whether RMs are hamartomas or true neoplasms is controversial. Cytogenetics examination of an ARM has demonstrated clonal chromosomal abnormalities which supports a neoplastic origin [886]. Extracardiac RMs should be distinguished from those in the heart. Cardiac RMs are hamartomas and often associated with tuberous sclerosis. Extracardiac RMs, with the rare exception of a FRM.

Leiomyoma

ICD-O code 8890/0

Leiomyomas (angioleiomyoma) of the larynx comprise less than 0.2% of all laryngeal neoplasms. The tumour has been reported in all age groups, but primarily in adults, and is somewhat more common in males. The ventricle and false vocal cord are sites of predilection.

Fig. 3.55 Rhabdomyoma of the hypopharynx in an adult. Note the characteristic tan colour and multinodularity.
occurring in a few patients with the nevoid basal cell carcinoma syndrome, are virtually never associated with a phakomatosis [929].

Localization
RM s of the larynx and hypopharynx are uncommon [1225]. In the larynx, they tend to centre around the true and false vocal cords and ventricles.

Clinical features
The tumours generally present as hoarseness, airway obstruction, dysphagia, or sensation of a foreign body in the throat.

Macroscopy
FRMs are usually 1-5 cm, circumscribed and grey-white to tan-pink with a mucoid cut surface. ARMs are circumscribed, tan to red-brown and multinodular. Most are less than 5 cm, but may be larger.

Histopathology
FRMs vary from sparse to moderately cellular and are composed of immature cells with little cytoplasm and small, round to oval nuclei, sometimes with prominent nucleoli. The cytoplasm contains abundant glycogen, often appearing as vacuoles and producing a characteristic “spider cell”. Rod-shaped cytoplasmic crystals (“jackstraws”) may also be apparent. Cross striations are infrequent and, mitoses and necrosis are absent. JRMs contain a large number of strap-shaped muscle cells with abundant eosinophilic cytoplasm with centrally located nuclei. Cytoplasmic vacuoles are common. The tumour often co-exists with typical areas of FRM.

Immunoprofile
RM s are positive for muscle specific actin, smooth muscle actin, desmin, and myoglobin. ARMs are also variably weakly positive for vimentin (35% of cases) and even S-100 protein (67% of cases), but negative for glial fibrillary acidic protein (GFAP), cytokeratin, and epithelial membrane antigen. FRMs are also variably positive for vimentin (75% of cases), S-100 protein (50% of cases), and GFAP (50% of cases).

Differential diagnosis
The FRM must be distinguished from embryonal rhabdomyosarcoma. The lack of significant infiltration of adjacent tissues; absence of cellular pleomorphism, mitoses, and necrosis; and the presence of muscle maturation at the periphery of the lesion are features indicative of a rhabdomyoma.

Haemangioma and Lymphangioma

ICD-O-codes
Haemangioma 9120/0
Lymphangioma 9170/0

Haemangiomas of the larynx are divided into juvenile (congenital) and adult types based on age of presentation, histologic appearance, and possibly patient outcome. Pediatric patients present at or within several months of birth with subglottic lesions that may result in potentially life-threatening airway obstruction and haemorrhage. In addition, about half of all pediatric patients with subglottic haemangiomas may have haemangiomas in other locations, most of which are cutaneous, rarely visceral. Adult haemangiomas are more often found in the supraglottic larynx. Grossly, haemangiomas are soft and compressible and range from red to blue, depending on the degree of vascularity. They may be either flat and diffuse or bulging and polyoid. The term ‘haemangiomatosis’ is sometimes used when the lesion is widespread and involves contiguous or non-contiguous sites. Microscopically, haemangiomas are categorized into capillary and cavernous types, and often demonstrate a lobular pattern of growth. Juvenile haemangiomas are usually cellular and of the capillary type while in adults, they are are more often cavernous. Haemangiomas should be distinguished...
Tumours of the hypopharynx, larynx and trachea

...from telangiectasia, vascular stage of vocal cord polyps and granulation tissue. The distinction between haemangioma and telangiectasia may be difficult. But in the correct clinical setting of a positive family history of hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber syndrome), typical lesions (in any location) and episodic bleeding can help to define the syndrome. Vascular vocal cord polyps occur exclusively on the true vocal cord and are separated from haemangiomas by a large amount of extravascular fibrin. Fibrin, if seen in haemangiomas, is always intravascular. The lobular growth of haemangioma distinguishes it from granulation tissue. If the lesion is biopsied rather than excised, unusually excessive bleeding may give a clue as to the type of lesion encountered. Although the preferred treatment is laser excision, therapy has included expectant management, systemic steroids, intralesional sclerosing agents and surgical excision (277,439,1235,1487).

**Granular cell tumour**

**Definition**
A neural tumour composed of round and/or spindle cells with pink, granular cytoplasm due to abundant intracytoplasmic lysosomes.

**ICD-O code**
9580/0

**Synonyms**
Granular cell myoblastoma, granular cell schwannoma, Abrikossoff tumour.

**Epidemiology**
Granular cell tumours (GCT) of the larynx affect both sexes equally and occur over a broad age range (4-70 years), with a mean of 34 years (2247). They are uncommon in children. Only 20 cases were identified in 1998 in patients less than 17 years of age (1114). GCTs of the trachea are even more unusual. Of 30 cases, 84% occurred in women and the peak incidence was the fourth decade (range 6-56 years) (315).

**Localization**
GCTs may occur anywhere in the larynx. In adults, the most common site is the posterior half of the true vocal cord, while in children the subglottis is the site of predilection. Tracheal tumours, in turn, arise most often in the cervical trachea.

**Clinical features**
GCTs are especially common in the Black population. Most patients have only a single tumour, but in 2-10% of individuals, multiple tumours may be found (924). Hoarseness is the usual presenting symptom of laryngeal tumours while stridor or airway obstruction (often mistaken for asthma) is characteristic of those in the trachea.

**Macroscopy**
The majority of tumours are firm, polypoid or sessile, and less than two centimetres. They are covered by an intact (rarely ulcerated) mucosa, and on cross section are grey-white or yellow.

---

**Fig. 3.58** Granular cell tumour. A Prominent pseudoepitheliomatous hyperplasia. The granular cells are spindle-shaped and may be confused with a desmoplastic stromal reaction. B Higher magnification of the pseudoepitheliomatous hyperplasia.

**Fig. 3.59** Granular cell tumour. A Periodic acid-Schiff (PAS) stain with diastase accentuates the cytoplasmic granularity. B The granularity of the cytoplasm is due to lysosomes. C Strong immunoreactivity for S-100 protein.
Histopathology
GCTs are poorly circumscribed and composed of round or spindle cells, often in a syncytial pattern. The nuclei are small, hyperchromatic, and centrally located. The cytoplasm is eosinophilic and contains numerous periodic acid-Schiff-positive, diastase-resistant granules. The granules are also S100 protein and CD68 positive, and ultrastructurally represent lysosomes.

Malignant granular cell tumour
Approximately 1-2% of all GCTs are malignant and exhibit either aggressive local behaviour or distant metastasis (lung, bone) [253,713]. Criteria for malignancy include: 1) necrosis, 2) spindling of cells, 3) vesicular nuclei with large nucleoli, 4) greater than 2 mitoses per 10 high power fields at 200X magnification, 5) high nuclear to cytoplasmic ratio, and 6) pleomorphism. Neoplasms that meet 3 or more of these criteria are classified as malignant. Those that meet only one or two criteria are regarded as atypical while those that show only focal pleomorphism but none of the other features are classified as benign.

Differential diagnosis
Small biopsies with sparse granular cells associated with pseudoepitheliomatous hyperplasia can easily be mistaken for squamous cell carcinoma. In the larynx, GCTs are typically non-ulcerated and occur on the posterior half of the true vocal cord in patients less than 50 years of age. In contrast, squamous cell carcinomas of the larynx are often ulcerated and arise on the anterior half of the true vocal cord in patients over the age of 50 years.

Prognosis and predictive factors
GCTs are radioresistant. Most can be removed endoscopically. Larger lesions may require an open excision. Although initial therapy is usually curative, 2-8% of patients may develop local recurrences. Some “recurrences”, however, may represent new primary lesions in a patient with multifocal disease.

Haematolymphoid tumours

Non-Hodgkin lymphoma
Primary non-Hodgkin lymphomas (NHL) of the hypopharynx, larynx or trachea are very rare. They account for 1% of all primary extranodal NHL [809]. By contrast, secondary laryngeal lymphomas are more common and represent spread from cervical and mediastinal lymph nodes, and thyroid gland. Patients present with hoarseness, foreign body sensation, or mild airway obstruction. Supraglottic tumours are more frequent, but all regions of the larynx can be involved.

Most primary laryngeal NHL are B-cell lymphomas, especially diffuse large B-cell lymphoma (DLBCL) and extranodal marginal zone B-cell lymphoma of MALT type [63,601,1285,1771]. Rare cases of extranodal NK/T cell lymphoma of nasal type [371,1761] and peripheral T-cell lymphoma [1285,1632,1761] have also been reported. Most patients (>90%) present with low clinical stage (Stage IE/IIE) [63,1285,1771], but occasional patients can succumb to acute laryngeal obstruction [1771]. NK/T cell lymphomas and peripheral T-cell lymphomas have a poorer outcome as compared to B-cell lymphomas [63,1285,1761,1771].

Patients with primary tracheal NHL may present with airway obstruction, dyspnoea, wheezing or cough. Most reported cases are extranodal marginal zone B-cell lymphoma of MALT type [762,1275]. Primary hypopharyngeal NHL is extremely rare [809]. Both extranodal NK/T cell lymphoma of nasal type [2455,2605] and extranodal marginal zone B-cell lymphoma of MALT type have been reported [2773].

Plasmacytoma
Definition
Plasmacytoma is a monoclonal plasmacytic proliferation. A soft tissue plasmacytoma without bone marrow involvement is referred to as extramedullary plasmacytoma (EMP).

ICD-O code
9734/3

Localization
The larynx and pharynx are the most common head and neck sites for extramedullary plasmacytoma. For details see Chapter 1 on sinonasal tumours (pp. 61-63).
Chondrosarcoma

Definition
Chondrosarcoma is a malignant tumour of the laryngeal framework characterized by the formation of neoplastic hyaline cartilage.

ICD-O code 9220/3

Epidemiology
Laryngeal chondrosarcoma (LCS) is the most common non-epithelial malignancy of the larynx, and comprises 75% of laryngeal sarcomas (1489). Cartilaginous neoplasms are estimated to represent 0.07-0.2% of all laryngeal tumours (255). Approximately 300 cases of cartilaginous laryngeal tumours have been reported; the majority are represented by chondrosarcomas. They affect adults in the 6-9th decades, with a mean age at diagnosis of 60-65 years. The male to female ratio is approximately 3:1.

Localization
LCS arise predominantly in the ossified hyaline cartilages. The cricoid ring is the most frequently involved, especially its posterior or posterolateral aspect, followed by the thyroid cartilage. Bulky tumours may encompass both structures, obscuring the exact site of origin. Chondrosarcoma of the epiglottis has only been rarely reported.

Clinical features
Patients with LCS typically present with hoarseness, and/or airway obstruction and dyspnoea. An external neck mass may be noted when it arises in the thyroid lamina. These tumours grow slowly and can be asymptomatic until they reach considerable size. On examination, the usual appearance is that of a subglottic swelling with intact mucosa. Vocal cord paralysis is a common finding at presentation. LCS have characteristic features on CT examination, with expansion of the affected cartilage by a relatively circumscribed, hypodense mass containing stippled to coarse calcifications. MR imaging may show better definition of the tumour boundaries but is less likely to detect internal calcifications (255,1888, 2598). LCS are notoriously difficult to biopsy. Their characteristic imaging appearance precludes the necessity for preoperative biopsy.

Macroscopy
LCS are bulky, lobulated neoplasms that expand and distort the involved site. The cut surface is firm to hard, translucent, pale grey-blue, with gritty calcifications. Myxoid change, if present, is characterized by soft, cystic, or gelatinous areas. Dedifferentiated chondrosarcoma reveals fleshy areas resembling high-grade sarcoma.

Histopathology
The diagnosis and grading of LCS is based on general criteria for chondrosarcoma (1509). The low power architecture of LCS is that of a lobulated neoplasm with pushing borders. The tumour periphery shows invasive growth of neoplastic lobules into adjacent soft tissue or the marrow spaces of ossified cartilage. The overwhelming majority of LCS are low or intermediate grade, with variability from area to area (28,255,1152,1888).
High-grade LCS are generally considered rare; although in the largest reported series they comprised 5% [2598]. Metaplastic bone formation and calcification are also common to LCS. Myxoid change is infrequent. Dedifferentiated and clear cell variants of LCS have been reported, albeit rarely [28,255,1888,2598]. Dedifferentiated chondrosarcoma is characterized by the presence of two distinct components: well-differentiated chondrosarcoma and a high-grade, non-cartilaginous sarcoma. Clear cell chondrosarcoma is composed of chondrocytes with abundant clear cytoplasm and prominent cell membranes. LCS, similar to chondrosarcoma found elsewhere, expresses S-100 protein (strongly) and vimentin (focally) in immunohistochemical studies [255, 1888].

**Differential diagnosis**

Low-grade LCS may be difficult to distinguish from chondroma. Grade 1 LCS show subtle increases in cellularity, with nuclear hyperchromasia and occasional binucleate forms. Irregular clustering of cell groups, or “cluster disarray” is found in all grades of LCS [1152] and may be a useful feature in the distinction of low-grade chondrosarcoma from chondroma. The diagnosis of laryngeal chondroma should be reserved for small (less than 1-2 cm), clinically insignificant lesions, without discernible atypia. Any recurrent cartilaginous tumour of the larynx should be considered a chondrosarcoma [255]. Chondrometaplasia is characterized by small (less than 1 cm) nodules of bland, fibroelastc cartilage which are found in the submucosal soft tissue of the glottic region [747,1161].

**Precursor lesions**

Understanding of the biologic potential of laryngeal cartilaginous neoplasms has evolved in recent years such that many reported laryngeal chondromas would now be interpreted as low-grade LCS [1888,2178,2598]. (See section on Chondromas).

**Histogenesis**

LCS usually develop in ossified cartilage. A pluripotential mesenchymal stem cell, which may be recruited in the process of ossification, is postulated to be the cell of origin [255]. Several authors have proposed that LCS may develop in a benign chondroma [2598]; this hypothesis remains highly controversial.

**Prognosis and predictive factors**

LCS are more indolent than chondrosarcomas arising elsewhere [2598]. This may be due to the fact that LCS are symptomatic at a smaller size when compared to their skeletal counterparts. LCS are managed with conservative surgery [255,1489,2598]. Incomplete resection (shelling out) is associated with local recurrence [2178]. Metastases from LCS, usually pulmonary, are distinctly unusual (<10%), and related to higher grade or dedifferentiation [2598]. LCS related mortality is very low [1489]. Myxoid change involving greater than 10% of the neoplasm correlates adversely with outcome [2598].

**Osteosarcoma**

**Definition**

Osteosarcoma is a malignant tumour characterized by the direct formation of osteoid by neoplastic cells.
ICD-O code 9180/3

Epidemiology
Laryngeal osteosarcoma (LOS) is extremely rare, with fewer than 20 documented cases. LOS affects an older age group than osteosarcoma arising in long bone. They manifest in patients from about 50-80 years of age, nearly exclusively in males.

Localization
These sarcomas usually arise from the endolaryngeal soft tissue, vocal cords and/or anterior commissure, rather than the laryngeal framework.

Clinical features
LOS is typically a polypoid mass that impinges on the airway. Symptoms depend on the tumour site; hoarseness, dyspnoea, and airway obstruction are the most frequent complaints. Imaging studies reveal an invasive, mineralized mass, either situated primarily in the soft tissue of the glottis or expanding one of the laryngeal cartilages. LOS affects an older age group than osteosarcoma arising in long bone. They manifest in patients from about 50-80 years of age, nearly exclusively in males.

Macroscopy
LOS of the vocal cord soft tissue is usually polypoid, and may show an intact or ulcerated mucosa. In the laryngeal framework, it forms a poorly defined, infiltrative mass. The cut surface is hard and gritty, with variable colouration.

Histopathology
Similar to other primary mesenchymal neoplasms, LOS typically retains a “Grenz zone” of tumour-free, superficial submucosa just beneath the non-dysplastic epithelium. LOS is uniformly high-grade, composed of pleomorphic spindle cells. The amount of osteoid produced by the malignant cells can vary, but characteristic lace-like osteoid is present at least focally. Tumour giant cells may also be identified. Laryngeal osteosarcoma may also represent the high-grade sarcomatous component of dedifferentiated chondrosarcoma of the larynx.

Differential diagnosis
LOS must be distinguished from spindle cell carcinoma (SPCC) with heterologous osteoid production, since the spindle cell component of the latter tumour may be highly pleomorphic and focally produce osteoid. In contrast to LOS, SPCC is characterized by either 1) a concomitant squamous abnormality (dysplasia, carcinoma in-situ, or invasive SCC) or 2) evidence of epithelial differentiation in spindle cells. In addition, the malignant spindle cells of SPCC usually abut the overlying mucosa or merge with its basal layer in a feathering pattern, without the presence of a Grenz zone.

Prognosis and predictive factors
Reported cases of LOS have demonstrated aggressive clinical behaviour. Local recurrence is frequent, as are distant metastases, typically involving the lung. At least half of the reported patients have died of disease, most within a year of diagnosis.

Chondroma

Definition
A benign tumour composed of mature hyaline cartilage

ICD-O code 9220/0

Epidemiology
True chondromas of the larynx are extremely unusual and are greatly outnumbered by laryngeal chondrosarcoma (LCS). The age incidence is difficult to estimate as many previous reports of chondroma probably represent LCS.

Clinical features
Chondromas of the larynx primarily affect the cricoid and thyroid cartilages. Chondroma may be an incidental finding, or cause minor symptoms such as hoarseness. A clinically significant cartilaginous tumour is more likely to be LCS than a chondroma.

Macroscopy
Chondromas are well-circumscribed tumours. The cut surface is uniform, with a translucent, pale grey-blue appearance. A cartilaginous neoplasm greater than 2 cm in dimension more likely represents LCS.

Histopathology
Chondromas are composed of benign chondrocytes producing hyaline cartilage. They may show a lobular growth pattern. The appearance is uniform and monotonous with overall low cellularity. The chondrocytes are relatively evenly distributed, lack nuclear pleomorphism and mitotic activity and contain a single nucleus per lacuna. In LCS, the neoplastic chondrocytes are distributed in cell groups of varying size and cellularity (cluster disarray). However, because the histopathology of LCS is variable within a tumour, thorough sampling of any cartilaginous tumour is recommended. The diagnosis of chondroma should be reserved for small lesions that have been completely excised and entirely examined.

Prognosis and predictive factors
Chondromas do not recur after conservative excision. Any recurrent cartilaginous neoplasm of the larynx should be interpreted as LCS.
**Giant cell tumour**

**Definition**
A benign but locally destructive neoplasm composed of sheets of ovoid to spindle-shaped mononuclear cells with uniformly dispersed osteoclast-like giant cells.

**ICD-O code**
9250/1

**Synonym**
Osteoclastoma

**Epidemiology**
Giant cell tumours of the larynx are very rare (590, 982, 1092, 1642, 2163). They represented only 0.09% of almost 9000 benign and malignant laryngeal tumours (2785). In total 28 cases have been reported comprised of 25 men and 3 women, aged 23-62 years (mean about 40-45 years).

**Localization**
The thyroid cartilage is most commonly involved, followed by cricoid cartilage and epiglottis (2785).

**Clinical features**
The tumours enlarge slowly and manifest as painless neck masses, hoarseness, airway obstruction, dysphagia or sore throat. On imaging, it often appears as a tumour exploding from within the cartilage, destroying it and extending into soft tissue of the neck or endolarynx.

**Macroscopy**
Most tumours have ranged from 2.4-7cm (mean about 4-4.5cm) and have been centred in the thyroid or cricoid cartilages, especially in the normally ossified portions of these cartilages (2785). On cut section, they are soft, red to grey-pink and frequently extend beyond the cartilage into the adjacent soft tissue. Haemorrhage and cystic degeneration are common.

**Histopathology**
The tumours are similar histologically to the giant cell tumour of bone and, as such, consist of a dual population of cells: mononuclear cells and osteoclast-like giant cells. The mononuclear cells appear as broad sheets of cells reminiscent of histiocytes. They are round, ovoid or spindle-shaped and have pink to amphophilic cytoplasm and round, vesicular nuclei with occasional prominent nucleoli. The giant cells are evenly distributed throughout the tumour and contain up to 20 or more nuclei per cell. The nuclei of the giant cells are identical to those of the mononuclear cells. The stroma is vascular and contains many thin-walled vessels with small areas of haemorrhage and haemosiderin-laden macrophages. Mitoses are usually seen, averaging 4 per 10 high power fields (range 1-12 per 10 high power fields) (2785). Atypical mitoses are not seen.

**Differential diagnosis**
This includes giant cell (reparative) granuloma, brown tumour of hyperparathyroidism, fibrous histiocytoma and a pleomorphic carcinoma. Giant cell granuloma of the cricoid cartilage is exceptionally rare (2587). The giant cells in this tumour are not evenly distributed, but rather concentrate around areas of recent and/or old haemorrhage. A giant cell granuloma also exhibits more stromal fibrosis. A brown tumour is identical histologically to the giant cell granuloma, but is associated with elevated serum calcium. A benign fibrous histiocytoma contains a more uniform storiform arrangement of fibroblasts and does not show a symmetrical distribution of giant cells. A malignant fibrous histiocytoma (giant cell type) exhibits significant nuclear pleomorphism and abnormal mitoses, none of which are seen in a giant cell tumour. A pleomorphic carcinoma will not only show abnormal mitoses and pleomorphism, but will also be positive for cytokeratin.

**Prognosis and predictive factors**
Complete, but conservative surgical excision is the treatment of choice. Large tumours may require a partial or total laryngectomy. Adjuvant therapy is unnecessary. There have been no convincing records of local recurrence or malignant behaviour secondary to giant cell tumour of the laryngeal framework (1138, 1181).
Definition
Primary laryngeal mucosal malignant melanomas (PLMMM) are neural crest-derived neoplasms originating from melanocytes and demonstrating melanocytic differentiation.

ICD-O code
8720/3

Epidemiology
Approximately 15-20% of all malignant melanomas arise in head and neck sites, and of these over 80% are of cutaneous origin. Of the approximate remaining 20%, the majority are of ocular origin; mucosal malignant melanomas (MMM) of the upper aerodigestive tract represent from 0.5-3% of melanomas of all sites [735]. In the upper aerodigestive tract, the most common site of occurrence is the sinonasal tract. PLMMM are extremely rare, with less than 60 cases reported in the literature [51,77,831,1277,1516,1668,2754,2755]. PLMMM are much more common in men than in women with over 80% of cases occurring in men [2754]. PLMMM occur over a wide age range from 35-86 years with an average age of 58 years, and are most frequent in the 6th and 7th decades of life. Most cases of PLMMM occur in Caucasians but Blacks are also affected.

Etiology
There are no known etiologic factors for PLMMM. Melanosis [912,2022], intralaryngeal naevi [2263,2287] and lentigo [2630] of the larynx have been reported. It has been suggested that PLMMM may arise from malignant degeneration of intralaryngeal melanocytes or melanocytic lesions [2754].

Localization
The majority (more than 60%) of PLMMM occur in the supraglottic larynx [2754,2755], including the epiglottis, arytenoids, aryepiglottic folds, ventricle, false vocal cord, and pyriform sinus [2755]. Other less common sites of occurrence include the glottic region along the true vocal cord and the posterior commissure. To date, there are no documented reports of PLMMM involving the subglottic region.

Clinical features
The clinical presentation of PLMMM includes hoarseness, dysphagia, sore throat, intermittent haemoptysis, neck or jaw pain and a cervical neck mass. Symptoms generally occur over short periods of time, ranging from 3-6 months [2755]. Multicentric (synchronous, metachronous) MMM of other upper aerodigestive tract sites are not typically present.

Macroscopy
The macroscopic appearance of PLMMM vary and include nodular, mul-
Primary laryngeal mucosal malignant melanoma is characterized by berry-like, sessile, polypoid, exophytic or pedunculated lesions with equally variable colour, including black, brown, red-pink, tan-grey and white (2754). The size of the tumours range from 3-4 mm up to 8.0 cm in greatest dimension (2754).

Histopathology
PLMMM are identical to melanomas at other sites. In the presence of an intact laryngeal mucosa, continuity of the tumour with the surface epithelium (i.e., junctional or pagetoid changes) can be identified; however, even in the presence of intact surface epithelium, junctional changes may not be seen. Given the fact that normal melanocytes may localize to the submucosal compartment within minor mucoserous glands or within the stroma (2754,2755), junctional change is not required to render a diagnosis of PLMMM.

Prognosis and predictive factors
PLMMM has a poor prognosis. The average survival rate is usually less than 3.5 years (2159,2754) with a 5-year survival rate of less than 20% (2754). Radical surgical excision is the treatment of choice. Adjuvant radiotherapy and chemotherapy are of questionable value in the management of PLMMM. Approximately 80% of patients with PLMMM have metastatic disease to the regional lymph nodes as well as to distant viscera (e.g., brain, lungs, bone). Pathologic criteria that are used to predict the biologic behaviour in association with cutaneous melanomas, including the depth of invasion, age and gender of the patient, and cytomorphology generally do not apply for PLMMM (2754,2755). Further, prognostic significance has not been found for tumour thickness, level of invasion, ulceration, mitotic index or nerve/nerve sheath involvement for PLMMM (2080).

Fig. 3.70 Primary laryngeal mucosal malignant melanoma. Prominent and obvious intracytoplasmic melanin deposition is seen in this PLMMM; this extent of melanin deposition is unusual for MMM.

Fig. 3.71 Primary laryngeal mucosal malignant melanoma. Immunohistochemical reactivity in this epithelioid melanoma includes: A HMB-4 B S100 protein. C melan A and D vimentin.
Secondary tumours

Definition
Tumours involving the hypopharynx, larynx and/or trachea that originate from, but are not in continuity with, other primary malignant neoplasms. Leukemias and lymphomas are excluded.

Epidemiology
Metastases to the larynx are uncommon. Only 11 cases over 20 years were identified in one series (160). Eight additional cases were found in a review of more than 4000 laryngeal malignancies (7353). In 1993, 134 cases were recorded in the world literature (735). Metastases to the hypopharynx and trachea are even more unusual.

Age and sex distribution
Laryngeal metastases increase with age (median 58 years, range 24-83 years) and are more common in males by a ratio of 2:1 (160,741).

Etiology
The overwhelming majority of tumours that metastasise to the larynx are either malignant melanomas or carcinomas. Only 5% or fewer are from mesenchymal tumours (bone and soft tissue sarcomas).

The sites of origin of 12 tumours metastatic to the larynx are shown in Table 3.08.

Localization
Metastases to the larynx may be submucosal, cartilaginous or both. If cartilage is involved, it is usually only in the portion which has undergone ossification. The most frequently affected site is the supraglottis (35-40% of all cases) followed by the subglottis (10-20%) and glottis (5-10%). Synchronous involvement of multiple laryngeal sites, however, is common and observed in about 35% of all cases (160,741).

The pyriform sinus is the most frequent site of metastasis in the hypopharynx.

Clinical features
Generally, metastatic tumours to the larynx present with the usual supraglottic or glottic symptomatology. Richly vascular tumours, such as renal cell carcinomas and thyroid carcinomas, often result in haemoptysis. On rare occasions, the metastasis is the only evidence of an otherwise occult primary tumour.

Tracheal metastases result in cough, stridor, wheezing, dyspnoea and/or haemoptysis.

Tumour spread and staging
The majority of metastases to the larynx are haematogenous through the systemic circulation or the paravertebral venous plexus.

Prognosis and predictive factors
Metastases to the larynx, trachea or hypopharynx are usually associated with terminal, widespread disseminated disease. In some instances, the metastasis may be isolated or localized and, with appropriate therapy, a prolonged survival can be achieved.