Pathology of Head and Neck Cancers

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1 Head and Neck Pathology

1.1 Introduction

The head and neck area is complex, with the skin, soft tissue, upper airways and other organs making up its anatomy. The pathology of this area is diverse, requiring clinicopathological correlation for diagnosis. Sometimes, a diagnosis can be made through a patient's history and exam, but pathology is the gold standard, especially for malignant diseases. Tumour grade, type and stage are prognostic indicators and may determine whether adjuvant therapy is needed after surgery. Molecular pathology has enabled a more individualized treatment.

1.2 Pathological Evaluation

There are several methods for acquiring samples for pathological analysis.

The following list includes some of the usual methods.

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1.2.1 Fine-Needle Aspiration Biopsy

Fine-needle aspiration biopsy (FNAB)/cytology is the primary study for patients who report cervical lymphadenopathy or a lesion in the major salivary glands or thyroid gland [1].

Advantages

- Simple method
- Inexpensive
- Highly accurate in distinguishing between benign and malignant lesions

A negative FNAB test does not rule out illness, and a 'triple evaluation' consisting of clinical, imaging and cytopathology is necessary to diagnose correctly.

The Most Frequently Used Stains in FNAB

- Haematoxylin and eosin (H&E)
- Papanicolaou
- Romanowsky
- May-Grunwald-Giemsa (MGG)

1.2.2 Core Biopsy

A core biopsy is similar to FNAC because the biopsy needle used during a core biopsy is larger; it will produce a cylinder of tissue that may be subjected to histological investigation. The tissue volume removed and the maintained tissue architecture improve the diagnostic value. There is also a chance that the procedure will produce enough tissue for histochemistry.

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Benefits of a Core Biopsy

- Simple and affordable
- Greater diagnostic yield than FNAC and histological examination of the sample
- Higher likelihood of lymphoma subclassification

1.2.3 Incisional Biopsy

It involves removing a wedge-shaped sample typical of the lesion for histological investigation. This method is employed for more easily accessible tumours affecting the larynx, pharynx, oral cavity and hypopharynx.

Incisional Biopsy Benefits

- Able to deliver a conclusive histopathological diagnosis

1.2.4 Excisional Biopsy

It involves the whole lesion being removed, offering a firm histological diagnosis. This might include anything from a major en-bloc resection to the excision of the vocal cord polyp.

Excisional Biopsy Benefits

- Can provide definitive histological diagnosis
- Can be the definitive treatment for the tumour

1.2.5 Sentinel Lymph Node Biopsy

Patients with clinically T1/T2 N0 oral cavity squamous cell carcinoma (SCC) are advised to use this approach [2]. A radioactively tagged colloid tracer is injected into four places around oral cancer before surgery. The first echelon of lymph nodes is where the tracer drains after entering the lymphatic system. The imaging may then be used to map the radioactive lymph nodes. The sentinel lymph nodes are harvested by a tiny incision in the neck after the surgeon utilizes gamma radiation detecting equipment to confirm their location. There might be as many as four sentinel nodes. After that, each 'hot node' is processed in the pathology lab using a technique that samples every lymph node at intervals of 125 μm.

To increase the test's sensitivity, cytokeratins are stained using immunohistochemistry (IHC).

Elective neck dissection can be avoided by monitoring the neck after a negative sentinel lymph node biopsy, which has a high negative predictive value per cent.

A neck dissection must be completed in a subsequent procedure if a lymph node is positive.

1.2.6 Histochemistry

The following are the processes involved in tissue preparation before a histopathological investigation:

- In the operating room, tissue samples are treated with 10% formalin.
- Macroscopically describe the specimen, dissect it, and send a sample tissue slice for analysis.
- A tissue slice goes through cycles of dehydration where alcohol replaces the tissue's aqueous fixative, xylene is used for clearing instead of alcohol during infiltration, and molten paraffin is used for clearing during embedding to prepare for microtomy.
- Slices of 3–5 μm are produced using a microtome.
- Usually, the slices can be stained with H&E. Haematoxylin colours tissue glycoproteins light blue and nuclei dark blue. Collagen and the cytoplasm are stained pink by eosin.

Special stains used are:

- Deep purple periodic acid-Schiff (PAS) stain is used to highlight carbohydrates.
- Simple carbohydrate moieties are first removed by the enzyme diastase, leaving mucins present in glandular secretions and fungal hyphae.
- To understand the architecture of the tissue, particularly the blood vessels, use the elastin van Gieson stain; elastin fibres stain black and collagen red.
- Ziehl-Neelsen stain—acid-fast bacilli in tuberculosis.

1.2.7 Immunohistochemistry

Immunohistochemistry (IHC) is a technique used to detect the presence of a specific antigen or epitope by having it attached to a particular antibody. This antibody is then coupled to a label, such as a fluorescent dye or enzy-

matic substrate, that can be seen under a microscope. Monoclonal antibodies are typically preferred because they are more specific than polyclonal antibodies; however, even in the case of monoclonal antibodies, no single antibody is 100% sensitive and specific. Therefore, immunophenotyping is best done with a panel of multiple antibodies, both positive and negative, to ensure the accuracy of the results. Furthermore, using multiple antibodies allows for a more comprehensive analysis, as it is possible to identify several different antigens or epitopes that may be present in a tissue sample.

Antibodies directed against:

- Intermediate filaments like cytokeratins, neurofilament, desmin, and vimentin
- Epithelial markers—BerEP4, epithelial membrane antigen
- Structural proteins—calponin
- Storage granules/products—calcitonin, synaptophysin, chromogranin, thyroglobulin
- Hormone receptors—progesterone, oestrogen
- Nuclear epitopes—p16, thyroid transcription factor-1
- Lympho-reticular epitopes—CD3, CD20, CD79a, etc.
- Cell proliferation—Ki67

1.2.8 In Situ Hybridization

Using the in situ hybridization, a particular nucleic acid segment may be precisely localized inside a histologic slice. A complementary strand of nucleic acid with a reporter molecule attached is used to accomplish this.

ISH probes:

- Double-stranded DNA (dsDNA) probes
- Single-stranded DNA (ssDNA) probes
- RNA probes (riboprobes)
- Synthetic oligonucleotides (PNA, LNA)

It is used in head and neck oncology:

- RNA ISH is used to detect EBV.
- RNA ISH is used to detect kappa and lambda light chains in B lymphocytes.
- DNA ISH can be used to identify low-risk and high-risk human papillomavirus infections.
- Chromosomal abnormalities, such as amplifications, translocations and deletions, can be identified by fluorescence ISH.

1.2.9 Molecular Testing

To create a high-resolution genetic profile of tumours, molecular testing is employed.

The following are some applications of molecular testing in head and neck oncology:

- Molecular tests for early detection of malignancy:
  - Proteomic and serum multiplexed cytokine profiling
  - Saliva genomic and proteomic analysis for early oral SCC detection
- Molecular tests for prognosis in head and neck malignancy:
  - HPV detection as a good prognostic indicator [3].
  - Epidermal growth factor receptor (EGRF) genetic abnormality is a negative prognostic indicator [4].
  - Genomic profiling for genomic profiling for molecular characterization.
  - Epstein-Barr virus detection as a predictive biomarker.
- Molecular tests for prediction of treatment response in squamous cell carcinoma:
  - Expression of ERCC1 as a cisplatin response predictor [5].
  - A sign of radiation sensitivity is hypoxia.
  - Prediction of EGRF inhibitor response.
  - Anti-angiogenic agent reaction forecast [6].

1.2.10 Subsites in the Head and Neck

The head and neck regions are divided into several subsites as outlined in Table 1.

1.3 Tumours of the Head and Neck

According to the origin (histogenesis) and/or differentiation route of the tumour cell, benign and

Table 1 Head and neck cancer sites and subsites

Head and neck site	Subsite
Oral cavity	• Lip – External upper lip (vermilion border) – External lower lip (vermilion border) – Commissures • Floor of mouth • Cheek mucosa • Retromolar trigone • Lower alveolus and gingiva • Anterior 2/3 of the tongue • Mucosa of the upper and lower lips • Upper alveolus and gingiva • Bucco-alveolar sulci, upper and lower • Hard palate
Oropharynx	• Tonsillar fossa • Lateral wall • Tonsil • Vallecula • Posterior wall • Uvula • Inferior surface of soft palate • Tonsillar pillar • Base of tongue
Hypopharynx	• Posterior pharyngeal wall • Postcricoid region • Pyriform fossa/sinus
Larynx	• Supraglottis – Arytenoid – Ventricular bands (false cords) – Infrahyoid epiglottis – Aryepiglottic fold, laryngeal aspect – Suprahyoid epiglottis (including tip, lingual [anterior], and laryngeal surfaces) • Glottis – Anterior commissure – Posterior commissure – Vocal cords • Subglottis
Nasopharynx	• Superior wall • Floor: superior surface of the soft palate • Lateral wall: including the fossa of Rosenmuller • Posterior wall: from the level of the junction of the hard and soft palates to the superior wall
Ear	• External auditory canal • Middle ear • Inner ear
Nose and paranasal sinuses	• Nasal cavity – Septum – Floor – Lateral wall – Vestibule • Maxillary sinus • Ethmoid sinus
Salivary gland	• Parotid gland • Submandibular gland • Sublingual gland • Minor salivary glands
Thyroid gland	
Parathyroid glands	
Neck	• Level I, submental IA and submandibular IB nodes. • Level II, upper jugular nodes divided by spinal accessory nerve into IIA and IIB • Level III, middle jugular nodes • Level IV, lower jugular nodes • Level V, posterior triangle nodes divided by spinal accessory nerve into VA and VB • Level VI, anterior compartment
Skin	

malignant tumours can be distinguished. The benign and malignant tumours that are more frequently seen in clinical practice will be covered in this section.

1.3.1 Benign Tumours

Benign Epithelial Tumours

Squamous Cell Papilloma

A localized benign exophytic growth of the squamous epithelium is known as a squamous papilloma. It can affect the nasopharynx, larynx, sinuses and oral cavity. The proliferation of stratified keratinizing squamous epithelium supported by cores of the fibrovascular connective tissue characterizes its typical microscopic appearance.

Depending on the place and subtype, there may be a single lesion or many:

- Oral squamous papilloma:
  - Squamous cell papilloma or verruca vulgaris
  - Condyloma acuminatum
  - Multifocal epithelial hyperplasia
- Laryngeal papilloma
- Sinonasal papilloma:
  - Exophytic sinonasal papilloma
  - Inverted sinonasal papilloma
  - Oncocytic sinonasal papilloma

Benign Salivary Gland Tumours

Benign epithelial salivary gland tumours encompass a range of different types as per the 2017 WHO Classification of Head and Neck Tumours [7].

These include pleomorphic adenoma, basal cell adenoma, oncocytoma, Warthin's tumour, canalicular adenoma, cystadenoma, myoepithelioma, ductal papillomas, sialadenoma papilliferum, lymphadenoma and sebaceous adenoma.

Pleomorphic Adenoma

The most frequent tumour affecting the salivary glands is a pleomorphic salivary adenoma, often known as a benign mixed tumour or mixed tumour. According to reports, the frequency is between 2.4 and 3.05 per 100,000. About 50% of all salivary gland tumours, 60% of parotid tumours, and 40% of intra-oral minor salivary gland tumours are made up of it [8].

With a peak age of occurrence in the fourth to fifth decade, it is more prevalent in females.

Gross Findings

- A well-defined rounded to oval and irregularly enclosed bulk
- The cut surface that is white-tan, glossy or transparent

Microscopic Findings

- Epithelial glands and ducts
- Chondromyxoid matrix with myoepithelial cells and ductal components incorporated in it
- Spindle, plasmacytoid, epithelioid, stellate or basaloid morphologies of myoepithelial cells
- Myxoid, mucochondroid, hyalinized, osseous and/or fatty mesenchymal stroma

Pathologic Differential Diagnosis

- Benign: basal cell adenoma, myoepithelioma
- Malignant: polymorphous adenocarcinoma, adenoid cystic carcinoma

Warthin's Tumour

Adenolymphoma and papillary cystadenoma lymphomatosum are other names for Warthin's tumour. It is the second most frequent salivary gland tumour [9]. The biphasic tumour is made up of papillary fronds and bilayered oncocytic cells that form cysts and are embedded in a thick, lymph node-like stroma. It is believed to develop from the salivary tissue that has been stuck in intraparotid or periparotid lymph nodes.

With a peak incidence in the sixth to seventh decade, it is more prevalent among white males who have smoked in the past.

Gross Findings

- Brown, yellow or red mass that is circumscribed and firm to cystic

Microscopic Findings

- Oncocytic epithelium comprises two layers, having columnar luminal cells above the cuboidal basal cells
- Many papillary infoldings and cysts
- Dense stroma resembling lymph nodes that may have reactive germinal centres

Immunohistochemical Findings

- The epithelial component reacts with keratin.
- B- and T-cell markers react with the lymphoid component.

Pathologic Differential Diagnosis

- Cystadenoma, sebaceous lymphadenoma and lymph node metastasis

Benign Mesenchymal Tumours

Benign mesenchymal tumours are a group of non-malignant, non-epithelial cell tumours that

arise from mesenchymal cells, which form the connective tissue in the body. Mesenchymal cells are typically located in the bone, cartilage, fat, muscle, fibrous tissue and certain other connective tissues. These tumours behave in a non-aggressive manner and do not usually spread to other parts of the body.

Schwannoma

Neurilemmomas are another name for schwannomas, benign, well-encapsulated tumours from Schwann cells in the sheath surrounding peripheral nerves, from the sympathetic chain; cervical or cranial nerves V, VII, and XII; brachial plexus; or head and neck region.

Gross Findings

- Usually enclosed, whereas those that involve the temporal bone frequently are not.
- The tumour is often connected to a distinguishable nerve and is firm, rubbery and brown to yellow in colour.

Microscopic Findings

- Verocay bodies and tightly backed bundles of spindled cells can be seen in cellular Antoni A regions.
- Areas of Antoni B with hypocellularity and microcystic degeneration.
- Fusiform cells having cytoplasm that is fibrillar.
- Wavy/buckled, pointed and spindly nuclei (often palisaded).
- Hyalinized, medium-sized dilated vessels.

Immunohistochemical Findings

- S100 protein, SOX10 and vimentin responses that are widespread and powerful.
- In degraded regions, there are sometimes positive CD34 fibroblasts for glial fibrillary acidic protein and neuron-specific enolase.

Genetic Studies

- Ninety percent of the mutations in type 2 neurofibromatosis Merlin coded it at 22q12.

Pathologic Differential Diagnosis

- Malignant peripheral nerve sheath tumours, meningiomas, neurofibromas, solitary fibrous tumours, paragangliomas and neurofibromas.

1.3.2 Malignant Tumours

Squamous cell carcinomas, which develop from the epithelial lining of the upper aerodigestive tract, account for the majority (90%) of head and neck malignancies.

Tumour Staging

A technique for expressing the disease's relative severity or extent is used in the staging of head and neck cancers.

The main objectives of staging are:

- To support the doctor in making treatment plans
- To provide some prognostic information
- To aid in assessing the effectiveness of the treatment
- To make it easier for treatment facilities to communicate with one another
- In order to aid in the ongoing study of human cancer

The TNM staging system, created and maintained by AJCC and UICC, is the most commonly used and is kept under review by international expert committees. AJCC and UICC published the eighth edition in 2017 [10].

The TNM staging system's fundamental tenets are:

- Clinical—Based on clinical data, TNM or cTNM (physical examination and imaging).
- Pathological—Based on the cTNM, the pTNM is modified by additional data from the postoperative pathological examination.

Autopsy—When there is no sign of cancer before death and the malignancy is only identified based on the findings of the post-mortem examination, aTNM is utilized.

There may also be other TNM descriptors employed on occasion, such as:

- The 'y' prefix—when classification is done during or after the first multimodality therapy, ycTNM or ypTNM
- The 'm' suffix—when there are multiple primary at a single site, pT(m)NM
- The 'y' suffix—when there is only one primary at a single site, pT(m)NM

Typically, tumours are histologically subtyped based on how differentiated they are components:

- Gx—grade cannot be assessed.
- G1—well-differentiated.
- G2—moderately differentiated.
- G3—poorly differentiated.

The presence or absence of residual tumour is classified as:

- Rx—the presence of residual tumour cannot be assessed.
- R0—no residual tumour is present.
- R1—microscopic residual disease.
- R2—macroscopic residual tumour.

The TNM approach is built on three elements to describe the anatomical extent of the illness:

- T—the initial tumour's size
- N—regional lymph node metastases: the presence, absence and extent
- M—whether there are any distant metastases or not

Method of Staging

Regional Lymph Nodes

Prognostic factors for head and neck cancers include the condition of local lymph nodes. As shown in Table 2, lymph nodes are now classified into seven tiers and distinct anatomical places.

For the majority of head and neck locations (oral cavity, p16-negative pharyngeal carcinoma, larynx carcinoma, sinus carcinoma and salivary gland cancer), the criteria of the N categories are the same and are as stated in Table 3.

Table 2 Nomenclature of anatomical site of lymph node

Nomenclature of anatomical site of the lymph node	
Level I	Consists of the submental and submandibular triangles, separated by the digastric muscle's posterior belly, the hyoid bone and the mandibular body, respectively
Level II	Extends from the level of the hyoid bone inferiorly to the base of the skull superiorly, containing the upper jugular lymph nodes
Level III	Contains the middle jugular lymph nodes that run inferiorly from the cricothyroid membrane to the hyoid bone in the superior position
Level IV	Consists of the lymph nodes in the lower jugular region, which run from the clavicle to the superior cricothyroid membrane
Level V	Contains the lymph nodes of the posterior triangle, which are bordered by the clavicle inferiorly, the anterior border of the trapezius and the posterior border of the sternocleidomastoid muscle
Level VI	Contains the anterior compartment lymph nodes from the suprasternal notch inferior to the hyoid bone superior. The lateral boundary is formed on each side by the carotid sheath's medial border
Level VII	Contains the lymph nodes in the upper mediastinum below the suprasternal notch

As seen in Tables 4 and 5, the most recent version has also added two distinct staging systems (cTNM and pTNM) for neck metastases of human papillomavirus (p16-positive) oropharyngeal carcinoma.

The influence of treatment response on prognosis varies, which justifies a separate N categorization for thyroid and well-differentiated nasopharynx tumours. According to Tables 6 and 7, it is as stated.

Primary Tumour

Lip and Oral Cavity

The oral cavity extends from the line of the circumvallate papillae below anteriorly to the junction of the hard and soft palate above and to the junction of the skin-vermilion of the lips posteriorly. Table 1 lists the anatomical locations and subsites. Table 8 provides the TNM clinical classification for the lip and oral cavity and the T—

Table 3 Clinical N staging of regional neck nodes in head and neck cancers

Clinical N stage of regional neck lymph nodes (LN)	
NX	Regional LN cannot be assessed
N0	No regional LN metastasis
N1	Single ipsilateral LN metastasis, ≤3 cm in the greatest dimension without extra-nodal extension (ENE)
N2	N2a—Single ipsilateral LN metastasis, > 3 cm and ≤6 cm in the greatest dimension without ENE N2b—Multiple ipsilateral LN metastasis, none >6 cm in the greatest dimension, without ENE N2c—Bilateral or contralateral lymph nodes metastasis, none >6 cm in the greatest dimension, without ENE
N3a	LN metastasis >6 cm in the greatest dimension without ENE
N3b	LN metastasis in single or multiple LN with clinical ENE

Table 4 Clinical N stage for HPV-related (p16-positive) oropharyngeal cancer

Clinical N stage for HPV-related (p16-positive) oropharyngeal cancer	
Nx	Regional LN cannot be assessed
N0	No regional LN metastases
N1	One or more ipsilateral LN, none >6 cm
N2	Contralateral or B/L LN, none >6 cm
N3	Lymph node(s) > 6 cm

Table 5 Pathological N stage for HPV-related (p16-positive) oropharyngeal cancer

Pathologic N stage for HPV-related (p16-positive) oropharyngeal cancer	
Nx	Regional LN cannot be assessed
pN0	No regional LN metastases
pN1	Metastasis in four or fewer LN
pN2	Metastasis in more than four LN

primary tumour clinical classification which considers the greatest tumour dimension along with depth of invasion (DOI).

Pharynx

There are three distinct parts to the eighth edition of the AJCC staging manual:

Table 6 N staging for the nasopharynx

N staging for the nasopharynx	
NX	Regional LN cannot be assessed
N0	No regional LN metastasis
N1	Unilateral cervical lymph node(s) metastasis and/or unilateral or bilateral metastasis in retropharyngeal LN, ≤6 cm in the greatest dimension, above the caudal border of the cricoid cartilage
N2	Bilateral cervical lymph node(s) metastasis, ≤ 6 cm in the greatest dimension, above the caudal border of cricoid cartilage
N3	Cervical lymph node(s) metastasis, > 6 cm in dimension and/or extension below the caudal border of cricoid cartilage

Table 7 N staging for thyroid carcinoma

N staging for thyroid carcinoma	
NX	Regional LN cannot be assessed
N0	No regional LN metastasis
N1	Regional LN metastasis
N1a	Level VI (pretracheal, prelaryngeal, paralaryngeal) LN metastasis or upper/superior mediastinal LN
N1b	Unilateral, bilateral or contralateral cervical (levels I–V) or retropharyngeal LN metastasis

- Nasopharynx
- HPV-associated (p16-positive) oropharyngeal cancer
- Hypopharynx and non-HPV-associated (p16-negative) oropharyngeal carcinoma

To more accurately represent the range of pharyngeal illnesses [10].

Oropharynx

The oropharynx reaches from the hyoid bone's superior surface to the plane of the soft palate's superior surface. The oropharynx's subsites are listed in Table 1.

With two exceptions, T categories were identical in p16-positive, HPV-associated oropharyngeal cancer and p16-negative, non-HPV-associated oropharyngeal carcinoma. Because of the non-aggressive pattern of invasion of p16-positive oropharyngeal carcinoma and the absence of a distinct basement membrane in the epithelium of Waldeyer's ring, there

Table 8 T—primary tumour clinical classification for the lip and oral cavity

T—primary tumour clinical classification for the lip and oral cavity	
T1	≤ 2 cm in the greatest dimension and ≤5 mm DOI
T2	≤ 2 cm in the greatest dimension >5 mm but ≤10 mm DOI or > 2 cm but ≤4 cm in the greatest dimension and DOI ≤ 10 mm
T3	> 4 cm in the greatest dimension or >10 mm depth of invasion
T4a	Lip: tumour invades through the skin (chin or nose), floor of mouth inferior, alveolar nerve or cortical bone Oral cavity: tumour invades through the skin of the face and maxillary sinus or into deep/extrinsic muscle of the tongue and cortical bone
T4b	Lip or oral cavity: tumour invades the pterygoid plates, masticator space or skull base or encases the internal carotid artery

is no carcinoma in situ (Tis) in the p16-positive classification, and the T4b category has been eliminated from p16-positive oropharyngeal carcinoma (OPC) (because of no difference in the survival curves of the T4a and T4b) [11]. Tables 9 and 10 summarize these changes.

Nasopharynx

The nasopharynx starts anteriorly from the posterior choana and continues along the airway's plane to the level of the soft palate's free border. Table 1 provides a description of the subsites in the nasopharynx. Table 11 provides the clinical categorization for T—primary tumours.

Hypopharynx

The hypopharynx extends from the plane corresponding to the lower border of the cricoid cartilage to the plane of the superior border of the hyoid bone (or floor of the vallecula). It contains the:

- The lateral and posterior pharyngeal walls
- Piriform sinuses
- The postcricoid area

Table 9 T—primary tumour clinical classification of the oropharynx: p16-negative cancers or p16 immunohistochemistry not performed

Oropharynx: p16-negative cancers or p16 immunohistochemistry not performed	
T1	≤2 cm in the greatest dimension
T2	>2 cm but ≤4 cm in the greatest dimension
T3	>4 cm in the greatest dimension or extension to the lingual surface of the epiglottis
T4a	Invading any of the following: larynx, deep extrinsic muscles of the tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), medial pterygoid, mandible and hard palate
T4b	Invading any of the following: lateral pterygoid muscle, pterygoid plates, lateral nasopharynx and skull base or encases the carotid artery

Table 10 T—primary tumour clinical classification of the oropharynx: p16-positive cancers

Oropharynx: p16-positive cancers	
T1	≤ 2 cm in the greatest dimension
T2	> 2 cm but ≤4 cm in the greatest dimension
T3	> 4 cm in the greatest dimension or extension to the lingual surface of the epiglottis
T4	Tumour invades any of the following: larynx, deep extrinsic muscles of the tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), medial pterygoid, mandible and hard palate, lateral pterygoid muscle, pterygoid plates, lateral nasopharynx and skull base or encases the carotid artery

Table 11 T—primary tumour clinical classification of the nasopharynx

Nasopharynx	
T1	Tumour confined to the nasopharynx or extends to the oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumour with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid and/or prevertebral muscles
T3	Tumour invades bony structures of skull base cervical vertebra, pterygoid structures and/or paranasal sinuses
T4	Tumour with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or infiltration beyond the lateral surface of the lateral pterygoid muscle

Table 12 provides a review of the hypopharynx's current stage.

Larynx

Table 1 provides a description of the larynx's anatomical locations and subsites. Tables 13, 14 and 15 list the detailed T stages of the various laryngeal carcinoma locations.

Table 12 T—primary tumour clinical classification of the hypopharynx

Hypopharynx	
T1	Limited to one subsite of the hypopharynx and ≤2 cm in the greatest dimension
T2	Invades >1 subsite of the hypopharynx or an adjacent site or measures 2–4 cm in the greatest dimension, without fixation of the hemilarynx
T3	>4 cm in the greatest dimension or with fixation of the hemilarynx or extension to the oesophagus
T4a	Invades any of the following: thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus, central compartment soft tissue
T4b	Invades the prevertebral fascia, encases the carotid artery or invades the mediastinal structures

Table 13 T—primary tumour clinical classification of the supraglottis

Supraglottis	
T1	Limited to one subsite of supraglottis with normal vocal cord mobility
T2	Invades the mucosa of more than one adjacent subsite of the supraglottis or glottis or he region outside the supraglottis (e.g. mucosa of the base of the tongue, vallecula, medial wall of the pyriform sinus) without fixation of the larynx
T3	Limited to the larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic tissues, paraglottic space and/or with minor thyroid cartilage erosion (e.g. inner cortex)
T4a	Invades through the thyroid cartilage and/or invades tissues beyond the larynx, e.g. trachea, soft tissues of the neck, including deep/extrinsic muscle of the tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), strap muscles, thyroid and oesophagus
T4b	Invades the prevertebral space and mediastinal structures or encases the carotid artery

Table 14 T—primary tumour clinical classification of the glottis

Glottis	
T1	Limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility T1a—tumour limited to one vocal cord T1b—tumour involved both vocal cords
T2	Extends to the supraglottis and/or subglottis and/or with impaired vocal cord mobility
T3	Limited to the larynx with vocal cord fixation and/or invades the paraglottic space and/or with minor thyroid cartilage erosion (inner cortex)
T4a	Invades through the thyroid cartilage or invades tissues beyond the larynx, e.g. trachea, soft tissues of the neck including the deep/extrinsic muscle of the tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), strap muscles, thyroid and oesophagus
T4b	Invades the prevertebral space and mediastinal structures or encases the carotid artery

Table 15 T—primary tumour clinical classification of the subglottis

Subglottis	
T1	Limited to the subglottis
T2	Extends to the vocal cord(s) with normal or impaired mobility
T3	Limited to the larynx with vocal cord fixation
T4a	Invades through the cricoid or thyroid cartilage and/or invades tissues beyond the larynx, e.g. trachea, soft tissues of the neck including the deep/extrinsic muscle of the tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), strap muscles, thyroid and oesophagus
T4b	Invades the prevertebral space and mediastinal structures or encases the carotid artery

Nose and Paranasal Sinuses

Table 1 lists the anatomical locations and sublocations of the nose and paranasal sinuses. Tables 16 and 17 provide descriptions of the T—primary tumour clinical categorization of cancer.

Salivary Gland

The major salivary glands are the only ones included by categorization.

Table 16 T—primary tumour clinical classification of the maxillary sinus

Maxillary sinus	
T1	Tumour limited to the antral mucosa with no erosion or destruction of the bone
T2	Tumour causing bone erosion or destruction, including extension into the hard palate and/or middle nasal meatus, except extension to the posterior wall of the maxillary sinus and pterygoid plates
T3	Tumour invades any of the following: bone of the posterior wall of the maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa or ethmoid sinuses
T4a	Tumour invades any of the following: anterior orbital contents, skin of the cheek, pterygoid plates, infratemporal fossa, cribriform plate and sphenoid or frontal sinus
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve, nasopharynx, clivus

Table 17 T—primary tumour clinical classification of the nasal cavity and ethmoidal sinus

Nasal cavity and ethmoid sinus	
T1	Tumour restricted to one subsite of the nasal cavity or ethmoid sinus without bone erosion
T2	Tumour involves two subsites or extends to involve an adjacent site within the nasoethmoidal complex, with or without bony invasion
T3	Tumour extends to invade the medial wall or floor of the orbit, maxillary sinus, palate or cribriform plate
T4a	Tumour invades any of the the following: anterior orbital contents, skin of nose or cheek, minimal extension to the anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve, nasopharynx, clivus

The primary salivary glands are

- Parotid glands
- Submandibular glands
- Sublingual glands

Table 18 provides descriptions of the T—primary tumour clinical categorization of salivary gland cancer.

Table 18 T—Primary tumour clinical classification of the salivary gland

Salivary gland	
T1	Tumour 2 cm or less in the greatest dimension without extraparenchymal extension*
T2	Tumour more than 2 cm but no more than 4 cm in the greatest dimension without extraparenchymal extension*
T3	Tumour more than 4 cm and/or tumour with extraparenchymal extension
T4a	Tumour invades the skin, mandible, ear canal or facial nerve
T4b	Tumour invades the base of the skull and pterygoid plates or encases the carotid artery

Except for the tissues specified under T4a and T4b, extraparenchymal extension is clinical or macroscopic evidence of invasion of the skin, soft tissues or nerve. For categorization purposes, microscopic data by itself does not support extraparenchymal extension.

Thyroid Gland

The four major histopathologic types are:

- Papillary carcinoma (including those with follicular foci)
- Follicular carcinoma (including Hürthle cell carcinoma)
- Medullary carcinoma
- Undifferentiated (anaplastic) carcinoma

The current staging system is summarized in Table 19.

Skin Carcinoma of the Head and Neck

The eighth edition of the UICC/AJCC handbook now presents this in a distinct chapter [10]. The categorization includes malignant melanoma, Merkel cell carcinoma and cutaneous carcinomas of the head and neck that do not include the eyelid (as an anatomical location). Table 20 shows the T stage, and the N stage is shown after nodal metastases from various head and neck locations.

The following sites are recognized:

- Lip
- External ear

Table 19 T—primary tumour clinical classification of the thyroid gland

Thyroid gland	
T1	Tumour 2 cm or less in the greatest dimension, limited to the thyroid T1a—tumour 1 cm or less in the greatest dimension, limited to the thyroid T1b—tumour more than 1 cm but not more than 2 cm in the greatest dimension, limited to the thyroid
T2	Tumour more than 2 cm but not more than 4 cm in the greatest dimension, limited to the thyroid
T3	Tumour more than 4 cm in the greatest dimension, limited to the thyroid or any tumour with gross extrathyroid extension involving only the strap muscles (e.g. sternohyoid, sternothyroid or omohyoid muscles) T3a—tumour more than 4 cm in the greatest dimension, limited to the thyroid T3b—tumour of any size with gross extrathyroidal extension invading the strap muscles (sternohyoid, sternothyroid or omohyoid muscles)
T4a	Tumour extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve
T4b	Tumour invades the prevertebral fascia and mediastinal vessels or encases the carotid artery
T4a[a]	Anaplastic carcinoma only—tumour (any size) limited to the thyroid
T4b[a]	Anaplastic carcinoma only—tumour (any size) extends beyond the thyroid capsule

[a]All anaplastic carcinomas are considered T4

Table 20 T—primary tumour clinical classification of head and neck skin cancer

Head and neck skin cancer	
T1	Tumour 2 cm or less in the greatest dimension
T2	Tumour >2 cm and <4 cm in the greatest dimension
T3	Tumour >4 cm in the greatest dimension or minor bone erosion or perineural invasion or deep invasion*
T4a	Tumour with gross cortical bone/marrow extension
T4b	Tumour with skull base or axial skeleton invasion including foraminal involvement and/or vertebral foramen involvement to the epidural space

*Deep invasion is defined as invasion beyond the subcutaneous fat or > 6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumour), perineural invasion for T3 classification is defined as clinical or radiographic involvement of named nerves without foramen or skull base invasion or transgression.

Table 21 T—primary tumour clinical classification of malignant melanoma of the upper aerodigestive tract

Malignant melanoma of the upper aerodigestive tract	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T3	Tumour limited to the epithelium and/or submucosa (mucosal disease)
T4a	Tumour invades the deep soft tissue, cartilage, bone or overlying skin
T4b	Tumour invades any of the following: brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, mediastinal structures

- Other and unspecified parts of the face
- Scalp and neck

Malignant Melanoma of the Upper Aerodigestive Track

Only head and neck mucosal malignant melanomas are subject to the categorization in Table 21. Stages I and II as well as T1 and T2 are skipped due to the aggressive nature of malignant melanoma tumours.

Squamous Cell Carcinoma

With the exception of the thyroid and major salivary glands, squamous cell carcinoma (SCC) is the most prevalent histological form of malignancy in the head and neck area, accounting for about 95% of cases. The precursor lesion of SCC is known as squamous epithelial dysplasia, which is described as an accumulation of cytological and architectural abnormalities. Due to 'field cancerization', these dysplastic regions might be confined or widespread. The malignant transformation rate for oral dysplastic lesions is 12%, and the mean time to transformation is 4.3 years, according to a meta-analysis [12]. This suggests that the development into invasive malignancy is not always the case. Clinically, these lesions look irregular, confined, white (leucoplakia), red (erythroplakia) or variegated (erythroleukoplakia). Defined as a dynamic process with a continuous morphological range, dysplasia is so.

Pathogenesis

The histological evolution of head and neck squamous cell carcinoma (HNSCC) from the normal epithelium to hyperplasia, dysplasia and, ultimately, invasive carcinoma is influenced by a

number of variables, including genetic alterations that cause genetic instability leading to cellular transformation [13]. The inactivation of tumour suppressor genes and the activation of proto-oncogenes, or both, are examples of genetic alterations. Tobacco-related carcinogens cause p53 mutations that are linked to HNSCC. A number of genetic abnormalities, including the loss of heterozygosity (LOH) of 9p21, which is present in 70–80% of HNSCC, are responsible for the molecular changes. The viral oncoproteins E6 and E7 in HPV16 infection render the tumour suppressor molecules pRb and p53 inactive. Cell growth becomes uncontrolled when pRb is lost. Genomic stability derives from p53-mediated response to DNA damage loss. Additionally, telomerase is reactivated, which promotes cell immortality [13, 14].

Macroscopic Appearance

HNSCC can emerge as an exophytic or ulcerative lesion, among other things.

Microscopic Appearance

- Evidence keratinization and intercellular prickles are often seen in well-differentiated and moderately differentiated SCC (desmosomes). SCC with poor differentiation lacks keratinization signs.
- Some characteristics of malignant squamous cells include:
- Coarse and clumped chromatin
- Nuclear hyperchromatism
- Disordered cell polarity
- Prominent nucleoli
- Increased and abnormal mitosis
- Loss of keratin production
- Increased nucleus-cytoplasmic ratio
- Nuclear pleomorphism
- Disorganized growth
- Premature keratinization (dyskeratosis)

The distinguishing characteristic of SCC is the rupture of the sub-epithelial basement membrane, which enables the malignant cells to invade the healthy connective tissue beneath.

An SCC is described microscopically as follows:

- Histological subtype
- Histological grade (well-, moderate-, poorly differentiated)
- Invasive front (cohesive or non-cohesive)
- Vascular invasion
- Neural invasion

Immunohistochemistry

IHC utilized for reliable diagnosis since the weakly differentiated SCC lacks keratinization and is difficult to recognize histologically. The nuclear proteins p40 and p63, as well as the cytokeratins 5, 6 and 14, are utilized to support the diagnosis of poorly differentiated SCC. HPV testing is carried out for oropharyngeal SCC since it has prognostic importance. It is found using p16 IHC and high-risk HPV DNA ISH. More than 70% of malignant cells exhibit strong and widespread nuclear and cytoplasmic staining. Oncogenic HPV infection is known to be represented by the surrogate marker p16; the test is extremely sensitive but unspecific. The nasopharynx is often where EBV-positive SCCs are found.

Head and Neck Squamous Cell Carcinoma Variants

The morphological variants of SCC include:

- Verrucous carcinoma
- Spindle cell carcinoma (sarcomatoid carcinoma)
- Papillary SCC
- Adenosquamous carcinoma
- Basaloid SCC

Nasopharyngeal Carcinoma

The distinct kind of SCC known as nasopharyngeal carcinoma (NPC) develops in the nasopharynx. The age-adjusted incidence for both sexes of this neoplasm is fewer than one per 100,000 people worldwide, with southern China, northern Africa and Alaska having substantially higher rates of the illness. Inuit people from Alaska and ethnic Chinese residents of the province of Guangdong are particularly vulnerable to the illness [15]. In Hong Kong, which is geographically close to Guangdong

province, the reported incidence of nasopharyngeal cancer is 20–30 per 100,000 and 15–20 per 100,000, respectively [16]. Immigrants from China to Southeast Asia or North America continue to have a high risk of nasopharyngeal cancer [17]. According to this result, environmental, racial and genetic variables may all have a part in the development of the disease. EBV and dietary variables, particularly a high consumption of salted fish and preserved vegetable items, are additional contributors.

The tumour might appear clinically as a bulging, exophytic, lobulated or ulcerative mass. Occasionally, a blind biopsy of the nasopharynx is necessary when there is no visible tumour.

According to the WHO classification system, NPC is categorized microscopically based on the presence or lack of keratinization.

Nasopharyngeal cancer is histologically categorized by the WHO [18]:

- Keratinizing squamous cell carcinoma (WHO type I)

This kind of nasopharyngeal carcinoma is characterized by the presence of squamous differentiation with intercellular bridges and/or keratinization across the majority of its range.

- Non-keratinizing carcinoma

These tumours typically have greater connections with the Epstein-Barr virus and are more radiosensitive than SCC:

1. Differentiated non-keratinizing carcinoma (WHO type II)

   The tumour cells differentiate in a way that causes them to mature in a way that prevents squamous differentiation from being seen under a light microscope.
2. Undifferentiated carcinoma (WHO type III)

   The nuclei of the tumour cells are spherical or oval with large nucleoli. The tumour seems syncytial rather than pavemented, and the cell boundaries are indistinct.

Malignant Salivary Gland Tumours

According to GLOBOCAN 2020 statistics, malignant salivary gland tumours are rare, accounting for 5% of all head and neck cancers, 5% of all malignancies and having an annual incidence of 0.57 per 100,000 people worldwide [19]. Despite having a low prevalence, there are over 20 distinct types of designated malignant salivary gland neoplasm. Malignant epithelial salivary gland tumours encompass a diverse array of types as per the 2017 WHO Classification of Head and Neck Tumours [7]. These include adenoid cystic carcinoma, basal cell adenocarcinoma, myoepithelial carcinoma, carcinoma ex-pleomorphic adenoma, clear cell carcinoma, adenocarcinoma NOS (not otherwise specified), oncocytic carcinoma, squamous cell carcinoma, large cell neuroendocrine carcinoma, sialoblastoma, epithelial/myoepithelial carcinoma, secretory carcinoma, carcinosarcoma, mucoepidermoid carcinoma, undifferentiated carcinoma, intraductal carcinoma, sebaceous adenocarcinoma, salivary duct carcinoma, lymphoepithelial carcinoma, polymorphous adenocarcinoma, small cell neuroendocrine carcinoma, poorly differentiated carcinoma and acinic cell carcinoma.

Mucoepidermoid Carcinoma

The most frequent malignant salivary gland neoplasm, accounting for 12–29% of all salivary gland malignancies, is mucoepidermoid carcinoma [7]. The parotid gland is the salivary gland that is most frequently affected. The peak age group in the fifth decade is when females are more likely to develop mucoepidermoid carcinoma.

Gross Findings

- Infiltrative or varyingly encapsulated.
- The solid portion, which ranges in colour from tan-white to pink, is more noticeable.
- There are often cysts that contain a viscous, dark fluid.

Microscopic Findings

- Contains cells that are mucous, intermediate, and epidermoid.

- Clear cells, columnar cells, and oncocytes are further types of cells.
- Cystic and solid regions appear in various amounts along with other patterns in tumours.
- Characteristic of reactive tumour-associated lymphoproliferation.
- Fibrosis and inflammation are frequent.
- There are three classes of tumours: low, moderate and high grades.

Immunohistochemical Findings

- Cytokeratin, p63, p40 and commonly EMA are immunoreactive in intermediate and epidermoid cells.

Molecular Findings

- Independent of grade, MAML2 rearrangement is seen in 78% to 85% of patients.

Fine-Needle Aspiration

- Cellular stains with a mucinous material background.
- Sheets of cells and cells flowing in the mucus can be found in cohesive epithelial clusters.
- When intermediate and epidermoid cells are present, mucocytes aid in the diagnosis.

Mucoepidermoid carcinoma exhibits a wide range of behaviours, and several methods have been put forth to try and grade tumours and, as a result, predict outcomes. The grading system for mucoepidermoid carcinoma [20] incorporates various parameters and assigns point values to each. These parameters include the percentage of intracystic component (<20%), the presence of neural invasion, the presence of necrosis, the number of mitoses (>4 per 10 high-power fields) and the presence of anaplasia. Each parameter is assigned a specific point value, with intracystic component and neural invasion carrying 2 points each, necrosis and mitoses carrying 3 points each and anaplasia carrying 4 points. The total score is calculated by summing the points for each parameter. Based on the total score, the grade of the carcinoma is determined. A total score of 0–4 corresponds to a low-grade carcinoma, with an estimated overall survival rate of 90% at 10 years. A total score of 5–6 indicates an intermediate-grade carcinoma, with an estimated overall survival rate of 70% at 10 years. A total score of 7–14 signifies a high-grade carcinoma, with an estimated overall survival rate of 25% at 10 years. This grading system provides valuable information for assessing the prognosis and guiding the treatment of mucoepidermoid carcinoma.

Acinic Cell Carcinoma

Approximately 7–17.5% of malignant salivary gland tumours are acinic cell carcinomas.

Distribution of acinic cell carcinoma according to occurrence in various salivary glands is as follows:

- 80% of acinic cell carcinomas are found in the parotid.
- 20% are found in the submandibular and minor salivary glands.
- 1% is found in the sublingual gland.

Males predominate, and they begin to appear around the third decade of life [7].

Gross Findings

- Usually less than 3 cm, rubbery or hard tumours
- Typically limited (occasionally irregular)
- May exhibit bleeding or a cystic transformation

Microscopic Findings

The various growth patterns of acinic cell carcinoma are mentioned in Table 22.

Table 22 Growth patterns of acinic cell carcinoma [7]

Growth patterns of acinic cell carcinoma	
Growth pattern	Features
Solid	Lobules or nodules are formed when cells group together into sheets
Microcystic	The microcysts present give the tumour a sieve-like appearance
Papillary—cystic	Significant cysts with intraluminal papillary projections are seen in the tumour
Follicular	Include many cysts of various sizes that somewhat resemble thyroid parenchyma

- Serous acinar cells with basophilic zymogen granules in the cytoplasm are the distinctive cell type (usually accentuated at the lumen).
- Vacuolated and transparent cells are among the other types of cells.
- Follicular and solid growth patterns.
- TALP/infiltrate (tumour-associated lymphoid proliferation) is occasionally evident.

Ancillary Studies

- Zymogen granules are diastase-resistant and PAS-positive.
- Acinic cells may exhibit amylase, transferrin, lactoferrin, DOG1 and SOX10-positive staining.
- Ten percent or so demonstrate some S100-positive protein (usually weaker than adjacent nerves).

Fine-Needle Aspiration

- Clear cellular stains on a backdrop.
- Cohesive, compact and close clusters.
- There is a lot of granular to vacuolated cytoplasm around the spherical, regular nuclei. The chromatin is coarse (lymphocyte-like nuclei).

Adenoid Cystic Carcinoma

- Ten to 12% of malignant salivary gland tumours are adenoid cystic carcinomas (ACC).
- Submandibular gland cancer is the most prevalent kind.
- It accounts for 30–50% of small salivary gland neoplasms and around 5% of parotid neoplasms.
- No gender preference.
- Most prevalent between the fourth and sixth decades, infrequent in people under the age of 20 [7].

Gross Findings

- Typically solid, frequently well-circumscribed, but not encased

Microscopic Findings

- Including modified myoepithelial cells and duct lining cells.
- In a decreasing order of occurrence, the primary patterns are cribriform, tubular and solid; mixed patterns are frequent.
- Pseudocysts contain hyaline, eosinophilic or basophilic mucoid substance (reduplicated basement membrane material).
- Perineural invasion occurs often and is usually severe.
- Small cells have a large nuclear-to-cytoplasmic ratio.
- Nuclei have a dense distribution of nuclear chromatin and can range in form from carrot-shaped to peg-shaped.
- In ACC with high-grade transformation, stroma is desmoplastic and hyalinized in typical ACC.

According to the prevalent development pattern, ACC may be rated [7]:

- Grade I—Most of which are tubular, and some of which are cribriform.
- Grade II—Cribriform/tubular having less than 30% solid component or fully cribriform.
- Grade III—Any tumour that has solid growth that is higher than 30%.

Ancillary Studies

- Pseudocysts are positive for type IV collagen, laminin, PAS and Alcian blue.
- Low-molecular-weight keratins, EMA and CD117-positive epithelial cells.

Fine-Needle Aspiration

- Cellular smears that are often cohesive sheets of monotonous, sporadic epithelial cells.
- Hyaline globules, which are best observed on air-dried preparations and are reduplicated basement membrane material that resembles pink ‘gum balls’, are surrounded by cells (bright magenta on Romanowsky stains).
- High nuclear-to-cytoplasmic ratio cells contain hyperchromatic nuclei that are peg-shaped or cuboidal.

Carcinoma Ex-Pleomorphic Salivary Adenoma

A carcinoma ex-pleomorphic adenoma develops within or at the location of an earlier pleomorphic adenoma, roughly 6.2% of all pleomorphic

adenomas and 12% of all salivary gland tumours [7, 21].

Risk factors for a pleomorphic adenoma's development into cancer include [7, 21]:

- Older age of the patient (mean, 61 years)
- Male gender
- Prolonged duration of tumour
- Multiple recurrences

The sublingual gland and the parotid gland are less frequently affected.

Gross Findings
- Larger than its benign equivalent.
- Tan-white, firm, poorly delimited, heavily infiltrative masses.
- Sometimes they are well-circumscribed and seem contained.
- The malignant component, assuming it is, tends to radiate centrifugally from this nidus.

Microscopic Findings
- High-grade adenocarcinoma and salivary duct carcinoma, frequently with squamoid differentiation, make up the malignant component in most cases.
- Salivary carcinoma also occurs in other particular subgroups, some of which are monotypic rather than mixed.
- Pleomorphic adenoma, carcinoma and sarcoma (also known as carcinosarcoma, a truly malignant mixed tumour) are extremely uncommon together.

The prognostic importance of the tumour invasion into the capsule of the initial lesion has been described as [7]:

1. Intracapsular carcinoma
2. Minimally invasive carcinoma (less than 4–6 mm invasion)
3. Widely invasive carcinoma

In principle, [1] and [2] have a favourable prognosis compared to [3].

Lymphomas

The second most frequent primary cancer that affects the head and neck is lymphoma. The head and neck region is where around 25% of extranodal lymphomas are found.

An interested reader is directed to the detailed WHO classification of tumours of haematopoietic and lymphoid tissue after reading this general review of lymphoma (fourth edition, 2008) [22].

Non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) are the two main types of lymphomas (NHL).

Hodgkin Lymphoma (HL)
- Characterized by Reed-Sternberg cells
- Subdivided into:
  - Classical HL:
    - Nodular sclerosing
    - Mixed cellularity
    - Lymphocyte-rich
    - Lymphocyte-depleted
  - Nodular lymphocyte predominant HL

These traditional HL subtypes are divided based on the location of involvement, clinical characteristics, growth pattern, cellular background composition, presence of fibrosis, number and/or degree of atypia of the tumour cells and frequency of EBV infection. Neoplastic cells in all of these subtypes share the same immunophenotype.

Non-Hodgkin Lymphoma (NHL)
- The majority of NHLs—about 85%—are B-cell lymphomas.
- Among aggressive NHLs, diffuse large B-cell lymphoma is the most prevalent.
- Aggressive NHLs that can occasionally be seen in the head and neck area include Burkitt lymphoma and mantle cell lymphoma.
- Rarely observed in the head and neck area are plasma cell neoplasms, most frequently plasma cell myeloma and extramedullary plasmacytoma.
- The head and neck skin may be affected by cutaneous T-cell NHLs; however mucosal areas are seldom affected.
- Strongly linked to EBV infection, extra-nodal NK/T-cell lymphoma prefers the upper aerodigestive tract, often the nasal cavity. It is angiocentric and angio-destructive in nature, mimicking the histological characteristics of polyangiitis in granulomatosis.

Malignant Mesenchymal Tumours

In the head and neck area, malignant mesenchymal tumours (sarcomas) include:

- Liposarcoma
- Rhabdomyosarcoma
- Malignant fibrous histiocytoma
- Osteosarcoma
- Kaposi sarcoma
- Chondrosarcoma
- Angiosarcoma
- Synovial sarcoma
- Mesenchymal chondrosarcoma
- Leiomyosarcoma
- Malignant peripheral nerve sheath tumour

Neuroectodermal Tumours

Mucosal Malignant Melanoma

An uncommon kind of tumour called mucosal malignant melanoma develops from melanocytes that are generated from the neuroectoderm [23].

Epidemiology

- Roughly 15–20% of cases occur in the head and neck, and more than 80% have cutaneous or upper aerodigestive tract origins.
- Between 0.5 and 3% of malignant melanomas across all sites are mucosal [24].
- The sinuses and oral cavity, particularly the palate, are frequent locations for mucosal malignant melanoma.
- More typical in males (findings are not consistent).
- A broad age span (20 to 80).

Gross Findings

- Depending on the quantity of melanin produced, they are often pigmented and range in colour from a light tan to black.

Microscopic Findings

- Often made up of spindle and/or epithelioid cells.
- The cells have a distinct pleomorphic appearance and might be pigmented.
- Intra-nuclear inclusions are common, and nucleoli are obvious.
- Necrosis and inflammatory infiltrates might also be found nearby.
- Melanocytic atypia or melanoma in situ may be seen in the background mucosa.
- For the S100 protein, cells exhibit nuclear and cytoplasmic positivity.
- Typically, MelanA, HMB-45 and SOX10 are positive.
- Epithelial markers are negative.
- All these indicators may not be present in the desmoplastic form of melanoma.

Olfactory Neuroblastoma

Uncommon sinonasal malignant tumour originating from the superior turbinate, cribriform plate and superior third of the nasal septum affects the specialized olfactory mucosa.

There is no sex- or race-specific preference, and the reported incidence is four instances per million with a bi-modal distribution in the second and sixth decades [7].

Gross Findings

- Soft, highly vascular, polypoidal, mucosa-covered tumour.

Microscopic Findings

- The chromatin of the malignant cells is finely stippled (like salt and pepper); has tiny, spherical nuclei and little cytoplasm; and is homogenous.

Table 23 lists the four grades of olfactory neuroblastoma according to Hyams' categorization scheme [25].

Table 23 Hyams' grading classification of olfactory neuroblastoma [25]

Hyams' grading classification of olfactory neuroblastoma				
Histological feature	Grade I	Grade II	Grade III	Grade IV
Architecture	Lobular	Lobular	May be lobular	May be lobular
Mitoses	Absent	Present	Prominent	Marked
Nuclear pleomorphism	Absent	Present	Prominent	Marked
Neurofibrillary matrix	Prominent	Present	May be present	Absent
Rosettes	Homer-Wright rosettes	Homer-Wright rosettes	Flexner-Wintersteiner rosettes	Flexner-Wintersteiner rosettes
Necrosis	Absent	Absent	Present	Prominent

However, there is not a single distinct positive indication.

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