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Review

Epidemiology, diagnosis, symptoms and TNM classification of head and neck cancers

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Abstract

Head and neck cancers occur predominantly by transformation of squamous cells lining the mucous membranes of the upper aerodigestive tract and affect one of the most complex regions of the human body. Head and neck cancers are very common, with more than half a million new cases annually, and have a mortality rate of around 50%, and early diagnosis can improve treatment outcomes and increase the life expectancy of those affected. In this paper, we review the epidemiology, the main symptoms, the diagnostic methods, highlighting the few genetic markers identified so far, and the TNM classification of each type of upper aerodigestive cancer.

Keywords head and neck cancer, epidemiology, diagnosis, symptoms, TNM classification

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Introduction

The head and neck region is very complex and comprises the organs and all the tissue structures of the upper airways (nasal cavity; oral cavity and its appendages, including the lips, oral floor, hard palate, palatine veil, tongue, gums and salivary glands; pharynx, with its three sectors: nasopharynx, oropharynx and laryngopharynx, or hypopharynx, with the tonsils and Eustachian tube communicating with the middle ear; larynx, with the vocal cords), where the cancers of the head and neck, cranial cavity, eyes, ears, their appendages, endocrine glands, cervical spine, all cranial and cervical musculature, and the blood vessels, nerves and integument covering them occur (*fig. 1*). In this context, head and neck cancers (ICD-10 code) define only tumours of the upper aerodigestive tract and include a wide variety of malignancies of epithelial origin (*Table 1*).

More than 90% of head and neck cancers originate in the squamous cells lining the mucous membranes of the upper aerodigestive tract and are some of the most common cancers, with more than half a million new cases annually. They also have a high mortality despite cytoreductive surgery, radiotherapy and chemotherapy (when necessary), as diagnosis occurs at advanced stages with involvement of regional lymph nodes. Early diagnosis of head and neck cancers can replace the need to combine surgical resection with radiotherapy with radiotherapy treatment alone, with reduced recovery time and fewer complications after surgery. Distant metastasis is rare and occurs in less than 10% of cases. Survivors of head and neck cancers carry the risk of death for the rest of their lives due to heart and respiratory problems and the development of second primary tumours, especially in smokers. Secondary primary tumours can affect any part of the aerodigestive tract and are developed by 3-5% of cases each year. Head and neck cancers are multistep processes, frequently triggered by mutations in a single gene produced by carcinogens and leading to significant dysregulation of metabolic processes.

Table 1. Major types of neoplasms of the head and neck region according to the 10th revision (ICD-10) of the International Statistical Classification of Diseases and Related Health Problems, 2019 [1,2].

ICD-10 code	Main site of neoplasy
C00	Malignant neoplasms of lip
C01	Malignant neoplasm of base of tongue
C02	Malignant neoplasm of other and unspecified part of tongue
C03	Malignant neoplasm of gum
C04	Malignant neoplasm of floor of mouth
C05	Malignant neoplasm of palate
C06	Malignant neoplasm of other and unspecified parts of mouth
C07	Malignant neoplasm of parotid gland
C08	Malignant neoplasm of other and unspecified major salivary glands
C09	Malignant neoplasm of tonsil
C10	Malignant neoplasm of oropharynx
C11	Malignant neoplasm of nasopharynx
C12	Malignant neoplasm of piriform sinus
C13	Malignant neoplasm of hypopharynx
C14	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
C30	Malignant neoplasm of nasal cavity and middle ear
C31	Malignant neoplasm of accessory sinuses
C32	Malignant neoplasm of larynx
C76	Malignant neoplasm of other and ill-defined sites

The main factor causing head and neck tumours is smoking (active and passive), followed by alcohol consumption, alone or in combination with smoking, viral infections such as HPV (human papillomavirus) and EBV (Epstein-Barr virus), chewing Areca nuts in the form of betel quid, other eating habits which can also introduce carcinogens into the

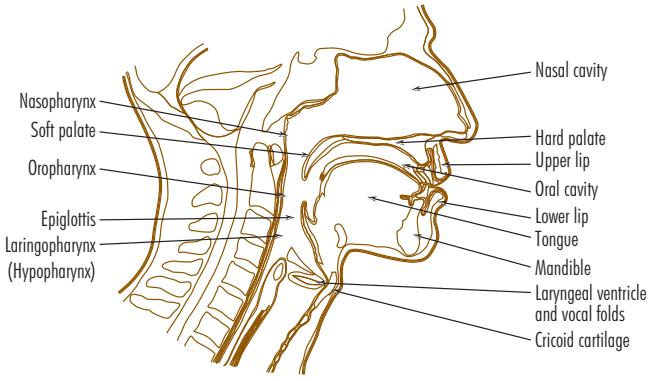

Figure. 1. Sagittal section through the head and neck region, showing the main anatomical landmarks used to define head and neck cancers.

body, as well as oral hygiene and the compounds with which people in various occupations come into contact [3–6]. From a molecular point of view, head and neck cancers are poorly known and characterized, although there are references on: (1) the positive correlation of N6-adenosine methylation and tumorigenesis of head and neck cancers [7]; (2) the relationship between increased expression of programmed death receptor 1 (PD1) and its ligand (PDL1) and increased size of head and neck tumors, suggesting the inclusion of these two molecules among tumor markers of laryngeal cancers and monoclonal antibodies in therapeutic regimens targeting laryngeal tumors [8]; (3) the possibility of using mi-RNAs (microRNAs - non-coding RNAs of about 22 nucleotides, involved in the post-translational regulation of gene expression) as biomarkers for head and neck cancers [9].

Epidemiology of head and neck cancers

Globally, the incidence of head and neck cancers ranks sixth, accounting for about 6% of all cancers (estimated 650,000 new cases annually) [3]. Thus, in 2020, the incidence of head and neck cancers was 699,840 cases in men (264,211 cases of lip and oral cavity cancers, 29,694 cases of salivary gland cancers, 79,045 cases of oropharyngeal cancers, 96,371 cases of nasopharyngeal cancers, 70,254 cases of laryngopharyngeal or hypopharyngeal cancers and 160, 265 cases of laryngeal cancers) and 232,091 cases in women (113,502 cases of lip and oral cavity cancers, 23,889 cases of salivary gland cancers, 19,367 cases of oropharyngeal cancers, 36,983 cases of nasopharyngeal cancers, 14,000 cases of laryngopharyngeal or hypopharyngeal cancers and 24,350 cases of laryngeal cancers). The mortality rate in people who develop head and neck cancers is very high, at around 350,000 annually. Thus, the total number of deaths in people with head and neck cancers in 2020 was 353,713 in men (125,022 cases of lip and oral cavity cancers, 13,353 cases of salivary gland cancers, 39,590 cases of oropharyngeal cancers, 58,094 cases of nasopharyngeal cancers, 32,303 cases of laryngopharyngeal or hypopharyngeal cancers and 85, 351 cases of laryngeal cancers) and 113,412, in women (52,735 cases of lip and oral cavity cancers, 9,425 cases of salivary gland cancers, 8,553 cases of oropharyngeal cancers, 21,914 cases of nasopharyngeal cancers, 6,296 cases of laryngopharyngeal or hypopharyngeal cancers and 14,489 cases of laryngeal cancers) [10]. The overall incidence of head and neck cancers shows an increasing trend in both developed and developing countries, with the Southeast Asia and Asia-Pacific regions showing an increasing number of oral cancers due to the habit of chewing Areca nuts (betel quid, a highly potent drug), whether or not associated with smoking, while in Europe and the USA, HPV infection (*fig. 2*). By 2030, the number of cases may increase by 30% annually [2]. The incidence of head and neck cancers is at least twice as high in men as in women, with the proportions varying by country. For example, according to https://gco.iarc.fr/today/, in Romania, where the incidence of head and neck cancers in both sexes is 19.0/100,000 inhabitants (ranking third in the world after Papua New Guinea with 26.7/100,000 and Bangladesh with 22.2/100,000), the incidence in men is 35.8/100,000 (the second highest after Papua New Guinea with 37.6/100,000), while in women it is much lower at 4.1/100,000. The gender gap tends to become smaller in some countries, such as Papua New Guinea, with a total incidence of 26.7/100,000 population (37.6/100,000 for men and 17.1/100,000 for women), India, with a total incidence of 17.0/100,000 population (26.3/100,000 for men and 7.0/100,000 for women) and the United Republic of Tanzania, with a total incidence of 4.4/100,000 for men and 4.4/100,000 for women. 6/100,000), France, with a total incidence of 16.2/100,000 (men 24.8/100,000 and women 8.5/100,000), United Kingdom, with a total incidence of 11.4/100,000 (men 16.2/100,000 and women 6.8/100,000), USA, with a total incidence of 10. 4/100,000 inhabitants (in men 15.8/100,000 and in women 5.4/100,000), Germany, with a total incidence of 10.3/100,000 inhabitants (in men 14.9/100,000 and in women 5.9/100,000), or Israel, with a total incidence of 5.1/100,000 inhabitants (in men 7.1/100,000 and in women 3. 4/100,000), or even close to balance in other countries, including Saudi Arabia, with a total incidence of 4.4/100,000 (in men, 5.1/100,000, and in women, 3.3/100,000), or the United Mexican States, with a total incidence of 2.7/100,000 (in men, 3.5/100,000, and in women, 2.0/100,000).

Main symptoms

Depending on location, head and neck cancers produce a plethora of symptoms. Thus, cancers occurring in the nasal cavity and nasopharynx may unilaterally obstruct the airways, reduce olfactory sensitivity, produce mucus, with or without the presence of blood, which may flow outwards or inwards towards the throat. Oral or oropharyngeal cancers may initially appear as single or multiple precancerous lesions or as persistent ulcerations due to viral or fungal infections (e.g. candida leukoplakia), repeated consumption of betel quid or other causes. They may progress to oral or oropharyngeal cancers synchronous (occurring simultaneously or up to 6 months after lesion formation) or metachronous (occurring more than 6 months after lesion formation), which may occupy less or more space in the oral cavity or oropharynx, affecting the digestive function of these organs. Laryngopharyngeal (hypopharyngeal) cancers can cause persistent sore throat, earache, painful swallowing and hoarseness. On the

other hand, pharyngeal cancers (of the nasopharynx, oropharynx and laryngopharynx) cause obstruction of the pharynx and frequently dysphagia and sore throat much delayed after onset, as well as painless damage to a cervical lymph node. Due to impaired vocal cord functionality, laryngeal cancers frequently produce hoarseness, while cancers of the epiglottis area cause difficulty swallowing. Head and neck cancers also produce many non-specific symptoms, such as enlargement of cervical lymph nodes, unilateral otalgia (ear pain) or wheezing, which can be mistaken for other conditions, delaying correct diagnosis. Persistent enlargement of cervical lymph nodes in people aged 30-50 years, non-smokers and non-smokers who do not consume excessive alcohol or betel quid, may be caused by the presence of small tonsillar tumours of viral (HPV) origin, which may be mistaken for benign conditions, delaying their correct diagnosis. Unilateral pain occurring in people over 30 years of age without signs of otitis may be caused by neoplasms of the pharynx. In people over 40 years of age who smoke heavily or drink alcohol excessively, the occurrence of wheezing may be caused by slow-growing laryngeal neoplasms, although these can be diagnosed as bronchial asthma [11,4].

Diagnosis of head and neck cancers

The appearance of one or more of the symptoms listed may be just one indication of the likelihood of developing head and neck cancer and a good reason to visit the doctor. Most of the time, these are not sufficient for an accurate diagnosis of head and neck cancer, but are the start of more detailed investigations, including direct visual assessment or endoscopy, biopsy, imaging explorations and detection of specific biomarkers. To begin with, the doctor will perform

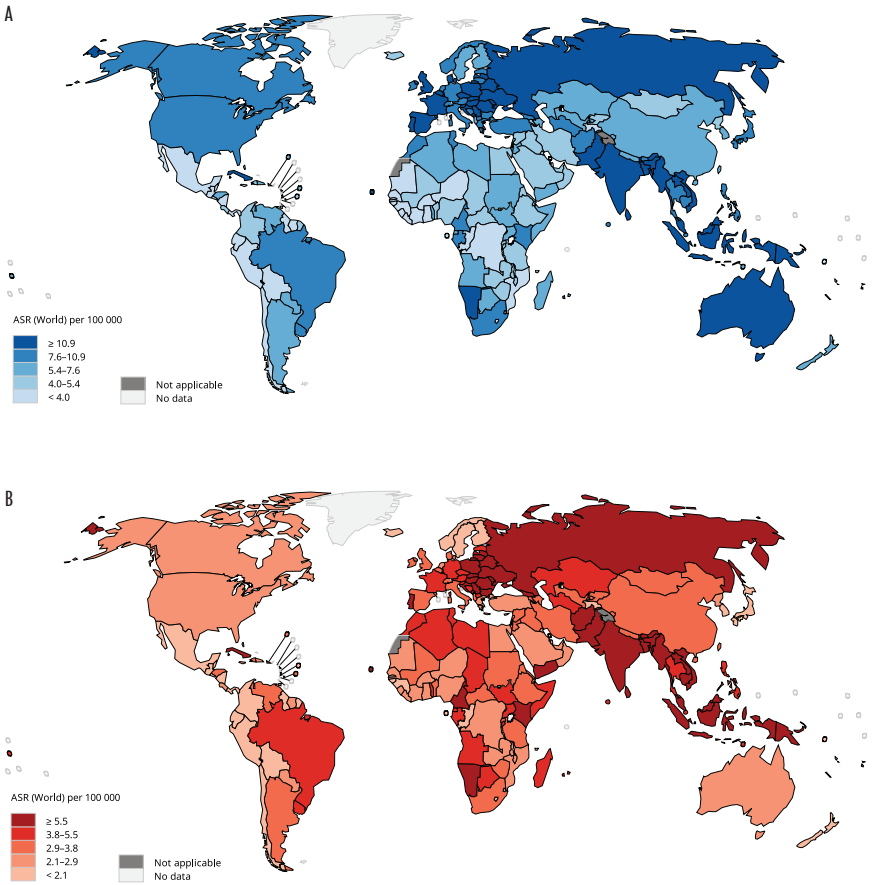

Figure. 2. World estimated age-standardized incidence rates in 2020, for head and neck (lip, oral cavity, larynx, hypopharynx, nasopharynx, salivary glands, and oropharynx) cancers, for both sexes of all ages. Maps are reprinted from International Agency for Research on Cancer, Cancer today – Data visualization tools for exploring the global cancer burden in 2020, Copyright 2022, available at http://gco.iarc.fr/today, and accessed in December 2022.

a visual assessment of accessible tissues to identify areas of macroscopically altered appearance. When these are not directly accessible, endoscopic examination of the suspicious area may be recommended. In endoscopy, an endoscope (a tube with a camera and a light at the tip) is used, which, in the case of upper aerodigestive tract explorations, is inserted through the nose or mouth. In the upper aerodigestive sphere, three common types of endoscopy are possible, nasopharyngoscopy, pharyngoscopy or laryngoscopy, which require local anesthesia, and the fourth type, panendoscopy, which requires general anesthesia [12].

After identifying the suspicious area, the physician will extract a tissue sample, necessary for microscopic or molecular examination (biopsy), which will allow him to correctly diagnose the altered area [13]. The biopsy is minimally invasive, surgical or aspiration. Thus, minimally invasive biopsy usually requires very small incisions (2-5 mm) and consists of sampling using a needle, directed by duplication with radiology imaging, ultrasound or CT. Recovery from the minimally invasive biopsy procedure occurs within 48 hours and results are released after two working days. Surgical biopsy is invasive, consists of making an incision to remove a tissue sample or tumour nodule, and may require local or general anesthesia. Because some tumours, such as appendiceal tumours, are discovered during or after appendectomies, by pathological examination, the incision is larger, deeper and leads to removal of the entire affected organ. In head and neck squamous cell carcinomas, surgical biopsies are much less extensive. Fine needle aspiration biopsy is the insertion of a very fine needle into areas of altered tissue, from which a small sample is taken to check for neoplastic cells. Generally, biopsy specimens are sent for pathological examination. This may be limited to staining of the sample, microscope slide staining and microscopic visualization for identification of transformed cells, or may include paraffin embedding for immunohistochemical examination [14].

After receiving results confirming the presence of transformed cells in the suspicious area, detailed imaging exploration of the area of interest may be performed by computed tomography (CT) scan, MRI scan, PET scan or ultrasound. Computed tomography is the acquisition of a suite of images of the area of interest using a source of X-rays that passes through living tissue and capture the signals via a computer-connected device, where they appear as image files. By viewing the image sequences, doctors observe the three-dimensional extent of the tumour and its relationship to neighbouring structures. Nuclear magnetic resonance MRI scans use magnetic fields and radio waves to capture detailed image sequences of the head and neck region, which are then stored in a computer and provide information on the extent of the tumour and its relationship to neighbouring tissues. Both CT and MRI scans can use contrast agents, through which tissue structures are better highlighted. PET (positron emission tomography) scans use a radioactive tracer (dye) administered intravenously, which provides very detailed detail about the health and function of organs and tissues at the microscopic level, generating images that provide clues to the presence of tumour transformation before it becomes visible on other types of images [15,14]. In head and neck squamous cell carcinomas, a very useful tool for diagnosis, staging and assessment of response to treatment is positron emission tomography using 18F-fluorodeoxyglucose (FDG-PET). Applied to patients with cervical lymph node metastases and unidentified origin, this method can identify the primary tumour in 25-38.5% of cases [15,16].

Earlier studies of head and neck cancers in the early third millennium identified several chromosomal aberrations, such as amplification of the 11q13 region, and genetic aberrations, including in *TP53* (Tumor Protein 53/Tumor Suppressor P53), *EGFR* (Epidermal Growth Factor Receptor), *STAT3* (Signal Transducer And Activator Of Transcription 3), *VEGFR* (Vascular Endothelial Growth Factor Receptor), *RB*, including *RB1* (RB Transcriptional Corepressor 1), *RBL1* (RB Transcriptional Corepressor Like 1) and *RBL2* (RB Transcriptional Corepressor Like 2), *p16/INK4A/CDKN2AI* (Cyclin Dependent Kinase Inhibitor 2A), *CCND1* (Cyclin D1), *XRCC1* (X-Ray Repair Cross Complementing 1) and *XPD/ERCC2* (ERCC Excision Repair 2, TFIIH Core Complex Helicase Subunit), affecting the functionality of the proteins encoded by them and signal transduction through the signaling pathways in which they are included [17–21]. Since the introduction of modern sequencing techniques (next-generation sequencing, NGS), knowledge of genetic alterations in some subtypes of these tumours has been continuously enriched, with the signaling of mutations in *PIK3CA* (Phosphatidylinositol-4, 5-Bisphosphate 3-Kinase Catalytic Subunit Alpha), *HRAS* (HRas Proto-Oncogene, GTPase), *PTEN* (Phosphatase And Tensin Homolog), *NOTCH1* (Notch Receptor 1) [22], *OGG1* (Human 8-oxoguanine glycosylase 1, the enzyme responsible for excision 7, 8-dihydro-8-oxoguanine, a mutagenic by-product resulting from exposure to reactive oxygen species) [23], *CHECK2* (Checkpoint Kinase 2), *ATR* (ATR Serine/Threonine Kinase), involved in the TP53 signaling pathway, which determines the fate of cells whose genetic material is altered, in HPV-negative smokers) [24], *RAD51C* (RAD51 Paralog C) [25], *FAT1* (FAT Atypical Cadherin 1), *AJUBA* (Ajuba LIM Protein), both involved in the WNT signaling pathway; in addition, *AJUBA* undergoes EGFR–RAS–RAF–MEK–ERK-dependent phosphorylation and participates in the HIPPO signaling pathway and in the ATR-mediated response

to DNA damage), *NSD1* (histone methyltransferase H3K36), *TRAF3* (TNF Receptor Associated Factor 3), *NFE2L2* (NFE2 Like BZIP Transcription Factor 2), *CASP8* (Caspase 8, whose product is involved in the caspase pathway of apoptosis), *KMT2D/MLL2* (Lysine Methyltransferase 2D, involved in chromatin remodeling), *HLA-A/CMH-IA* (Major Histocompatibility Complex, Class I, A, involved in immune surveillance, which becomes deficient when mutated), *SCN9A* (Sodium Voltage-Gated Channel Alpha Subunit 9), *PTCH1* (Patched 1), *MYC* (MYC Proto-Oncogene, BHLH Transcription Factor) and *PIK3R1* (Phosphoinositide-3-Kinase Regulatory Subunit 1). In addition to these, whole exome sequencing of oral squamous cell carcinomas from Taiwanese men also identified mutations in *RASA1* (RAS P21 Protein Activator 1), *CHUK* (Component of Inhibitor of Nuclear Factor Kappa B Kinase Complex) and *ELAVL1* (ELAV Like RNA Binding Protein 1) genes, the latter two affecting the function of tumor suppressor and oncogene suppressor genes [26]. Rarely, the genes *ASXL1* (ASXL Transcriptional Regulator 1), encoding a transcription factor, and *RPTN* (Repetin), encoding an epithelial differentiation factor, are affected [27]. Of these, *TP53*, *HRAS*, *EGFR* and *PIK3CA* genes have important functions in cell survival and proliferation (wild-type *TP53* controlling them negatively and the other three positively), *CDKN2A* and *CCND1* in cell cycle control, *NOTCH1* in cell differentiation, and *FAT1* in cell invasiveness and adhesion. The most frequent somatic mutations occur in the *TP53* gene, with 50-80% of cases (predominantly in introns 4 and 6), in the early stages of carcinogenesis, and in *CDKN2A*, with important roles in the development of head and neck tumours (inactivation of p53 protein, encoded by *TP53*, being of major importance in preventing apoptotic guidance of genetically defective cells, and inactivation of p16 protein, encoded by *CDKN2A*, blocks cell cycle progression from G1 to S phase by inhibiting cyclin D1), followed by *FAT1*, *PIK3CA*, *NOTCH1*, *KMT2D/MLL2*, *NSD1*, *CASP8*, *AJUBA* and *NFE2L2* [27–29]. Early studies on genetic alterations in head and neck tumors showed that mutations in the TP53 gene are frequently reported in HPV-negative tumors and rarely in HPV-positive tumors, amid its inactivation by the viral protein E6 via ubiquitination [18–20,27].

Currently, there are a small number of biomarkers used for the diagnosis of head and neck squamous cell carcinomas, including HPV infection and specific molecular targets. Since HPV infection is present in approximately 90% of oral squamous cell carcinomas, the association between symptoms and HPV infection may lead to the diagnosis of these and oropharyngeal cancers [16]. For the assessment of the risk of malignancy of oral pre-malignant lesions, loss of heterozygosity for the 9p and 13p regions can be used as a molecular biomarker [30]. Candidate genes for use as biomarkers for head and neck cancers include *CDKN2A*, *ARF* (ADP Ribosylation Factor) (located in 9p21), *TP53* (located in 17p13), *PTEN* [31], *PD1* and *PDL1* [8], but these need to be validated. A 2019 study indicates the serum presence of three miRNAs (hsa-mir-383, hsa-mir-615 and hsa-mir-877) as an effective biomarker for the diagnosis of head and neck squamous cell carcinomas [32].

TNM classification of head and neck cancers

The TNM classification of head and neck cancers includes the same parameters considered in the general staging of tumours, T (presence of primary tumour), N (lymph node metastasis) and M (presence of metastases in distant regions).

Oral cancers

For the definition of the T-parameter, in oral cancers the largest size of these tumours and the depth of invasion (DOI) are taken into account, as deeper tumours increase the risk of ganglion metastasis and reduced survival, with an increase of 5 mm each advancing the category by one T stage. Assessment of primary tumour thickness is a criterion used in clinical staging and is performed by manual palpation by experienced surgeons, with primary tumours <5 mm considered thin, 5-10 mm thick and >10 mm very thick [33–35] (*Table 2*).

Table 2. T staging of oral cancers, according to AJCC Staging Manual [38]

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Primary tumor ≤ 2 cm, DOI ≤ 5 mm
T2	Primary tumor ≤ 2 cm, DOI > 5 mm and ≤ 10 mm or tumor > 2 cm and ≤ 4 cm, DOI ≤ 10 mm
T3	Primary tumor > 2 cm and ≤ 4 cm, DOI > 10 mm or tumor > 4 cm, DOI ≤ 10 mm
T4	Moderately/very advanced local disease
T4a	Moderately advanced local disease, with primary tumor > 4 cm, DOI > 10 mm or tumor invading adjacent structures only
T4b	Very advanced local disease, with primary tumor invading masticator space, pterygoid plates, or skull base and/or encasing the internal carotid artery

In addition to lymph node involvement, the definition of N-parameter categories also includes extra-nodal extension of lymph node metastases (ENE), as this greatly influences the prognosis of head and neck cancers, with the exception of HPV-positive tumours. Thus, correct identification, supported with radiological evidence, of the presence of extra-nodal ex-

enteration (ENE+), advances the N category to N3b, and inconclusive cases are categorized ENE– [35–37] (*Table 3*).

Table 3. N staging of oral cancers, according to AJCC Staging Manual [38]

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm, ENE(−)
N2	Metastasis in a single ipsilateral node > 3 cm and ≤ 6 cm, ENE(−); or metastases in multiple ipsilateral lymph nodes, ≤ 6 cm, ENE(−); or in bilateral or contralateral lymph nodes, ≤ 6 cm, ENE(−)
N2a	Metastasis in a single ipsilateral node > 3 cm and ≤ 6 cm, ENE(−)
N2b	Metastases in multiple ipsilateral nodes ≤ 6 cm, ENE(−)
N2c	Metastases in bilateral or contralateral lymph nodes ≤ 6 cm, ENE(−)
N3	Metastasis in a lymph node > 6 cm, ENE(−); or metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node > 6 cm, ENE(−)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

Oropharyngeal and laryngopharyngeal/hypopharyngeal cancers

In the TNM classification of oropharyngeal cancers, the presence or absence of HPV infection is taken into account due to the different biological behavior of the two types of cancers, with HPV-positive tumours offering better diagnosis and survival rates compared to HPV-negative ones [39]. For this reason, the T classification system has some peculiarities for each of the two tumour types, with the same categories maintained overall. Thus, for HPV-positive tumours the Tis category has been excluded, the T0 category is used only for HPV-positive metastatic lymph nodes, where the primary lymph node is considered the primary tumour, and the T4b category is eliminated (*Table 4*). For HPV-negative tumours, the T-system comprises a wider range of categories (*Table 4*), also found in laryngopharyngeal/hypopharyngeal carcinomas, with some particularities regarding the criteria (*Table 5*). The N classification of oropharyngeal cancers also takes into account the presence or absence of HPV. Thus, for HPV-positive oropharyngeal cancers, the transformation of at least one ipsilateral lymph node less than 6 cm in size is considered N1, contralateral or bilateral lymph nodes less than 6 cm in size are considered N2, and nodes larger than 6 cm are included in the N3 category [40,35] (*Table 6*). The N system for laryngopharyngeal/hypopharyngeal carcinomas is complex and includes the same categories as for oral carcinomas, similarly, the presence of extra-nodal extension (ENE+), advancing the N category to clinically N3b (*Table 7*).

Table 4. T staging of oropharyngeal cancers, according to AJCC Staging Manual [38]

HPV-positive oropharyngeal tumors	
T Category	**T Criteria**
T0	No primary identified
T1	Primary tumor ≤ 2 cm
T2	Primary tumor > 2 cm and ≤ 4 cm
T3	Primary tumor > 4 cm *or* extended to lingual surface of epiglottis
T4	Moderately advanced local disease, with primary tumor invading the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond
HPV-negative oropharyngeal tumors	
T Category	**T Criteria**
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Primary tumor ≤ 2 cm
T2	Primary tumor > 2 cm and ≤ 4 cm
T3	Primary tumor > 4 cm *or* extended to lingual surface of epiglottis
T4	Moderately advanced and very advanced local disease
T4a	Moderately advanced local disease, with primary tumor invading the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
T4b	Very advanced local disease, with primary tumor invading lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encasing carotid artery

Table 5. T staging of laringopharyngeal/hypopharyngeal cancers, according to AJCC Staging Manual [38]

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Primary tumor limited to one subsite of hypopharynx and/or ≤ 2 cm
T2	Primary tumor invades more than one subsite of hypopharynx or an adjacent site, or > 2 cm and ≤ 4 cm without fixation of hemilarynx
T3	Primary tumor > 4 cm or with fixation of hemilarynx or extension to esophageal mucosa
T4	Moderately advanced and very advanced local disease
T4a	Moderately advanced local disease, primary tumor invading thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophageal muscle or central compartment soft tissue
T4b	Very advanced local disease, primary tumor invading prevertebral fascia, encasing carotid artery, or involving mediastinal structures

Table 6. N staging of oropharyngeal cancers, according to AJCC Staging Manual [38]

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none > 6 cm
N2	Contralateral or bilateral lymph nodes, none > 6 cm
N3	Lymph node(s) > 6 cm

Table 7. N staging of laringopharyngeal/hypopharyngeal cancers, according to AJCC Staging Manual [38]

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node ≤ 3 cm, ENE(−)
N2	Metastasis in a single ipsilateral node > 3 cm and ≤ 6 cm, and ENE(−); or metastases in multiple ipsilateral lymph nodes ≤6 cm, and ENE(−); or in bilateral or contralateral lymph nodes ≤ 6 cm, and ENE(−)
N2a	Metastasis in a single ipsilateral node > 3 cm ≤ 6 cm, and ENE(−)
N2b	Metastases in multiple ipsilateral nodes ≤ 6 cm, and ENE(−)
N2c	Metastases in bilateral or contralateral lymph nodes, ≤ 6 cm, and ENE(−)
N3	Metastasis in a lymph node > 6 cm, and ENE(−); or metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node > 6 cm, and ENE(−)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

Table 8. T staging of nasopharyngeal cancers, according to AJCC Staging Manual [38]

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No tumor identified, but EBV-positive cervical node(s) involvement
Tis	Tumor in situ
T1	Tumor confined to nasopharynx, or extension to oropharynx and/or nasal cavity with no parapharyngeal involvement
T2	Tumor extended to parapharyngeal space, and/or to adjacent soft tissue (including medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle

Table 9. N staging of nasopharyngeal cancers, according to AJCC Staging Manual [38]

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

Nasopharyngeal cancers

The TNM classification of nasopharyngeal cancers takes into account the presence of EBV infection, parapharyngeal structures involvement, lymphatic spread in the retropharyngeal and cervical lymph nodes, which is present from an early age and occurs in an orderly pattern, from close to close, without gaps, from the upper to the lower throat [41,42]. Metastatic lymph node hyperplasia to more than 6 cm or extension below the cricoid cartilage provides the worst prognosis. Because nasopharyngeal carcinomas are at increased risk of distant metastasis to the lung, bone, liver or distant lymph nodes, their TNM classification also includes category M, with a value of 0 for no distant metastasis and 1 for the presence of distant metastasis [38] (*Tables 8–9*).

Cancers of the nasal cavity and maxillary sinuses

Nasal cavity and maxillary sinus cancers have a differentiated course depending on the area of the maxillary sinus involved, with cancers extending into the antero-inferior portion of the maxillary sinus (infrastructure) having a favorable prognosis and those extending into the posterosuperior portion of the maxillary sinus (superstructure) having a poor prognosis, as they invade early on the critical structures at the base of the skull, including the orbit, pterygoid processes and infratemporal fossa. In terms of T staging, nasal cavity and maxillary sinus cancers are subdivided into maxillary sinus cancers and nasal cavity and ethmoid sinus cancers (*Table 10*). Nasal cavity and maxillary sinus cancers typically do not involve the regional lymph nodes, this occurs through the extension of maxillary sinus cancers, and the extra-nodal extension of metastases passes the tumour directly to stage N3 (*Table 11*). When present (M1), distant metastasis occurs in the lungs and rarely in the bones [38].

Table 10. T staging of maxillary sinus, and nasal cavity and ethmoid sinus cancers, according to AJCC Staging Manual [38]

Maxillary sinus		Nasal cavity and ethmoid sinus	
T Category	**T Criteria**	**T Category**	**T Criteria**
TX	Primary tumor cannot be assessed	TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ	Tis	Carcinoma in situ
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone	T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates	T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses	T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4	Moderately advanced or very advanced local disease	T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease, primary tumor invading anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses	T4a	Moderately advanced local disease, primary tumor invading any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Very advanced local disease, primary tumor invading any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus	T4b	Very advanced local disease, primary tumor invading any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V2), nasopharynx, or clivus

Table 11. N staging of maxillary sinus, and nasal cavity and ethmoid sinus cancers, according to AJCC Staging Manual [38]

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node ≤ 3 cm, and ENE(−)
N2	Metastasis in a single ipsilateral node > 3 cm and ≤ 6 cm, and ENE(−); or metastases in multiple ipsilateral lymph nodes, ≤ 6 cm, and ENE(−); or in bilateral or contralateral lymph nodes ≤ 6 cm, and ENE(−)
N2a	Metastasis in a single ipsilateral node > 3 cm and ≤ 6 cm, and ENE(−)
N2b	Metastases in multiple ipsilateral nodes ≤6 cm, and ENE(−)
N2c	Metastases in bilateral or contralateral lymph nodes ≤ 6 cm, and ENE(−)
N3	Metastasis in a lymph node > 6 cm, and ENE(−); or metastasis in any node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node > 6 cm, and ENE(−)
N3b	Metastasis in any node(s) with clinically overt ENE (ENEc)

Laryngeal cancers

Laryngeal cancers can occur in the supraglottic region, in the glottis or under the glottis. T-staging of supraglottic carcinomas takes into account the involvement of surrounding regions and vocal cord mobility, extension into the paralaryngeal fat in the preepiglottic space or erosion of the inner cortex of the thyroid cartilage advancing tumours to stage T3, whereas erosion of the outer cortex of the thyroid cartilage classifies tumours as T4a. T-staging of glottis tumours takes into account the impairment of vocal cord mobility, and T-staging of subglottic space tumours takes into account their extension to the vocal cords with impaired mobility, or disease progression to the cricoid or thyroid cartilages, in which case the tumours are stage T4 (*Table 12*). Lymph node metastasis and hyperplasia are criteria used for N classification of laryngeal tumours. Extra-nodal extension of metastases directly moves the tumor to stage N3 [38] (*Table 13*).

Anatomical staging of head and neck cancers

Based on the association of TNM criteria, anatomical stages of head and neck tumours are defined, which indicate the size of the primary tumour and the extent of metastasis. Thus, low T parameters (Cis or T1–3) associated with N0, N1 or N2 and with M0 indicate early and middle stages in the development of neoplasia (Stage 0, I or II), and T4 generally characterises Stage IV, in which the disease is advanced. This stage is divided into stages IVA, in which the disease is moderately advanced and has local or regional spread, IVB, in which the disease is very advanced with local or regional spread, and IVC, in which the disease metastasizes to a distant site (*Tables 14–16*). Anatomical staging is a diagnostic and prognostic criterion for head and neck cancers [38].

Table 12. T staging of larynx cancers, according to AJCC Staging Manual [38]

	Supraglottis	Glottis	Subglottis
T Category	**T Criteria**	**T Criteria**	**T Criteria**
TX	Primary tumor cannot be assessed	Primary tumor cannot be assessed	Primary tumor cannot be assessed
Tis	Carcinoma in situ	Carcinoma in situ	Carcinoma in situ
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility	Tumor limited to the subglottis
T1a		Tumor limited to one vocal cord	
T1b		Tumor involves both vocal cords	
T2	Tumor 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	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage	Tumor limited to larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage
T4	Moderately advanced or very advanced	Moderately advanced or very advanced	Moderately advanced or very advanced
T4a	Moderately advanced local disease Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)	Moderately advanced local disease Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, cricoid cartilage, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)	Moderately advanced local disease Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Table 13. N staging of larynx cancers, according to AJCC Staging Manual [38]

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node ≤ 3 cm, and ENE(−)
N2	Metastasis in a single ipsilateral node, > 3 cm and ≤ 6 cm, and ENE(−); or metastases in multiple ipsilateral lymph nodes ≤ 6 cm, and ENE(−); or metastasis in bilateral or contralateral lymph nodes ≤ 6 cm, and ENE(−)
N2a	Metastasis in a single ipsilateral node > 3 cm and ≤ 6 cm, and ENE(−)
N2b	Metastases in multiple ipsilateral nodes < 6 cm, and ENE(−)
N2c	Metastases in bilateral or contralateral lymph nodes ≤ 6 cm, and ENE(−)
N3	Metastasis in a lymph node > 6 cm, and ENE(−); or metastasis in any lymph node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node > 6 cm, and ENE(−)
N3b	Metastasis in any lymph node(s) with clinically overt ENE(+)

Table 14. Anatomical staging of nasopharyngeal cancers [38]

Stage 0	Cis (Tis)	N0	M0
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Table 15. Anatomical staging of oropharyngeal/ hypopharyngeal cancers [38]

Stage 0	Cis (Tis)	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Table 16. Anatomical staging of laryngeal cancers [38]

Stage 0	Cis (Tis)	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N0	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Conclusions

More than 90% of head and neck cancers originate from squamous cells (squamous cell cancers of the head and neck), ranking 6th among all malignancies affecting the human body (with 931931 cases estimated in 2020 worldwide, followed by breast, with 2261419 cases in 2020, lung, with 2206771 cases in 2020, colon and rectum, with 1931590 cases in 2020, prostate, with 1414259 cases in 2020, and stomach, with 1089103 cases in 2020 [43,44]), invades, to some extent, neighbouring structures (thyroid and even tracheal cartilages, internal carotid artery, thyroid gland, eyeballs and bony structures, including orbits, jaw, infratemporal fossa, pterygoid processes, base of skull, mandible and cervical spine), metastasizes in a low proportion (about 10%) and has high mortality rate. Risk factors for head and neck cancers include smoking (active and passive), alcohol consumption, especially in combination with smoking, viral infections with HPV (human papillomavirus) and EBV (Epstein-Barr virus), chewing Areca nuts (betel quid), poor oral hygiene and other dietary or behavioral habits.

Symptoms of head and neck cancers are numerous and include obstruction of the upper airways, reduced olfactory sensitivity, mucus or blood production, ulceration of the oral cavity, sore throat, especially when swallowing, or earache, hoarseness, hyperplasia of the cervical lymph nodes and others.

The occurrence of some of these symptoms may indicate the likelihood of neoplasia in the upper aerodigestive sphere, which may be refuted or confirmed by specific investigations, including direct visual assessment, endoscopy, biopsy, imaging investigations and detection of specific biomarkers. Although affecting a relatively large number of genes, head and neck cancers have a small number of specific biomarkers, candidates include *CDKN2A*, *ARF*, *TP53*, *PTEN*, *PD1*, *PDL1* or a group of three miRNAs (hsa-mir-383, hsa-mir-615 and hsa-mir-877).

For TNM staging of head and neck cancers, categories T and N are relevant, the latter also taking into account the extra-nodal extension of lymph node metastases, while category M is only relevant for staging nasopharyngeal cancers and those arising in the nasal cavity and maxillary sinuses, in which cases distant metastases mainly target the lungs and bones. These categories are used to define anatomical stages of head and neck cancers with diagnostic and prognostic value for overall survival.

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