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Cancer of Oropharynx and Oral Cavity-Causes, Symptoms, Treatment and Reconstruction

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1. Introduction

Squamous cell carcinoma of the oropharynx is a common malignancy of the head and neck. World-wide age adjusted incidence rates for men and women 3.8 and 0.8 per 100.000 populations respectively, with a substantial variation in different regions and countries [1]. The primary location of oral cancer is an important prognostic factor because the affected anatomic area can determine the accessibility and extension of surgery [2]. Head and neck cancers (HNCs) of the lip, oral cavity, oropharynx, hypopharynx, and larynx predominantly begin in the squamous cells (ca. 90%) [3]. The low HNC survival rate is driven by both late diagnostic stage and risk-associated behaviors with long-term health consequences. Among patients with predictive markers for metastatic disease, nodal involvement and extracapsular tumor spread, survival rates 10%-25% [4-6]. Even after treatment, 30%-60% of patients diagnosed at late stage with succesfull remission will develop recurrent locoregional cancer or second primary cancers [5,6].

1.1. Pathophysiology

Our current knowledge of the carcinogenic process from infection to cancer in OPSCC is still limited and mostly extrapolated from the cervical cancer model.

HPVs are small viruses containing a circular double-stranded DNA genome of ca 8 kb organized into three major regions: (1) an upstream regulatory region (URR) that is the origin of replication and includes transcription factor-binding sites and controls gene expression, (2) an early region, encoding for six genes involved in multiple functions including viral replication and cell transformation (E1, E2, E4, E5. E6, E7), and (3) a late region, encoding for the L1 and L2 capsid proteins which self-assemble to yield the viron [7, 8].

More than 200 HPV genotypes have been identified[7]. Mucosal HPV types have been categorized into “high-risk” and “low risk” types according to their potential to induce malgnacy in the cervix [7, 8]. Among the HR-HPV types involved in head and neck carcinogenesis, HPV 16 is the most common, with a prevalence over the 80% in oropharyngeal cancer, followed by HPV18 (3%) [7, 9-12].

The mucosal lining of the tonsil and tonsillar crypts allows direct passage of not only immune cells but also of pathogens such as HPV [7]. When HPV infection is not cleared, its persistence can lead to a precancerous lesion that if it does not regress will eventually progress to invasive oropharyngeal cancer.

E6 and E7 early proteins have a main role in carcinogenesis due to HPV. E6 inhibits p53, while E7 binds to pRb, promotes its degradation and the release of the E2F transcription factor [7]. This results in the de-regulation of the G1/S cell cycle check point and the activation of S-phase re-entry and viral replication. pRb degradation also translates into the overexpression of p161, a tumor suppressor protein, and hallmark of HPV-16 positive cancer of the oropharynx.

Toll-like receptors (TLRs) are cell surface or intracellular transmembrane proteins which are xpressed on sentinel cells of the immune system such as macrophages and dendritic cells [12]. In addition, they are present on non-immune cells such as keratinocytes of skin [13] and oral mucosa [14] gastrointestinal [15] and female reproductive tract lining[16]. On these lining epithelia, TLRs act as sensors where they recognize pathogemns and are activated when the epithelium is disturbed. Microbial pathogen are characterized by specific arrangements of molecules known as pathogen-associated molecular patterns (PAMPs), which can be recognized by pattern-recognition receptors (PRRs), including TLRs[16]. TLRs are capable of recognizing bacterial, viral, fungal, and protozoal components. While their role as PRRs is important in host defense, it is their ability to regulate innate and adaptive immune responses via information from surface epithelial cells which is their most potent role, along with their ability to recruit immune cells[17-19]. Oral cancer develops in an immune cell-rich environment, where inflammatory cells in the tumor microenvironment establish an

anti-tumor response by secreting pro-inflammatory cytokines. The cancer cells may induce various mechanisms suppressing the anti-tumor response, such as regulating a network of suppressive cytokines and the recruitment of suppressive regulatory T-cells (Tregs). A previous study has shown that TLRs, particularly TLR2, play a role in Treg expansion and their suppressive capacity [18-20]. More keratinocytes in oral squamous cell carcinoma (OSCC) expressed TLR than keratinocytes in control epithelium [21].

Head and neck cancer cell lines and OSCC tissue specimens were found to express TLR3 and this was associated with high levels of expression and activity of NF-kB [22, 23]. Inhibition of TLR3 by siRNA resulted in decreased expression of the NF-kB-regulated oncogene c-myc and decreased cell proliferation [24].

2. Anatomical Aspects of Oropharynx and Oral Cavity

2.1. Oral Cavity

The anterior border of the oral cavity is defined by the intersection of the red lip (vermillion) and skin. The oral cavity site is bounded laterally by the cheek (buccal) mucosa. The posterior limit of the oral cavity is the intersection of the hard and soft palates superiorly, and the V-shaped line of circumvallate papillae of the tongue inferiorly. The eight subsites of the oral cavity are potential sites for the origin of HNSCC tumours and include the following: (i) the upper and lower vermillion lips; (ii) the buccal mucosa, which includes both cheek and inner lip mucosal linings; (iii) the lower alveolar ridge, which includes the mucosa lining the lateral and medial surfaces of the mandibular arch ending posteriorly at the mandibular ramus; (iv) the upper alveolar ridge, which includes the mucosa lining the lateral and medial surfaces of the maxillary arch; (v) the retromolar trigone mucosa, which lines the ascending mandibular ramus posterior to the third molar; (vi) the fl oor of mouth mucosa overlying the mylohyoid and hyoglossal muscles and also lining the undersurface of the tongue; (vii) the hard palate mucosa; and (viii) the oral tongue, which includes all portions of the tongue anterior to the circumvallate papillae. Understanding the oral cavity subsite boundaries is critical when assigning a tumour to an oral cavity or oropharyngeal origin, as the posterior limit of many oral cavity subsites abuts an oropharyngeal subsite. However, there are occasions when the true site of origin is not clinically discernible [25].

2.2. Oropharynx

The anterior border of the oropharynx is the intersection of the soft palate and the hard palate superiorly, and the circumvallate papillae inferiorly. Superiorly, a horizontal plane drawn through the posterior soft palate divides the oropharynx from the nasopharynx cephalad. A horizontal plane through the hyoid bone divides the oropharynx from the hypopharynx inferiorly. The seven primary subsites of the oropharynx include: (i) the palatine tonsils; (ii) the base of tongue, which includes the posterior third of the tongue behind the circumvallate papillae; (iii) the oral surface of the soft palate and uvula; (iv) the posterior pharyngeal wall; (v) the lateral pharyngeal walls; (vi) the mucosa of the anterior and posterior tonsillar pillars; and (vii) the glossotonsillar sulcus. Human papillomavirus (HPV)-related HNSCC tumours of the oropharynx originate most commonly in the lymphoid tissue of the palatine and lingual (base of tongue) tonsils [25, 26]. The oropharynx is situated approximately in the middle of the upper aerodigestive tract. It is directly in communication with the other sites of the head and neck, superiorly with the nasopharynx, anteriorly with the oral cavity, and posteroinferiorly with the supraglottic larynx and hypopharynx. Anatomically, it is bounded by the junction of the posterior extent of the hard palate superiorly, the circumvallate papillae of the tongue anteriorly, the hyoid bone inferiorly, and the pharyngeal walls in the posterolateral directions. The oropharynx is divided into four distinct subsites for the purpose of diagnosis and treatment planning.

There are (1) the base of tongue, (2) the tonsillar complex, (3) the soft palate, (4) the oropharyngeal walls.

2.3. Base of Tongue

The base of tongue is a muscular of the posterior tongue that is covered in squamous epithelium and contains numerous submucosal lymphoid nests; it is part of Waldeyer's ring. The base of tongue extends from the circumvallate papillae anteriorly to the base of the epiglottis inferiorly and to the glossopharyngeal sulci bilaterally. Primary tumors of the base of tongue cab grow either in an infiltrative , submucosal pattern that invade the intrinsic muscles of the tongue or in an exophytic pattern across the mucosa and into the lumen of the upper aerodigestive tract. As the tumors become larger, they go deeply through the intrinsic muscles of the tongue and affect the extrinsic musculature, inferiorly into the structures of the hypopharynx and larynx, or laterally to the glossopharyngeal sulci and tonsils. Tumors of the base of tongue tend to present with advanced stages since the tongue base is devoid of pain fibers, and lesions are frequently asymptomatic until quite large. However, due to the innervation of the base of tongue, tumors in this region can present with referred otalgia via cranial nerve IX as it joins the tympanic nerve (Jacobson's nerve) and the transverse the jugular foramen; this referred pain is typically deep in the ear canal. Tumors of the base of tongue frequently present with nodal metastases. The base of tongue frequently present with nodal metastases. The base of tongue drains to levels II, III and IV of the neck, as well as the retropharyngeal lymph node drainage is bilateral.

The base of tongue can be defined anteriorly by the circumvalate papillae, laterally by the glossopalatine sulci, and inferiorly by the vallecula [27]. The lymphatics of the BOT drain primarily to the upper two thirds of the jugular lymphatic chain, often bilaterally [28].

2.4. Tonsillar Complex

The tonsillar fossa is located between the palatoglossus and palatopharyngeus muscles, which when covered by their mucosa make up the anterior and posterior tonsillar pillars. Primary tumors of the tonsillar pillars can either grow as exophytic lesions along the mucosal surface, spreading onto adjacent subsites, such as the soft palate, tongue base, and pharyngeal walls, or as deeply invasive lesions into the stroma in an ulcerative or endolymphatic pattern. Advanced tumors are capable of significant submucosal spread, including invasion into the underlying pterygoid muscles and into adjacent regions of the head and neck, including the nasopharynx, hypopharynx, and larynx. Primary tumors may arise from the tonsillar pillars, the tonsillar fossae, or the tonsils themselves [28-30] .

Tumors of the tonsillar region frequently present with nodal metastases. The tonsillar region primarily drains to level II of the neck, but lymph nodes in level I and the retropharyngeal nodes may also be involved. Tumors that arise from the tonsillar fossa are more likely to involve lymph nodes than those from the tonsillar pillars. Since the tonsil is a lateral structure, bilateral lymphadenectomy is less common than other sites of the oropharynx. For tumors confined to the tonsillar fossa and posterior pillar, contralateral lymph node positivity is reported in up to 22 % of cases ; for tumors of the anterior pillar, this is only 6% [31].

The tonsillar complex is composed of the anterior and posterior tonsillar pillars, the true tonsil, and the tonsillar fossa. Primary tumors of the tonsillar complex frequently metastasize to the lateral nodes and the upper third of the ipsilateral jugular lymphatic chain, with a smaller proportion draining to the middle third of the jugular lymphatic chain [32].

2.5. Soft palate

The soft palate comprises one third of the posterior palate. The mucous membrane is a thin stratified squamous epithelium on both the nasal and oral surfaces. Near the Eustachian tubes this mucosa becomes stratified and ciliated. The minor salivary glands are present throughout the soft palate and extend into the uvula [34, 35]. The soft palate musculature includes the levator veli palatine, tensor veli palatine, uvula, palatoglossus, and the palatopharyngeus muscles. Anatomically, the soft palate attaches to the hard palate anteriorly and is contiguous with the tonsillar fossae on the lateral sides. The motor innervation of the muscles of the soft palate include cranial nerve V3 and X, which function to elevate the palate and close off the nasopharynx during swallowing and speech, preventing reflux of a food bolus superiorly and preventing breathinesss and nasality of phonation, respectively termed velopharyngeal incompetence (VPI). Five separate muscles form the substructure of the soft palate. The varying insertions and orientation are vital for deglutition and speech resonance, creating velopharyngeal competence. The other man function of the soft palate is to control the patency of the Eustachian tube. All the muscles of the soft palate are innervated by the pharyngeal branch of the vagus nerve except the tensor veli palatine, which receives its innervation from the medial pterygoid nerve from the mandibular branch of the trigeminal nerve [36].

Primary tumors of the soft palate typically arise from the squamous mucosa of the oral aspect of the soft palate. Lesions that arise from the nasopharyngeal portion are much less common. Typically, lesions grow along the mucosal surfaces and tend to be superficial. As the lesions increase in size, they may extend to the adjacent tonsillar fossae, pharyngeal walls, or the anterior palatoglossal arches. Compared to other sites of the oropharynx, lesions tend to be more symptomatic and present at earlier stages.

The soft palate is defined anteriorly by the hard palate, laterally by the palatopharyngeal and superior pharyngeal constrictor muscles and posteriorly by the palatopharyngeal arch and uvula. The lymphatics of the soft palate have three distinct systems, which drain (1) medially to the middle third of the jugular chain, (2) laterally to the retropharyngeal (RP) lymphatics, and (3) anteriorly to the hard palate and subsequently into the submental and submandibular nodal groups[37]. The lymphatics in the uvula drain primarily into the upper jugular chain, while the vessels draining the upper or posterior surface of the soft palate drain laterally via the pharyngeal lymphatics to end in the RP nodes[38].

2.6. Oropharyngeal Walls

The oropharyngeal walls are comprised of the mucosa of the lateral and posterior aspects of the upper aerodigestive tract within the confines of the oropharynx; specially, the posterior pharyngeal wall extends from the inferior aspect of the nasopharynx to the level of the epiglottis and the lateral pharyngeal wall extends in the same longitudinal region region on the right and left aspects of the oropharynx. The oropharyngeal walls consist of a squamous mucosal epithelium that overlies the pharyngeal constrictor musculature. The oropharyngeal wallstypically are sizuated adjacent to the second and third cervical vertebrae, and this region is innervated by cranial nerves IX (glo9ssopharyngeus) and X (vagus) [39].

Primary tumors of the oropharyngeal walls typically arise from the squamous mucosa abd grow toward the lumen of the aerodigestive tract and submucosally to other sites within the oropharynx. However, it is possible for lesions of the posterior pharyngeal wall to grow into the prevertebral musculature and bony involvement of the vertebral bodies, although rare, is possible. Lesions of the lateral pharyngeal wall may also grow directly into the structures of the neck and become confluent with the lymph node basins of that region. In many cases, lesions present at an advanced stage, due to the relative paucity of early symptoms until a critical size is reached. Tumors of both the posterior and lateral pharyngeal walls primarily drain to the lymph nodes in Level II and III, as well as the retropharyngeal nodes.

The posterior pharyngeal wall spans the area defined by the soft palate, the epiglottis, the borders of the tonsillar complexes, and the lateral aspects of the piriform sinuses inferiorly [39]. The lymphatic drainage from the posterior pharyngeal wall is primarily via the jugular nodes in the subdigastric group [39]. The midjugular group is frequently involved, as is the posterior cervical triangle, while supraclavicular disease is rather unusual.

3. Pathogenesis of Oropharyngeal Carcinoma

Squamous cell carcinomas of the oropharynx are considered the result of multiple events at the molecular level; each of these events may reflect a change due to a genetic predisposition or an exposure to an exogenous environmental agent [40]. Multiple independent events that cause the loss or inactivation of tumor suppressor genes and activation of oncogenes appear crucial to the development of oropharyngeal carcinomas; environmental agents can cause specific damage or trigger cascades that contribute to these pathways. According to Califano et al. the most common alteration is the loss of chromosomal region 9p21, a region which encodes two supressors p16 and p14; this abnormality is present in over 70% of dysplastic lesions, suggesting that its loss is an early event in the carcinogenic pathway[40-42].

Exogenous environmental factors appear to contribute to this cascade in a variety of ways. Carcinogen exposure, such as use of tobacco and alcohol, can cause direct genetic insult or act indirectly through mucosal damage. Damage of the mucosa may trigger inflamatory cascades that involve COX-2 and EGFR activation. Cyclin D1 activation, and increased proliferation: this compensatory mechanisms to the acute injury increases proliferation and puts the mucosa at increased risk of mutation [43].

Viral infection with high-risk HPV subtypes exerts direct influence on the pathways of carcinogenesis in oropharyngeal carcinomas. Most HPV-related cancers carry the viral DNA integrated into the cellular chromosomes at one or more loci[43, 44]. It is believed that expression of two early genes in the viral genome, E6 and E7, are crucial to viral mediated cancer development. The E6 protein, mediated by a cellular protein called E6-associated protein (E6AP), forms a complex with the tumor suppressor p53, causing degradation of p53 via ubluquitin-mediated proteolysis [45, 46]. The ability to inhibit the tumor suppressor activity of p53 has been shown to reduce the ability of the cell to respond to genotoxic stress[47] and genetic instability[48].

Mucosal HPV types are categorized as either low-risk or high-risk based on their carcinogenic potential of cervical HPV infections. Some low-risk HPV types have strong associations with benign anogenital lesions or warts, whereas others have no apparent clinical manifestations. High-risk HPV types have strong epidemiological association with anogenital and oral malignant lesions and are therefore thought to cause malignant transformation of squamous epithelial cells. Studies have consistently shown that HPV16 is the type most often associated with OPC[49-54]. Several lines of evidence have established the oncogenic potential of HPV in HNSCC, and since the early 1990s, HPV DNA has been consistently identified in many head and neck cancers[52, 55]. A systematic review and a meta- analysis have confirmed that more than 90 % of HPV-HNSCC involve HPV16[54-57]. Considerable heterogeneity has been observed between geographical regions with respect to HPV prevalence in head and neck tumours, although in all regions the oropharynx is the most common HNSCC site associated with HPV[57-58].

HNCs are typically caused by tobacco, alcohol, and viral exposure as opposed to cancers due to germline variants in high penetrance genes. This is consistent with what is known about HNC tumors arising in environmentally exposed epithelial tissue and is consistent with large population attributable to exposure to well-established genotoxic agents, including tobacco, betel nut, and alcohol and now human papillomavirus (HPV) [3, 4, 59]. Considering low survival of late-stage HNCs, reduction of risky behaviors and early detection of HNCs are keys in reducing incidence, cost burden, and mortality.

Head and neck squamous cell carcinoma (HNSCC) that comprising upper aerodigestive tract anatomic sites represents the third common cause of cancer death world wide[58]. The vast majority (more than 90%) are squamous cell carcinomas, and the disease typically appears in the oropharynx, oral cavity, hypopharynx and larynx. The development of HNSCC is the result of the interaction of both environmental factors and genetic inheritance. The 5-year life expectancy is about 50% when there are lymphnode metastases [52, 59-62]. (It has been demonstrated previously that cure rates in patients with advanced disease using tumor response to neoadjuvant chemotherapy is efficient. This is important because of the treatment intensity in future protocols so as to achieve the best cure rates with the least ototoxicity[61, 62]. Oral and oropharyngeal cancer has a survival rate < 50% after 5 years[63].

3.1. Risk Factors

Males are significantly more likely to develop HNC than females with an incidence ratio ranging from 2: 1 to 4:1[3, 4]. The average age of diagnosis is 50-70 years[3, 4]. Tobacco (smoked and smokeless) exposure is the largest known and most well-established contributor to HNCs. An estimated 75% of lip, oral cavity, and pharyngeal cancers are attributable to tobacco smoking and alcohol consumption in Western Europe[3, 4]. Tobacco smoking is well established as a dominant risk factor for HNSCC and this risk is correlated with the intensity and duration of smoking habit[58, 60]. The cigarette contains nitrosamines and polycyclic hydrocarbons carcinogens elements that have genotoxic effects and therefore may increase the risk of the disease.

Kumar et al. [64] showed that smoking cessation reduces but does not eliminate the risk of cancer development. Alcohol acts as a solvent to enhance mucosal exposure to carcinogens, increasing cellular uptake of these. The acetaldehyde, a metabolite of alcohol, can form DNA adducts, that interfere with DNA synthesis and repair [65] the consumption of tobacco associated with alcohol users develop HNSCC, suggesting that individual variation in the genetic susceptibility plays a critical role[66].

Smokeless tobacco products are also associated with an increased HNC risk, particularly for oral cancer[4]. HNC risk is increased in never smokers using snuff, compared with never-users of snuff[3, 4]. There is evidence that the carcinogenic effects of tobacco may modify HNC risk among individuals with genetic predisposition in metabolic enzymes[3, 4].

Alcohol drinking without smoking has been estimated to contribute 4% of HNCs worldwide [3, 4]. As the second major risk factor for HNCs, alcohol acts as a solvent to enhance mucosal exposure to carcinogens, increasing cellular uptake of other carcinogens, increasing cellular uptake of other carcinogens, increasing cellular uptake of other carcinogens such as those contained in smoking and diet [3, 4].

The majority of ethanol is eliminated in the liver via enzymatic oxidation to acetaldehyde and acetate, catalyzed by the various isoenzymes of alcohol dehydrogenase (ADH). Aldehyde dehydrogenase (ALDH) is a superfamily of 19 human isoforms that metabolizes reactive aldehydes produced from alcohol into non-active acids[3, 4]. The dose-response relationship has been consistent for both duration and amount of drinking and HNC risk[3, 4]. It remains unclear whether the type of alcoholic beverage affects HNC risk after adjaustment for total amount and alcohol concentration[3, 4].

The risk proves to be greater when both the above factors, alcohol and tobacco, are combined. More frequently, HNC occurs when both alcohol and tobacco are used in combination, explaining 85% of hypopharyngeal/laryngeal cancers, 75% of non-HPV oropharyngeal cancers (OPCs), and 61% of oral cavity cancers[3-5]. After repeated exposure of a long duration, multiple primary and secondary tumors can occur in the area affected by accumulation of carcinogenic alterations at the mucosal surface, a phenomenon described as ''field cancerization''[4,5].

It has been suggested that infection with HPV-16 is an independent risk factor for HNSCC, mainly for oropharyngeal squamous cell carcinoma [67]. Although the mode of transmission of HPV in head and neck cancer has not been determined with an increased risk[68]. Carcinogen exposure, oral hygiene, dental plaque formation, chronic irritation to the lining of the mouth, family history, low body mass index and exposure to ultraviolet light also play a role, because they can modulate toxin and carcinogenic metabolism.

Regarding oral hygiene, the polymicrobial supragingival plaque may be considered as a possible independent factor because it has a relevant mutagenic interaction with saliva, and individual oral health may be a co-factor in the development of oral cavity carcinomas. Periodontal diseases resulting from poor oral hygiene can lead to infections with consequent release of inflammatory mediators such as cytokines and the reactions against inflammation can promote cancer development. The loss of teeth can also contribute for oral cancer development, it leads for alteration of oral flora flavors the reduction of nitrites and nitrates and the production of acetaldehyde, which leads to the formation of DNA adducts [69-71].

Risk factors for oral HPV incidence and persistence are not yet well understood, but several studies have explored risk factors for prevalent oral HPV. The most important risk factors for oral HPV appear to be increasing age, sexual behaviors, male sex, current cigarette use, and host immunosuppression. Among adults, oral HPV prevalence increases with age [72-75].

It is currently unclear whether higher prevalence rates in older age groups are due to incident infections or to persistent infections caused by waning immunity in these age groups. Sexual behaviours, including oral–genital, oral–oral and oral–anal contact, have all been associated with oral HPV infection in cross-sectional studies[76, 77].

Tobacco use has also been found to be associated independently with oral HPV infection[78-80]. Furthermore, a dose–response effect is apparent for intensity of tobacco use and oral HPV prevalence[81] Smoking has been shown to have immunosuppressive effects and has been associated with higher prevalence and viral load among women with cervical HPV infection, as well as risk of progression of cervical disease[81, 82]. Smoking has also been shown to increase the persistence of oral HPV infection[83].

Numerous case series have established that patients with HPV-positive OPCs have unique demographic and behavioural characteristics. Patients with HPV-positive OPC tend to be middle-aged white men and of higher socioeconomic status [74, 34, 45]. Further, patients with HPV-positive OPC are more often non-smokers and non-drinkers than patients with HPV-negative OPC; tobacco and alcohol do not appear to be risk factors for this disease[74, 83, 84]. However, sexual behaviours do appear to be associated with this disease, and patients with HPV-positive OPC as a group have a higher number of sex partners-in particular oral sex partners-than HPV-negative patients[74, 84-86]. HPV-positive OPCs tend to occur in either the tonsils or base of tongue rather than other sites of the oropharynx, such as the soft palate or posterior oropharynx, and they tend to be of non-keratinizing histologies, including basaloid, lymphoepithelial, or poorly differentiated[87]. Finally,

patients with HPV-positive OPC tend to present for medical care because of nodal metastases, and the initial work-up tends to reveal a small primary tumour with multiple positive nodes (typically classified as T1-2 N2b-c)[88].

Sexual behaviour is an important risk factor for HPV-positive OPC, with increasing numbers of both lifetime sex partners and oral sex partners increasing risk for HPV-positive OPC. Interestingly, husbands whose wife had a history of cervical cancer also appear to be at increased risk for developing tonsillar cancer and tongue cancer[88]. Furthermore, among men, the risk of a subsequent oral/pharyngeal malignancy after an anogenital cancer or a subsequent anogenital cancer after an oral/pharyngeal malignancy appears to be greater than expected[89]. This risk appears greatest for never- married men. HIV-positive patients are at increased risk for HPV-related cancers, including OPC. In HIV/AIDS-positive men, the relative risk (RR) of tonsillar cancer was 2.6 (95 % CI 1.8–3.8) compared to the expected number of cases[90].

The first reports of the presence of a Cancer Stem Cells (CSC)-population has been related to the leukemic cells[91]. Positive and negative staining of the leukemic CSC population has been done with CD34 and CD 38. Researchers have widely investigated the CSC populations, and substantially determined them in different solid tumors like the prostate, neck, pancreas, colon, head, brain, and breast [91-94]. The existence of sub-populations of oral CSCs has been primarily proposed by the study of Mackenzie[95]. In this study has been shown that a sub-population of OSCC cells is able to create a developing tumor mass.

CSCs have the shared features with normal stem cells and several certain traits maintaining tumor growth and invasion [92, 93]. One of the primary feature of CSCs is their self-renewal capacities, so that it apparently is one of the motives to begin and maintain tumorigenicity[92, 93]. CSCs self-renewal may be retained through multiple endogenous signaling paths, including Wnt, Bmp, Pten, Notch, B cell-specific Moloney murine leukemia virus integration site 1 (Bmi1), TGF-β, and Hedgehog [94-100].

As the abnormal actuation and over-expression of the pro-inflammatory transcription agent, NF-kB contributes importantly to the regulation of different cellular procedures such as apoptosis, cell differentiation, signal transduction paths, and transformation, particularly over the development and metastasis process of multiple cancers such as oral cancer, unpaving the contribution of NK-kB proteins is of high importance[94, 97, 101]. Previous studies have revealed that the NF-kB path would be actuated commonly in the cancer and cancer stem cells of various malignances such as leukemia, ovary, breast, glioblastoma, pancreatic, prostate, and colon cancers. It has been reported that that its actuation induces radiotherapy and chemotherapy resistance[102-104]. miRNAs are still the other significant modulatory molecule engaged during carcinogenesis. They also can function as oncogenes or tumor inhibitor genes so that they practically interplay with NF-kB and additional molecules. It should be mentioned that the above molecules may function as oncogenes or tumor inhibitor genes so that they interplay with NF-kB and additional molecules.

4. Staging

The aim of cancer classification is to better understand prognosis of cancer, to improve diagnosis and compare outcome results for a consecutive improvement of treatment recommendations of distinct cancers at a specific stage of disease[104]. Current staging of head and neck squamous cell carcinoma (HNSCC) is primarily based on clinical primary tumor extension (cT), lymph node involvement (cN) and distant metastasis (cM). For surgically treated tumors, two histopathological parameters tumor grading (G) and radicality of resection (R) are added. Risk factors for locoregional relapse such as vascular invasion (V), lymph node capsular spread and tumor-free margin size of the resected tumor were recently identified[104]. Locoregional control is significantly improved when these HNSCC patients are treated with platinum-based chemotherapy[105, 106]. The American Joint Committee on Cancer (AJCC) staging system serves as the primary tool for staging cancer of the oral cavity (Table XXX). The AJCC staging system is based on surface dimensions[108]. Although staging of lip lesions is now subdivided into superficial extensive (T4a) and deeply extensive (T4b). The latter denotes unresectable invasion of the masticator space, pterygoid plates, and/or skull base, and these lesions often may encase the carotid artery.

The survival and prognosis of a patient suffering from oral cavity carcinoma is a result of several important factors including patient comorbidity, performance status, nutritional status, and the patient's intact immune response. Although age itself is not a prognostic indicator, the comorbidities which are commonly associated with advanced age may represent a negative prognostic predictor.

The presence of perineural invasion, lymphocytic response response, and depth of invasion are examples of histopathologic parameters that are not accounted for in the AJCC staging system. Additionaly, extracapsular spread, which may be associated with a 50% reduction in survival, may have a significant impact on the prognosis of a patient with oral cavity carcinoma and regional disease.

Tumor thickness has been demonstrated to predict the risk of local recurrence and survival for oral tongue carcinoma[108]. The exact depth of invasion and correlation with survival is not clear; however, several studies have suggested that tumor thickness greater than 4.0 mm significantly increases the risk for cervical metastases and the risk for cervical metastases and therefore has a negative impact on survival[109, 110]. Other studies have suggested that 5.0 mm of tumor depth of 4.0 mm or greater is associated with an

increased risk for regional metastases and as a result recommend elective treatment of the N0 neck even in the absence of high-risk histopathologic features.

The staging criteria and staging system for HPV-related oropharyngeal cancer recently underwent substantive modification. Immunochemistry for p16 overexpression has emerged as an important surrogate biomarker for HPV-mediated disease; p16 is upregulated with HPV16, and oncoproteins degrade p53 and pRb, leading to HPV-mediated carcinogenesis. All oropharyngeal cancer should be tested for p16, and those cancers which do not overexpress p 16 should be staged by use of the p16-negative staging system. The cut-point for determining p16 by immunohistochemistry is nuclear expression with greater than +2/+3 intensity and greater than 75% distribution, under which tumors shall be staged with the p16-positive system.

The primary tumor stage remains essentially the same in the modified p-16-positive staging system as in the traditional p-16-negative system, with the exception that the p-16-positive classification does not include a Tis category and there is not a T4b subcategory within T4 group. With these criteria, T1 tumors are less than or equal to 2 cm but less than or equal to 4 cm in greatest dimension. T1/T2 tumors by definition should be limited to the base of tongue and its intrinsic musculature and should not involve the extrinsic tongue muscles, muscles of mastication, mandible, or other pharyngeal subsites.

Nodal staging in the eight edition of the American Joint Committee on Cancer (AJCC)-Staging Manual has changed significantly. Traditional N0-N2b nodal stages are homogeneous for outcome within T1 and T2 categories (Stage I). N2c and T3 have an intermediate stage (Stage II), and T4 and N3 are the last favorable group (Stage III). Stage IV is reserved for distant metastasis. The revised p16-negative system includes extranodal extension as an important prognostic variable[111].

Pathologic staging is modified forp16-positive oropharyngeal cancer to reflect data that indicate that metastatic node number, laterality, or nodal size, is the prognostic factor in surgically resected, neck-dissected p16-positive disease[112]. (Any p-16-positive cervical lymph node metastases to level II or/III from an unknown primary are staged according to p16-positive classification[111] (Table 1 and Figure 1).

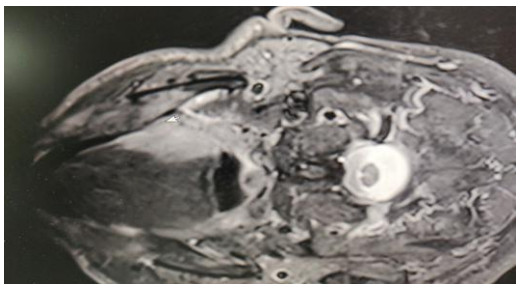

Figure 1. Oropharyngeal tumor by a heavy smoker. The basis of the tongue (right) and the the right tonsil are severely affected

Table 1

Staging of oropharyngeal carcinomas	
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Moderately advanced local disease. Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
T4b	Very advanced local disease. Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx or skull base or encases carotid artery.
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
Regional Lymph Nodes: Clinical (cN) for Human Papillomavirus-Positive Oropharyngeal Squamous Cell Cancer, 8th Edition	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none >6cm
N2	Contralateral or bilateral lymph nodes, none> 6cm
N3	Lymph node(s) larger than 6 cm
N3	Metastasis in a lymph node >6cm in greatest dimension
Regional Lymph Nodes: Pathological (pN) for Human Papillomavirus-Positive Oropharyngeal Squamous Cell Cancer, 8th Edition	
NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

5. Multidisciplinary Initial Assessment and Staging

5.1. The Role of History and Physical Examination

The primary evaluation of a patient with oropharyngeal cancer is a comprehensive history and physical examination. On history, the patient's symptoms depend highly on the location and extent of the tumor. Patients with early stage oropharyngeal carcinomas may present with few symptoms; the tumors may have been found incidentally on scans for other indications or dental evaluations[8, 7].

One common presenting symptom of oropharynx cancer is a painless neck mass, representing lymph node metastasis; in many cases, only after a full examination is a primary identified. When patients do develop symptoms due to local disease, pain at the site of the primary or referred pain to the middle ear. The latter occurs via the pharyngeal and tonsillar branches of cranial nerve IX, which innervate the middle ear. As tumors progress, odynophagia, dysphagia, dysarthria, and trismus may develop and cause the patient to seek medical attention[13, 15, 89].

The physical is a crucial part of the evaluation for oropharyngeal cancer patients, and it highly affects treatment decisions and planning. The head and neck examination should evaluate the local extent of the primary tumor and the presence and the location of lymph nodes. Inspection of the oropharynx can be performed by direct or indirect laryngoscopy or fiberoptic nasopharyngoscopy; there should be a complete evaluation of all mucosa surfaces to ensure there are no other lesions and to fully appreciate the extent of the primary tumor. A full evaluation of the adjacent oral cavity should be performed to understand whether the tumor invades these areas. While level II is the most common lymph node station affected, the other cervical nodal areas, as well the supraclavicular fossae, should be assessed. Cranial nerves V, VII, XI, X and XII are especially at risk for compromise due to invasion by oropharyngeal cancers, and these should be specifically assessed during the physical examination. In the case of an inadequate physical examination, the patient may require an examination under anesthesia to fully appreciate the extent of disease and establisch a diagnosis[3, 4, 9].

Even with contemporary advancements in medical imaging, physical examination remains foundational in the work-up of any head and neck cancer. Patients with a suspicious tonsillar or oral mass should undergo a thorough head and neck examination [3, 9, 23]. The tonsillae fossa and the surrounding tissues of the lateral pharyngeal wall should be closely inspected and palpated. This will give the clinician a sense of the size and extent of any suspicious lesion as well as its relationships to surrounding structures. The oral tongue, tongue base, and soft palate should also be thoroughly evaluated for signs of tumor involvement that would indicate a more advanced staged lesion. Careful examination of the neck should also be performed to assess for concomitant adenopathy[87]. A complete head and neck examination must include a comprehensive evaluation of the nasopharynx, oropharynx, and larynx that provides not only a more complete assessment of the primary lesion but also assists in ruling out any secondary malignancies[97, 101].

5.2. The Role of Imaging

Plain dental radiographs, such as a panoramic radiographs, such as a panoramic radiograph, may show a ‘’moth-eaten’’ destruction of lamina dura and surrounding bone, as well as cloudy maxillary sinuses. Computed tomography (CT) and magnetic resonance imaging (MRI) provide comprehensive visualization of the tumor and depict the prognostic factors: tumor thickness, depth of invasion, and bony involvement. While CT shows bone involvement, MRI delineates the tumor and perineural invasion and discriminates between tumor and mucus in an obstructed maxillary sinus[112].

Advanced imaging techniques are standard in the evaluation and staging of oropharyngeal tumors. The goal of imaging is to establish the extent and size of the primary tumor, evaluate nodal disease, and identify perineural spread and bony destruction. The optimal type of imaging for head and neck cancers depends on the site of disease and goals of the evaluation. Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound (US) are all complementary modalities and van be used to evaluate different aspects of the disease.

Standard imaging evaluation for an oropharynx tumor includes CT- or MRI-imaging of the head and neck, with intravenous contrast, to evaluate the primary tumor and nodal disease. CT is considered by many to be preferable to MRI for the imaging of oropharynx tumors because it is less affected by breathing and swallowing artifacts[112].

Positron emission tomography (PET) is an imaging technique that, in contrast to traditional anatomical imaging, maps biological phenomena[113]. Positron emission tomography (PET) is useful in identifying metabolically active tissues in the work-up and staging for head and neck cancer. Combined with traditional CT scan, PET-CT offers the advantage of fusing anatomic tomographic images. Although perhaps best suited for advanced-stage disease and assessment of regional and distant metastasis, PET has an important role in patients with oropharyngeal cancer as an aid in the detection of the primary tumor or in cases of an unknown primary. False-positive PET imaging is a well-recognized phenomenon in association with acute inflammation or tonsillitis. False-negative findings can also occur, particularly within necrotic lymph nodes, which are commonly associated with HPV-related oropharyngeal cancer[114]. PET/CT can be used to acquire a high-quality, integrated diagnostic CT scan for surgical planning along with the PET scan for metabolic imaging [114, 115]. In general, nodal status and distant metastases are best evaluated by the PET component of contrast-enhanced PET/CT, and the morphology of the primary lesion as it relates to adjacent critical anatomic structures is best evaluated by the CT component.

Contrast-enhanced neck CT provides more anatomic details about the primary tumor, involvement of adjacent structures or muscles, and vascular anatomy than does the attenuation-correction CT done routinely in PET/CT. When enhanced CT and PET are combined as a single study, the study provides more accurate anatomic details along with the biologic functional information about the primary tumor[115, 116].

Many studies have proposed that PET/CT imaging may improve the accuracy of posttreatment evaluation of Head and Neck Tumors [117, 118, 119]. It has been demonstrated that the metabolic response closely correlates with the histopathologic response, and survival is far better in responders and nonresponders[115]. The timing of posttherapy PET/CT is crucial in the posttherapy assessment. The optimum timing after chemotherapy and radiotherapy is not known, but an interval of 12 weeks has been generally recommended[115]. Accuracy is generally greater for scans performed more than 12 weeks after radiation, likely because of a

reduction in radiation-induced inflammation[115].

6. Treatment-Principles and Applications

6.1. Surgical Approaches

There are different approaches for the surgical treatment of the tumors of oropharynx and oral caviry. To these approaches belong the peroral approach, the lower cheek flap approach, the visor flap approach and the mandibulotomy approach. In the following paragraphs we will present the principles of each one.

A. Peroral approach

Early-stage primary carcinomas of the oral cavity (T1 and T2) of the mobile tongue, floor mouth , buccal mucosa, and the upper or lower gum can be safely approached through the oral cavity for satisfactory surgical resection and primary repair[116].

B. Lower cheek flap approach

Larger tumors of the oral cavity, particularly those requiring resection of any part of the mandible in the posterolateral part of the oral cavity require a lower lip-splitting midline incision with elevation of the lower cheek flap to expose the mandible and the contents of the oral cavity[188]. Through this approach, a marginal mandibulectomy, segmental mandibulectomy and any other additional procedures can be accomplished in conjuction with resection of the primary mucosal lession of the tongue, floor of mouth, buccal mucosa, upper or lower gum, retromolar trigone and soft palate[117].

C. Visor flap approach

Larger lessions of the anterior oral cavity, involving the anterior floor of mouth and lower gum can be resected adequately through a wide exposure gained via a visor flap approach[189]. This approach avoids the need for a lower lip-splitting incision but has the disantvantage of causing anesthesia of the skin of the chin because of the need to sacrifice both mental nerves[117].

D. Mandibulotomy approach

Larger lesions of the posterior oral cavity such as those of the posterior floor of the mouth, bulky tumors of the middle and posterior third of the tongue and tumors of the base of the tongue, pharyngeal wall and tonsil are through a mandibulotomy approach as long as the mandible is uninvolved by cancer[117, 118].

6.3. Neck dissection for oral squamous cell carcinoma

The most basic terms used to describe NDs are defined by surgical intent. The therapeutic ND is performed for a cN+ neck, while an elective ND is described for cN0 necks at high risk for occult metastases[171]. A staged ND often refers to a planned ND following primary radiation or radio-chemotherapy while a salvage ND refers to an ND performed to remove persistent (early salvage D) or recurrent (late salvage ND) nodal disease following nonoperative therapy[119]. The selective neck dissection has been found to offer an oncologically safe surgery while decreasing overall morbidity and increasing functional and cosmetic outcomes for the appropriately selected population[120]. During this dissection the non-lymphatic structures are preserved.

The treatment of oral squamous cell carcinoma is directed at controlling the primary tumor and regional neck metastases, and neck dissection is an integral treatment component [121-123]. The status of cervical metastasis is the single most important prognostic factor in survival of patients with oral squamous cell carcinoma[124, 125], with the cure rates dropping to nearly half with regional lymph node involvement[125-127].

The decision to perform neck dissections is based upon the knowledge of nodal metastasis patterns and risk factors for neck metastasis such as tumor site, size and thickness [127]. In patients clinically staged as N0 the lymph node levels at risk are I-III, while in N+ patients, the levels at risk are I-IV[128]. Neck levels I, II and III are at the greatest risk of nodal metastasis from primary squamous cell carcinoma of the oral cavity [122, 126]. Tumors of the tongue have the highest incidence of neck metastasis, followed by the floor of the mouth, the lower gums, the buccal mucosa, the upper gums, the hard palate, and the lips[125, 127, 128]. The incidence of pathologically-proven metastasis in the clinically N0 neck follows a similar pattern. Tumors of the upper gum, hard palate, and lips have such a low rate of occult metastasis that elective treatment of the neck is unnecessary. It should be mentioned, that the posterior triangle (level V) is seldom involved by metastases from these lesions[128, 129].

Management of the N0 neck in oral squamous cell carcinoma has been debated extensively, but several authors support the use of elective neck dissection[129-131] [SND (I-III)] or supraomohyoid neck dissection consists of removing the nodal regions I, II and III[132, 133]. These approaches remove the nodes at the highest risk of involvement from a primary tumor originating in the oral cavity.

Cunningham et al.[134] supported the use of elective neck dissection in patients with stage I and II oral cavity carcinoma. Furthemore, Kligerman et al. [135] conducted a study to determine the indication for elective neck dissection in patients with early oral cavity squamous cell car-

cinoma. The authors concluded that neck dissection was mandatory in early-stage oral squamous cell carcinoma due to the superior survival rates compared to resection alone and the poor salvage rate.

Tumors arising from the tongue and floor of the mouth have a high propensity for early metastasis, regardless of their size and differentiation. Unless the treatment of choice for the primary lesion is radiotherapy, elective neck dissection with removal of lymph node levels I through III (and level IV for tongue cancer) is the minimum recommended treatment of N0 squamous cell carcinoma of the oral cavity[136].

SND (I-III) has been used extensively as a staging procedure in patients with N0 oral squamous cell carcinoma, and it is also a potentially curative procedure in selected patients with limited metastatic disease of the neck[176]. Pathological studies of lymph node metastasis suggest that the use of SND is also appropriate in some patients with clinically obvious cervical lymph node metastases. When indicated, the application of postoperative radiation therapy further reduces the rate of regional failure in patients following SND[68, 79, 127, 128].

Radiation therapy (RT) with concurrent single-agent cisplatin at 100mg/m^2 given every 3 weeks for three cycles or single-agent cetuximab at 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly is the current standard initial treatment for patients with locoregionally advanced, non-metastatic tonsil cancer who have large primary tumors (T3/T4) [123, 129, 132]. Alternatives to cisplatin-based chemotherapy, such as carboplatin and 5-FU, should be based on patient intolerance or protocol and accompanied by standard radiation fractionation[139, 140](Figure 2).

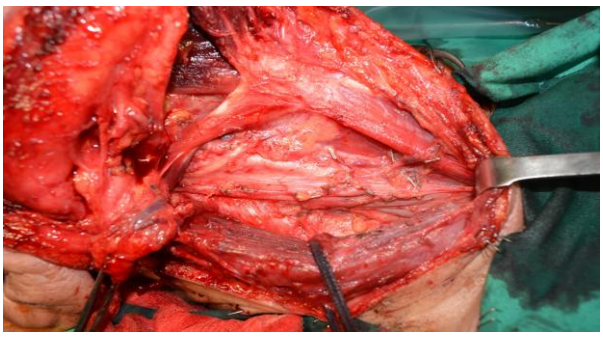

Figure 2. Selective Neck Dissection by a patient suffering from Tumor of the mouth floor.

6.3.1. Tumors Involving the Tongue

Surgical resection

The overwhelming majority of cancers involving the oral cavity are squamous cell carcinoma; however, minor salivary gland tumors may also occur. Epidermoid cancer of the oral cavity may be treated with either radiation, surgery or combined therapy. We can divide the therapeutic choices in two categories, according to stage of the disease[140, 141].

Superficial carcinomas of the oral cavity can be treated with equivalent cure rates with either radiation therapy or surgical excision. The choice of therapy is often based on factors such as patient preference, quality of life, cost, convenience and patient compliance. Because surgical therapy can be achieved with minimal morbidity, surgery has become the gold standard for management of early cancers of the oral cavity. Although radiotherapy is equally effective for the treatment of early disease, the rates of long-term sequelae including xerostomia, dysphagia, and osteoradionecrosis are unacceptably high[141, 142].

Advanced disease. Advanced disease of the oral cavity is best managed with multimodality therapy. Surgery coupled with preoperative or postoperative radiation therapy is often applied for advanced disease. The rationale for preoperative radiation is to decrease the tumor mass and therefore increase the resectability of the tumor[142].

Tumors involving the anterior two-thirds of the oral tongue can usually be managed through a transoral approach, however more extensive tumors and tumors involving the posterior one-third of the tongue may require a lingual release[143-145].

Radiation therapy

Early disease that measures less than 1.5 mm thick on imaging may be treated with interstitial implantation using iridium-192 to a dose of 60 to 60 Gy. Advanced diseas is commonly managed surgically. Acute complications of radiation therapy including mucositis and taste disorders generally resolve within 3 months of completion of radiation. The degree of xerostomia is related to dose and volume of salivary glands irradiated. Severe late complications, such as mucosal ulceration or osteonecrosis, occur in ca 10% of the patients and is usually related to tumor burden[141, 142].

6.3.2. Tumors Involving the Mandible

Surgical Treatment

Tumors invading the mandible can be managed either with a marginal resection or a segmental resection. The decision regarding the optimal method of tumor resection is largely dependent on the degree of invasion. It has been suggested that tumor invasion of the periosteum or cortical bone, without invasion of the mandibular resection. Tumors that erode into the medullary canal, however, require a segmental resection[143].

The periosteum is relatively resistant to cancer invasion. With the exception of tooth sockets, the periosteum acts as a dense barrier to the invasion of adjacent tumor. In spite of the protective periosteum, aggressive and long-standing tumors erode the periosteum and invade the adjacent mandible through a variety of pathways. Two distinct histologic patterns of tumor invasion have been identified. The first pattern is referred as infiltrative. The last is characterized by finger-like projections of tumor. The second pattern is referred to as erosive [144, 145].

Tumor within the oral cavity may invade the mandible and gain entrance into the mandibular canal through several routes. Tumor cells demonstrate a tendency to migrate into the dental sockets because this area represents a pathway of minimal resistance. In the edentulous patients, tumor cells will migrate onto the occlusal surface of the alveolous and enter the mandible through dental pits[194, 195], which are cortical bone defects at the location of prior dentition. Less commonly adjacent tumor may erode through the cortical bone directly into the mandibular canal[146].

Although the superficial invasion of the periosteum or cortical bone may be managed with a marginal mandibulectomy, once the tumor has eroded into the medullary cavity and mandibular canal, most advocate a segmental resection. Determining the presence of bone erosion represents an ongoing clinical dilemma. The poor predictability associated with preoperative imaging has led many to rely on preoperative clinical assessment as the primary method for determining the presence of mandibular invasion[146, 147](Figure 3).

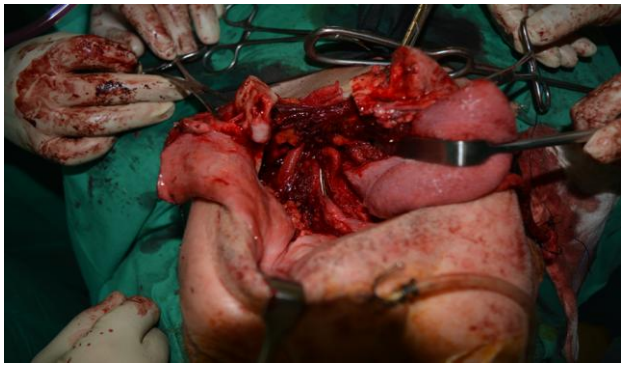

Figure 3. Excision of a tumor involving the mandible.

6.3.3. Tumors of the Buccal Mucosa

Surgical Treatment

Buccal carcinoma comprises less than 10% of oral cavity carcinoma, and when it occurs, it commonly arises from a preexisting leukoplakia[146, 147]. The principles of management of buccal carcinoma are no different than those of other subsites within the oral cavity. Surgical therapy is the preferred method of management. In early disease, surgical excision can usually be accomplished transorally. Tumors which invade the buccinator muscle and tumors that present with nodal disease or with poor prognostic factors should be treated with postoperative radiation therapy. Negative surgical margins are paramount, and in an effort to achieve this goal.

An MRI-scan is ideal for imaging of the buccal mucosa and soft tissue of the masticator space. Whereas early tumors of the buccal mucosa commonly present as an irregular mucosal mass, more than half of buccal tumors present as deeply invasive tumors which may track along the parotid duct, masseter muscle[148].

Deeply invasive lesions may break into the buccal fat pad. In this case it is advisable to resect the entire fat pad because negative surgical margins in this area are difficult to confirm. The rich lymphatic network characteristic of the buccal region and the high rate of lymph node metastasis mandate that the neck carefully evaluated and, in most cases, treated[149].

Radiotherapy

Although small tumors not involving the oral commissure are commonly treated surgically, radiation provides equivalent local control. Because buccal mucosal tumors are well lateralized, treatment consists of external beam radiation to a dose of 50 Gy to the primary tumor with a 2-cm margin. An external beam radiation boost is given to the primary tumor to achieve a final dose of 66 Gy for T1 and 70 Gy for T2 cancers. Brachytherapy administered to a dose of 25 to 30 Gy can be employed as a boost. Local control is ca 90% for T1 and 70% for T2. Advanced tumors are also usually treated surgically. Local control is ca 70% for T2. Advanced tumors are also usually treated surgically. Due to extension to midline structures, elective bilateral radiation to50 Gy is generally indicated followed by a boostto the primary tumot to 70 Gy[149-152].

6.3.4. Tumors of the Palate

Surgical Treatment

Unlike other areas of the oral cavity where squamous cell carcinoma makes up the overwhelming majority of pathology, the palate is rich in minor salivary glands and therefore is the site of both benign and malignant salivary gland tumors. The principles of management of tumors of the palate are similar to those of the mandible; obtaining tumor-free margins is essential to achieving a good outcome. Lateral tumors may represent a risk to invasion and perineural spread via the palatine or trigeminal neurovascular bundle[152-154].

The depth of invasion will dictate the extent of the surgical resection. Superficial lesions of the palatal rarely metastasize to the neck, and therefore a neck dissection is rarely warranted in the absence of demonstrable regional disease[145, 154].

6.3.5. Base of Tongue (BOT)

The management of oropharyngeal cancer is generally divided into the primary and salvage settings. Patients with advanced Base Of Tongue (BOT) or tonsil malignancy are at high risk for locoregional failure, distant metastasis, and therefore require multimodality therapy. Treatment regimens for patients with locally advanced oropharyngeal or hypopharyngeal cancer are multimodal, and success has been achieved in improving local, regional, and distant control, organ and quality of life[152, 155, 156].

Local Disease

The diagnosis of an oral cavity carcinoma can be relatively straightforward. A complete history including use of alcohol, tobacco, and oral hygiene should be documented. Because the oral cavity is readily accessible, changes in the mucosa are easily identified and evaluated.

Noninvasive lesions, dysplasia, and carcinoma in situ require minimal workup with regard to evaluation: however, the diagnosis of invasive carcinoma mandates a thorough evaluation to assess the extent of tumor. Once a definitive diagnosis has been achieved, imaging is essential to gain an understanding of the stage of the tumor and presence of metastasis. Although extensive lesions may be heralded by trismus, otalgia and hypesthesia, the lack of these signs does not exclude extensive invasion of the surrounding structures [148, 149, 157-159].

Mandibular Invasion

Plain radiography has been used extensively in the past for the diagnosis of extensive tumor invasion of the mandible; however, subtle changes associated with the cortex have been more difficult to identify. The introduction of the panoramic x-ray, CT- and MRI-scans have increased the accuracy of pre-operative imaging and staging. Although CT is a very accurate method for identifying gross bone invasion, prior work has suggested that bone invasion may be missed in as many as 27% of patients with preoperative CT scans[158, 160, 161].

The sensitivity of a CT scan for bone involvement of the retromolar trigone is ca 50% with a negative predictive value is ca 90%[162, 163]. It has been concluded that although the CT scan is accurate when bone erosion is clearly identified, its negative predictive value is unacceptably low and therefore an inaccurate indicator of bone invasion at the retromolar trigone. The CT scan renders an excellent view of both the soft tissue and bone of the mandible, however it has several limitations, the most significant being artifacts caused by dental amalgams.

The MRI scan offers the advantage of imaging soft tissue and potentially the medullary bone space. Some studies have examined the use of MRI in assessing mandibular invasion and it has been concluded that the MRI scan is superior for evaluating the medullary space of the mandible[12], but inadequate for assessing mandibular invasion. Shaha examined the value of various studies including panoramic x-rays, dental films, bone scans, CT scans and MRI and found that CT scanning was not very helpful mainly because of the presence of irregular dental sockets and artifacts[163-165].

Regional Disease

MRI and CT are both effective in identifying regional disease, however most centers prefer CT because it is well tolerated, highly sensitive, and less expensive than MRI. Both modalities are sensitive in identifying ECS. Fine-needle-aspiration (FNA) may be warranted. "Pathologic" lymph nodes are those nodes that demonstrate central necrosis, extracapsular spread, or are greater than 1 cm in diameter in Levels I, III, IV, V and VI or greater than 1,5cm in the jugulodigastric region[134]. Identification of a pathologic node in the face of a known oral cavity malignancy does not always require assessment, however in cases where there is an area outside the predictes nodal basin, FN is warranted[161, 163,166].

Distant Disease

Distant metastatic disease is rare in epidermoid oral cavity carcinoma. It occurs in only 15% of patients who succumb to their disease. Distant metastatic disease rarely occurs without evidence of regional metastasis; however, when distant disease is discovered, survival is poor. In contrast, early-stage nonepidermoid carcinoma may present with distant metastatic disease; however, patients can survive extended periods with distant disease [164-166].

Distant metastasis from epidermoid carcinoma may occur in the lung, bone, or liver. Although distant metastases rarely occur as a result of oral cavity carcinoma, when they do occur, histopathology often demonstrates aggressive patterns such as lymphatic, vascular, and/or perineural invasion. Although external beam radiation therapy has a positive impact on local regional recurrence, distant metastatic disease remains the most common cause of death from head and neck cancer[134].

6.4. Radiation Therapy

Identifying the gross tumor volume and its draining lymph nodes is the first and most crucial step in radiation treatment planning. Tumor target volumes and organs-at-risk (salivary glands, mandible, spinal cord) are contoured on the CT images taking into account staging imaging, pathology reports, and physical examination. The gross tumor volume (GTV) defines the areas of known measurable tumor and grossly positive lymph nodes either on imaging or examination, and it receives the highest dose of 70 Gy radiation. The Clinical Tumor Volume (CTV) is an expansion of the GTV to cover the subclinical spread of disease surrounding the GTV. Identifying the various lymph node groups on axial planning CT images is critical, but the CTV volume needs to be adjusted based on clinical judgement[179]. T3/T4 lesions of the tonsil, bilateral levels I-V plus retropharyngeal lymph node coverage is recommended[180].

Treatment of T3/T4 oropharyngeal tumors will require a large volume of healthy tissue to be exposed to radiation. Any head and neck radiotherapy can cause temporary or permanent damage to the parotids, submandibular glands, mandible, and teeth, among other tissues. Studies have shown that parotid gland function is preserved if the mean dose to the gland is kept lower than 24 to 26 Gy [181-183]. The first step in managing oral complications of head and neck radiotherapy begins with proper multidisciplinary assessment and dental consultation[183].

Carcinomas of the hard palate are most commonly managed surgically. However, radiation is an option for a superficial T1 lesion without bone invasion. When radiotherapy is applied, external beam radiation is directed at the primary tumor to 50 Gy, followed by a 16- to 20 Gy boost to the primary tumor. Local control after radiation is 65 to 70% for T1 and T2 cancers [13, 184].

As a single modality or with concurrent chemotherapy, radiation therapy is considered the standard of care for definitive treatment of oropharyngeal carcinomas[185].

Historically, oropharynx cancers were treated with conventional radiation therapy using 2-dimensional simulation to delineate standard treatment fields based on bony landmarks. Patients were typically positioned supine, with the neck extended on a fixed headrest, and immobilized with a thermoplastic mask device. For most types of cancer, traditionally, radiotherapy is a conventional treatment, a process by which a dose of radiation is delivered to the tumorigenic tissue [186]. However, the effectiveness of this technique is usually limited by the radiation tolerance of the surrounding tissue, which will also receive the dose and therefore limit the dose that can be delivered [187]. As opposed to traditional radiotherapy, IMRT is a new treatment which allows a higher dose to be delivered to the cancerous tissue alone, without affecting the surrounding regions [188].

The first step of this treatment is to obtain a CT scan (or a PET-CT scan) of the region, allowing the construction of a three-dimensional target volume as opposed to a general target area [187]. When using IMRT, the beams of radiation, which would usually be delivered at a uniform dose, are divided into hundreds of smaller beamlets, each with a variable dose, which can be delivered to a much more certain area [187, 188].

The radiation dose that is delivered targets cells that are currently dividing by damaging the DNA in the cells [189, 190]. As with traditional radiotherapy, the dose is delivered in a series of fractions over a treatment period to minimize damage to healthy tissue while delivering radiation until the neoplastic tissue can be eliminated. To ensure the fractions are given to as close as possible to the target volume, the patient is marked with small tattoos during the first treatment session, which is aligned to the same position, within a small margin of error, using lasers [191]. The margin of error is taken into account by using a planning target volume. This three-dimensional volume encompasses slightly more area than the clinical target volume, which is the estimated extent of the tumour [192]. This allows the treatment to account for internal structures moving due to natural processes such as breathing, which heavily affect the oropharynx through the trachea, esophagus, and the carotid artery.

It has been suggested [193] that the achieved 3-year cause-specific survival rate was 83% for 14 patients treated with CRCT using weekly cisplatin at least three times. In the retrospective study of Lee et al. [194]comparing efficacy of IMRT with conventional radiotherapy using delayed accelerated concomitant boost radiotherapy in the setting of concurrent platinum-based chemotherapy for locally advanced oropharyngeal carcinoma, the implementation of IMRT given with concurrent administration of cisplatin every 3 to 4 weeks in 41 patients with stage III/IV disease led to 3-year local-progression-free, distant metastasis-free, disease-free and overall survival rates of 95%, 94%, 92%, 86%, 82%, and 91% respectively.

6.5. Chemotherapy and Multidisciplinary Treatment for Locoregional Disease

The factors that influence the choice of initial treatment for primary carcinomas of the oral cavity are dependent on the characteristics of the primary tumor (tumor factors), those related to the patient (patient factors), and those related to the treatment team providing care to the patient (physician factors) [195, 196]. The ultimate goals in the treatment of cancer of the oral cavity are to eradicate disease, preserve or restore form and function, minimize the sequelae of treatment, and prevent subsequent new primary tumors. The tumor factors that influence the choice of treatment are as follows: site of the primary tumor, size (T-stage), location (anterior vs. posterior), proximity to bone (mandible or maxilla), the status of cervical lymph nodes, histology (type, grade, and depth of invasion), and previous treatment [195-197]. The risk of cervical lymph node metastasis increases with increasing T-stage, increas-

ing depth of infiltration, and posterior location. Early-stage tumors are equally well controlled by either surgery or radiotherapy used as single-modality treatment.

Advanced stage tumors do require combines modality treatment where surgery followed by postoperative radiation therapy remains the standard therapy. In patients with clinically negative neck cancer but increased risk (>15-20%) of micrometastases to regional lymph nodes, accurate staging is essential to implement appropriate adjuvant therapy [135, 197].

A variety of surgical approaches are available for resection of the primary tumor in the oral cavity. The choice of a particular method depends on the factors mentioned above, such as the site and the size of the primary tumor, as well as its depth of infiltration and proximity to mandible and maxilla.

The use of surgery, radiation, and/or chemotherapy depends on tumor respectability and location, as well as whether an organ preservation approach is feasible [196, 198]. The main treatment option for primary and secondary malignancy as well as recurrent disease, is surgical therapy [197]. The use of transoral laser-assisted surgery followed by radiotherapy is a common in the treatment of early-stage oropharyngeal, hypopharyngeal, and supraglottic carcinomas [198]. Although obtaining negative surgical margins is the primary goal of head and neck surgery, achieving this may be impossible in some cases because of the infiltration of vital structures such as the carotid artery or the prevertebral fasciae. The positive surgical margin status is associated with decreased survival. Therefore a patient should be re-operated if the tumor was not removed completely [199].

Recommendation of planned neck dissection regardless of the clinical response is supported by the high rates of residual disease observed in planned neck dissection surgical specimens. The data shows improved regional control and survival with planned neck dissection [200].

In general, there are three main approaches to the initial treatment of locally advanced dise

1. Concurrentrent platinum-based chemoradiation, with surgery reserved for residual disease
2. Surgerygery with neck dissection and reconstruction, followed by adjuvant radiation or chemoradiation
3. Inductiontion chemotherapy followed by definitive chemoradiation and/or surgery [201].

Because chemotherapy can be given in various clinical scenarios, the three most common strategies are the following:

1. Concurrent therapy with chemotherapy or targeted agents, given simultaneously with radiation to enhance its effect, also known as combined chemoradiation therapy (CRT).
2. Induction chemotherapy (IC), also known as neoadjuvant chemotherapy given before definitive treatment.
3. Postsurgical adjuvant therapy that includes concurrents CRT or RT alone.

6.5.1 Chemoradiation therapy (CRT)

Cisplatin remains the cornerstone of treatment in recurrent and metastatic HNSCC. Postoperative concurrent administration of high-dose cisplatin with radiotherapy is more efficient than radiotherapy alone in patients with locally advanced HNSCC. Radiation therapy combined with simultaneous 5-fluorouracil (5-FU), cisplatin, carboplatin, and mitomycin C as a single drug or combinations of 5-FU with one of the other drugs result in a large survival advantage irrespective the employed radiation schedule. Numerous concurrent modalities provide several therapeutic alternatives for clinicians to choose from depending on the clinical scenario, competing toxicities, and side effect profiles of individual patients [142, 143, 202].

The tonsil is the most frequently represented subsite by the base of tongue [144,145]. Oropharyngeal carcinomas are usually diagnosed as locoregionally advanced disease [146]. Thus, most of the primary tumors presents at an advanced stage (T2 or greater). The incidence of nodal metastases ranges between 60-70% [147], which is probably related to the rich lymphatic supply of the dominant subsites of the oropharyngeal cancer[148].

The treatment decision-making process for oropharyngeal carcinomas arising in this functionally important anatomic region must consider not only the most optimal treatment strategy for local/regional tumor control achievement but also the associated morbidity to this critical site in the upper aerodigestive tract [147]. The treatment for advanced but resectable oropharyngeal carcinoma has traditionally been radical surgery and postoperative radiotherapy, often resulting in suboptimal rates of locoregional control (LRC) and significant long-term functional deficits, or radiotherapy alone for advanced unresectable tumors[148].

The most common method used worldwide was the delivery of cisplatin every 3 weeks [140,152][140, 152]. However, based on the assumption that more frequent drug administration could provide more significant radiosensitizing benefit and taking into account the less induced morbidity with smaller individual doses of drug without compromising treatment efficacy[149].

6.5.2 Induction chemotherapy

As advances in concurrent chemoradiotherapy (CRT) for locally advanced SCCHN improve local control and overall survival, distant failure has become a significant cause of mortality in this patient population, especially among patients presenting with advanced nodal disease. Induction chemotherapy (ICT) may decrease distant metastatic failure, however no clear survival advantage has been shown with the use of ICT over conventional CRT[164, 165].

Induction chemotherapy has been a controversial but attractive option for managing patients in elected clinical situations, especially for patients with high risk of distant metastasis [166]. Now that the local-regional control benefit of addition of cisplatin to radiation has been established in adjuvant setting as well as in definitive setting, investigations started to focus on understanding the optimal dosing and schedule of cisplatin. Because the frequent omission of the third dose of cisplatin due to toxicity, it is generally accepted that cumulative dose of cisplatin greater or equal to 200mg/m2 confers a survival benefit [166, 167].

Dosing schedule optimizations have looked at weekly cisplatin dosing ranging from 30 to 40 mg/m2 or daily administration from 5 to 7 mg/m2. Weekly dosing has gained popularity compared to the traditional dose of 100 7 mg/m2 every 3 weeks [168-171].

6.5.3 Adjuvant Chemotherapy and Radiation

Risk-adapted adjuvant radiation therapy for patients who have undergone surgical resection of their primary tumor is dependent on known histopathologic risk factors that include advanced T status, two or more positive lymph nodes, perineural invasion (PNI), lymphovascular invasion (LVI)[172], positive or close resection margins, and extracapsular extension (ECE) [173, 174].

There is evidence to suggest, that the usual histopathologic risk factors seen in cancers of the oral cavity, hypopharynx, and larynx are not prognostic for patients with HPV-positive oropharyngeal disease [175].

6.5.4 Immunotherapy in head and neck squamous cell carcinoma

Head and neck squamous cell carcinoma (HNSCC) has been historically associated with tobacco and alcohol use; however , in the past decade, infection with high-risk human papillomaviruses (HPV) and especially type 16 has been implicated in the pathogenesis of a subset of HNSCCs, mainly those arising from the oropharynx. HPV-associated distinct biological and clinical entity with a more favorable prognosis [120, 121, 152, 168]. For recurrent/metastatic (R/M) disease, cytotoxic-based chemotherapy remains the standard therapeutic option and the median survival of patients treated with palliative chemotherapy alonge ranges from 6 to 10 month [123, 176, 177]. Viral oncoproteins E6 and E7 represent good targets for immunotherapy represents a therapeutic approach that might allow clinicians to use conventional treatment at lower doses, reducing treatment-related toxicity. Viral oncoproteins E6 and E7 represent good targets for immunotherapy, as they are continuously expressed by tumor cells and are essential to maintain the transformation status of HPV+ oropharyngeal cancer cells [120, 178].

Low survival rates in combination with significant toxicities caused by current treatment strategies used in HNSCC underlies the urgent need for enhanced treatment options. It has been widely accepted that the immune system plays a crucial role in cancer development, as tumor cells evade immunosurveillance by exploiting inhibitory checkpoint pathways that suppress antitumor T-cell responses [121, 122, 175, 176,177].

Cancer is a multistep process originating from genetic alterations in normal proliferation and differentiation. In a normally functioning environment, immune surveillance acts as an effective tumor suppressor mechanism, as these alterations trigger the development of tumor-related antigens initially recognized by the immune system [120, 121, 137].

Both the innate and adaptive immune systems have the ability to distinguish between self and non-self pathogens. Innate immunity is based on non specific defense mechanisms that are activated immediately after contact with pathogen; it uses a limited number of receptors that are encoded in the germline and are able to recognize features common to many pathogens [120, 121]. In contrast, adaptive immunity relies upon somatic cell gene rearrangements to produce a multitude of antigen receptors that discriminate between closely related molecules; it is mainly driven by highly specific antigen receptors on T and B cells and is highly specific to a particular pathogen [123, 124].

Emerging evidence supports a vital role of the immune system in the development and evolution of HNSCC. Furthemore, the status of the immune system is likely to be of prognostic value in HNSCC. HNSCC is considered an immunosuppressive disease, characterized by dysregulation of immunocompetent cells and impaired cytokine excretion [125].

Patients with HNSCC have reduced antitumor immune responses, and tumor progression or relapse is believed to be associated with immune dysfunction. Several mechanisms, such as the presence of tumor-secreted proteins that act as inhibitory stimuli, cytokines and T cell apoptosis have been suggested to contribute to immune deregulation [126]. The presence of T-regulatory cells has emerged as a potential mechanism of immunomodulation in HNSCC.

The role of the immune system is also important in HPV-associated OPC. HPV infection is common, but a minority of individuals will develop cancer. Failure of the immune system to clear the oncogenic infection accounts for a minority of cases that finally develop cancer; persistence of HPV infection in lymphoid tissue of the head and neck might be related to self-regulatory mechanisms that allow these tissues to sample the oral environment without continuous immune activation [127]. Following establishment of HPV infection, HPV specific effector T cells are responsible for elimination of the virus and HPV-induced oncogenesis has been shown to correlate with weak HPV-specific T cell responses [128, 163]. On the other hand, PD1, a protein functioning as immune checkpoint by preventing the activation of T-cells, has been found in tonsillar crypts and PD1 infiltrating lymphocytes have been identified in HPV (+)-OPC, PD1 pathway might play a key role in HPV-related OPC oncogenesis [129, 145].

Combining radiation with an EGFR-targeted therapy such as cetuximab is a biologically sensible approach to potentiate the effects of radiation with less toxicity than expected with a cisplatin-based chemoradiotherapy. The epidermal growth factor (EGFR) is upregulated in 90% of head and neck tumors. This overexpression is associated with poor prognosis. Inhibition of EGFR pathway by a monoclonal antibody gave rather disappointing results [150]. Activation of the proto-oncogene EGFR is an early event in head and neck carcinogenesis. EGFR mRNA is highly expressed in SCCHN and contributes to the pathogenesis of the disease[151-153, 178]. Radiation therapy has been shown to increase EGFR expression in cancer cells, which potentially promotes radioresistance, further increasing its attractiveness as a therapeutic target[154].

Cetuximab is a chimeric immunologlobulin G1 (IgG1) monoclonal antibody. Cetuximab efficacy is mediated by antibody-dependent cell mediated cytotoxicity, a mechanism of cell-mediated immune defense whereby NK cells, actively lyse a target cell, whose membrane-surface antigen has been bound by cetuximab. NK cells are activated upon binding to surface receptor FCγRIIa [155]. Cetuximab in combination with platinum/5-FU has emerged as an alternative regimen for uncreated patients based on results from the first-line Treatment of Recurrent or Metastatic Head and Neck Cancer trial. Cetuximab can be used with chemotherapy in first-line treatment of recurrent or metastatic disease, and in second-line treatment of platinum-refractory disease. Preclinical studies in SCCHN cell lines have shown a synergistic effect of cetuximab with cisplatin[156, 157].

Previous studies in SCCHN cell lines have shown a synergistic effect of cetuximab with cisplatin, and clinical data in the metastatic setting confirm the activity of this combination[158, 159]. Young et al in their study have suggested 212 patients with SCCHN for HPV status via IHC analysis of p16, EGFR gene copy number by FISH, and EGFR protein expression by IHC [160]. They found that EGFR expression was positive in 87% and increased gene copy number in 20% of the tumors, with both associated with worse failure-free and overall survival. Whether HPV positivity truly confers a clinically significant differential response to cetuximab versus cisplatin remain unknown and is the focus of the trial RTOG 1016.

We will present a number of novel EGFR-directed monoclonal antibodies, apart from Cetuximab. One of them is **Necitumumab**. In contrast to cetuximab, which is chimeric (mouse7human), necitumumab is a fully human IgG1 MoAb-targeting EGFR that has the potential advantage of fewer skin toxicities and severe hypersensitivity reactions. Necitumumab blocks EGFR with high potency, with an IC50 of 1-2 nM, and exhibits comparable antitumor efficacy with that of cetuximab in preclinical models [161, 162].

Zalutumumab is a fully human IgG1k MoAb/targeting EGFR. Preclinical work demonstrates competitive ligand-binding inhibition by EGF and TGF-a of EGFR that subsequently blocks receptor dimerization and activation, as well as antitumor effect via antibody-dependent cellular toxicity [163].

Panitumumab is a fully human IgG2 MoAb directed against EGFR[163]. Panitumumab has less potential for severe hypersensitivity reactions than cetuximab. As an IgG2 ntibody may limit panitumumab from inducing antitumor activity through antibody dependent cell cytotoxicity and NK cell activation[163].

Nimotuzumab (h-R3) is a humanized IgG1 MoAb-directed at EGFR and has demonstrated less skin toxicity than cetuximab or panitumumab [163]. Preclinical data have

shown nimotuzumab to bind EGFR% with high affinity, inhibit cell proliferation and enhance antitumor efficacy of radiation [163].

Nivolumab is a humanized monoclonal anti-PD-1 antibody which is approved for malignancies such as melanoma and renal cell carcinoma [163].

6.6. Reconstruction of Defects after Cancer Surgery

Because of the complex function and anatomy of oropharynx, reconstruction after ablation surgery for oropharyngeal cancer is always challenging to the head and neck reconstructive surgeon [215]. Defects of the palate following ablative oncologic surgery can cause severe functional and cosmetic deformities. The creation of large oronasal and oromaxillary fistulae and the loss of crucial tooth-bearing segments can extensively impair phonation, oral alimentation, lip and cheek support, and midface projection [216].

There are several different procedures available to surgeons for the reconstruction of significant soft palate defects [217, 218]. These include the use of various tongue, buccal, pharyngeal, palatal, and free flaps, as well as the use of prosthetic obturators [217-220]. The traditional method of reconstructing these palatal and maxillary defects is by placing a maxillofacial prosthesis to obturate the cavity and seal the palate [221, 222]. These appliances can be cumbersome and difficult to clean. Patients must also maintain meticulous hygiene of the surgical cavity. The defects of the soft palate are challenging to reconstruct because of their complicated anatomy and causing velopharyngeal incompetence for speech and swallowing function. Many reconstruction techniques have been described to improve postoperative function after oropharyngeal resection, including soft palate [215].

Microvascular free-flap techniques to reconstruct defects of the palate and maxilla allow immediate, 1-stage reconstruction. Sufficient bone and soft tissues can be transferred without the limitations of vascular pedicle length and tissue orientation. Various donor sites have been recommended in the literature [223-226]. The criteria for palate closure with a soft tissue free flap in a series reported by Funk et al. [227]included sufficient residual dentition to retain a dental prosthesis or, if the anatomy of the reconstruction would allow, retention of an upper denture despite the absence of teeth [178,179].

Davidson et al. [178] recommended free-tissue transfer closure of maxillectomy defects when substantial associated sino-orbital and/or soft tissue defects existed. They concluded their review, however, by stating ‘’refinement of microsurgical techniques with free vascularized bone may provide an ideal answer in providing surgical reconstruction that could support an implant-bone prosthesis’’. Various factors have determined flap selection. Whether to select a bone-containing free flap has been primarily determined by the amount, location, and quality of residual dentition and/or denture-bearing alveolar arch. A combined treatment of surgical resection and postoperative radiotherapy is another treatment option for palate cancer in the advanced stage [27, 21]. For surgical reconstruction, various reconstruction methods are used, such as uvulopalatal flap [228], buccal mucosal [229] and radial forearm flap [215, 224].

The type of flap utilized is based on operator preference. The resection of palatal cancer can result in a large defect in the palate, causing functional problems, including nose breathing, swallowing, digestion, and speech [230]. Palatal reconstruction solves these problems [231]. One of the primary aims of palatal reconstruction is the separation of the nasal and oral cavities. Without this separation, speech is altered, and swallowing is hindered [212, 231].

Many methods are used to reconstruct palatal defects, and it remains a controversial procedure. Many surgeons have used obturator prostheses. Patients with a prosthesis should maintain the hygiene of the prosthesis and the surgical site [231, 232].

At this point, we should refer to the classification of soft palate defects as Urken[232] adopts this. Urken adopted a classification depending on the size of the defect:

Type I: The defect area of the soft palate is 25% or less.

Type II: The defect area of the soft palate is more than 25%, but less than 50%.

Type III: The defect area of the soft palate is more than 50%, but 75% or less.

Type IV: The soft palate's defect area is more than 75%, but 100% or less.

Many reports [230-234] recommending free-tissue transfers for maxillary reconstruction describe the use of the scapular osteocutaneous flap. This flap has the advantage of having a soft tissue component that can be rotated around the adequate bone stock with greater freedom than other composite flaps. It is particularly useful in defects in which the orbital floor, zygoma bone, and palate must be reconstructed.Controversy exists in the literature concerning which flap is best to seal the palate. Schusterman et al. [234] recommended a bone- containing free flap for maxillary reconstruction when structural support

was needed, and previous irradiation precluded the use of nonvascularized grafts [231, 232].

Many surgeons have tried to perform palatal reconstruction using a pedicled flap near the palatal defect that preserves the vascular pedicle[233]. However, pedicled flaps also have disadvantages when used in the palatal reconstruction. Large flaps are not able to be harvested, and palatal defects cannot be covered entirely[234]. The length of the pedicle is also restricted. Microvascular free tissue transfer has been proposed as a safe method for stable palatal reconstruction [231, 235].

It is generally known that free flaps, including the ALT free flap, rectus abdominis muscle flap, LD free flap, and radial forearm free flap can be used to treat palatal defects [231, 235]. In the oral cavity, bulky flaps can make it difficult to speak and swallow food and drink. If radiation therapy has been applied after palatal cancer surgery, the tissue tends to be unstable due to radiological damage. The condition of blood vessels is not conducive to a good anastomosis. In such cases, a long pedicle is used in conjunction with a radial forearm flap, and anastomosis is performed in a healthy tissue area which was not subjected to radiation therapy [235].

For large defects, coverage was performed using free flaps. In these cases, a large flap could be elevated and divided into two skin paddles to cover both the nasal lining and the oral lining. Palatal turnover flaps that fit the defect sizes were not able to be harvested in cases of significant defects, so we harvested large flaps to reconstruct both the oral lining and the nasal lining [231,232].

In cases of early soft palate cancer, it can be cured using surgical treatment and radiotherapy. Simultaneously, in advanced cases, surgical resection, supportive radiotherapy, and additional chemotherapy can be applied. The soft palatal area is a dynamic muscular structure, which effectively separates the oral and nasal cavities pathway. Soft palate defects that occur after resection may cause hypernasal speech and food reflux into the nose upon swallowing [231, 235].

Prostheses and surgical reconstruction are used for the functional reconstruction of the soft palate [215]. Although reconstruction with a prosthesis is relatively easy to perform, it decreases function and patient compliance. The procedure is challenging to achieve in patients with a large defect or without teeth [215].

Radial forearm free flap is most frequently used among soft palate reconstructions using the free flap. It can be applied without the limitation of defect size but has disadvantages of requiring a longer operation time, skin transplantation to the donor site, and sacrificing the radial artery [215]. Gangloff et al. [236] reported that hypo-hyoid myocutaneous flap was performed to reconstruct small or intermediate soft palate defects. The pharyngeal flap is commonly used for velopharyngeal insufficiency.

Another alternative is the palatal island and the lateral pharyngeal wall flaps. The palatal island flap has been well described for head and neck cancer reconstruction to repair defects in sites such as the soft palate, hard palate, retromolar trigone, cheek, tonsil, and lateral pharyngeal wall[236, 237]. This flap is particularly versatile; however, when used alone for soft palate repair, the technique provides only an adynamic reconstruction. Harvest of the palatal island is initiated by making an incision around the hard palate mucosa's perimeter within a 5-mm gingival margin medial to the teeth. The incision is extended posteriorly to the hard and soft palate junction bilaterally [237].

The thin, pliable nature of the fasciocutaneous flaps is ideally suited for oropharyngeal reconstructions, especially when the defect involves multiple sites, such as the pharyngeal wall, soft palate, and tongue base. The radial forearm free flap has been widely used for soft palate reconstruction. Still, the reconstructed soft palate contracts during the healing phase, and there is a risk of an increasing space developing between the reconstructed soft palate and posterior pharyngeal wall [107]. RFFF is the most common flap to reconstruct the oral cavity and oropharynx because the skin is thin, pliable, abundant, and well vascularized.

Successful reconstruction of the base of tongue defects depends on the amount of remaining mobile tongue, the extent of pharyngeal defect, and the preservation of the lingual and hypoglossal nerves. The radial forearm free flap is the workhorse flap for most pharyngeal defects. If half of the base of the tongue remains, the function is often well preserved. Restoring function relies on the mobility of the soft palate and pharyngeal walls. It is necessary to use a flap of sufficient bulk to create a base of tongue mouth [3, 4, 173].

Isolated soft palate defects that include the posterior free edge of the soft palate and leave a break in the arch's continuity are best reconstructed using pharyngeal flaps. This has two distinct advantages. Using free pharyngeal myomucosal flaps restores a continuous muscular oropharyngeal sphincter. This also will decrease and surgically

narrow the oropharyngeal opening, improving on the compensation by unaffected areas [3, 4]. For smaller defects, undermining the lateral pharyngeal wall in a plane deep to the superior pharyngeal constrictor muscles and advancing it medially to close the defect primarily works well. For more extensive defects, a superiorly based posterior pharyngeal flap could be used. The defect in the posterior pharyngeal wall can be closed primarily [232, 239, 240]. For larger defects of the soft palate or defects that extend into the lateral pharyngeal wall, the posterior pharyngeal wall, the base of the tongue, or all of these areas, a regional or free flap is combined with the local flap [239, 240, 241].

A commonly seen presentation is a locally advanced tonsillar primary that extends onto the soft palate, leaving a significant lateral pharyngeal and soft palate defect, which may extend into the glossotonsillar sulcus and the base of the tongue. The mucosal side of the posterior pharyngeal flap faces the nasal cavity while the raw muscle faces the oropharynx. A radial forearm flap is used to cover the flap's muscle onto the base of the tongue [240, 242].

6.7. The Future-The Vaccine Therapy

Over the last several decades, it has become increasingly clear that the immune system plays a vital role in cancer prevention through immune surveillance [242,243]. Recently, there has been an intense focus on immunotherapy, which uses substances to stimulate or suppress the immune system to help the body fight cancer.

Anticancer vaccine therapies involve generating an antitumor immune response by presenting a tumor-associated antigen (TAA) plus an immunostimulatory adjuvant, resulting in immune sensitization to tumor antigens [241, 241]. Several vaccination strategies have been applied, including the transfection of TAA expression plasmids into patient tissues (DNA vaccines), the administration of TAA peptides (peptide vaccines), and the use of cultured human or microbial cells to generate an antitumor immune response. The primary goal of prophylactic vaccination is to induce an immune response such that high-titers of HPV-neutralizing antibodies are produced that are capable of preventing initial antibodies are produced that are capable of preventing initial infections, making HPV antigen-specific B cells the target cell type for these vaccines. On the contrary, therapeutic vaccines focus on the generation of CD8+ HPV-specific T cell immune response. E6 and E7 oncoproteins are most frequently targeted for vaccine development [130]. Vaccine mediated immune strategies are either prophylactic against primary infection with the view to prevent carcinogenesis or therapeutic in established HPV- associated HNSCC targeting E6 and E7 oncoproteins.

We will present a series of DNA Vaccines. One of them is **INO-3112**. INO-3112 is a combination of two previously developed DNA vaccines, VGX-3100 and INO-9012, originally developed for the treatment of cervical cancer. The expression plasmids contained within the vaccine produce E6 and E7 proteins from human papillomavirus HPV 16 and HPV 18, respectively [242]. This vaccine is administered s an intramuscular injection of plasmid DNA once every three weeks to a total of four doses. Because the plasmid-encoded antigens must be expressed to generate an immune response, each injection is accompanied by electroporation with the CELLECTRA device [242].

The **Allovectin-7** vaccine is a DNA/lipid complex containing plasmids encoding the Human Leukocyte Antigen-B7 (HLA-B7) heavy chain and β2 microglobulin, resulting in the expression oft he comkplete major histocompatibility complex type-I (MHC-I) molecules on the surface of tumor cells. Many tumor types evade immune recognition by reducing MHC-I expression, thereby preventing the presentation of tumor antigens on the cell, surface[242, 244, 245]. Increasing MHC-I may facilitate immune recognition of tumor antigens as foreign, promoting antitumor immunity.

The peptide vaccines can also prevent the development of Head and Neck Squamous Cell Carcinoma. In this category belong substances such as **MAGE-A3/HPV16, Mucin-1, AlloVax and ISA101/ISA201.** The **MAGE-A3** vaccine was originally developed for treatment of non-small cell lung carcinoma, although as phase III trial of>2000 patients failed to demonstrate efficacy over placebo for this patient population [242-244]. This vaccine targets MAGE-A3, a human protein which is highly expressed in a variety of tumors and during embryogenesis[244].

Mucin-1 (MUC1) is a glycosylated protein which undergoes proteolytic cleavage to form heterodimeric complexes on the cell surface, where it helps to provide a protective barrier between the cell and the external environment [242, 245]. MUC1 is expressed by most epithelial cells and is overexpressed in multiple tumor types. It has been shown that in tumor cells MUC1 promotes tumor growth, metastasis, and drug resistance [242, 243]. Tumor-associated MUC1 is characterized by altered glycosylation patterns, which enable differential targeting of tumor MUC1 for vaccine therapy [242].

The two-part **AlloVax** vaccine is comprised of chaperone protein-enriched tumor cell lysate from the patients own

tumor and the AlloStim adjuvant, an intentionally mismatched allogenic stem cell transplant. This combination produces a host-versus-graft response called the "mirror effect" [242-245].

The ISA101 vaccine is a mixture of 13 overlapping 25-35 amino acid synthetic peptides derived from the HPV16 E6 and E7242. The peptide mixture (nine E6 peptides and four E7 peptides) is combined with the Monanide ISA-51 adjuvant, which contains all potential T cell epitopes and therefore produces T cell activation irrespective of the HLA type of the patient [242].

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