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Chapter

# HPV-Positive Oral Squamous Cell Carcinoma

*Șerban Vifor Gabriel Berteșteanu, Raluca Grigore, Alexandru Nicolaescu and Mihnea Cojocărița-Condeescu*

## Abstract

Head and neck malignancies represent the sixth most frequent type of cancer currently in worldwide statistics. Of these, oral and pharyngeal cancers have steadily increased, being linked with the increase in HPV infection pandemic. This rise is not due to one cause, but rather multiple factors such as lifestyle and sexual behavior pattern changes and globalization. Because of the anatomy of the oral cavity and oropharynx, the proper diagnosis is easily delayed, and patients present with advanced stage disease, which requires aggressive and extensive surgery along with neck dissection and chemoradiotherapy. Patients with advanced stage disease have a high recurrence risk with a low 5-year survival rate. Preventing the HPV infection is of course desirable, but right now, for adults which already are infected and have a higher risk of developing HPV-related neoplasias, as well as for our head and neck cancer patients, alternative treatment algorithms are necessary.

**Keywords:** head and neck cancer, HPV, OPSCC, oral cancer, neck dissection

## 1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy in the world [1]. The tonsils are the most common location in oropharyngeal malignancy. Despite being easily accessible to examination, its symptoms are usually ignored especially in early stages, leading to high morbidity and mortality. Traditionally oral and oropharyngeal cancers were attributed to smoking and alcohol abuse, but in more recent years there has been an increase in numbers due to high prevalence of human papillomavirus (HPV) infection. The presence of HPV can alter the prognosis of the disease, and recently there was a change in the WHO classifications and TNM staging to reflect this [2]. Depending on the stage of the disease, treatment for oral and oropharyngeal cancers consists of surgery and/or chemoradiotherapy.

## 2. Etiology

Traditionally smoking is considered the major factor in developing tonsil cancer. More than three quarters of oropharyngeal cancers are associated with tobacco use in all its forms (cigarettes, cigars, pipes, chewed tobacco). Secondhand smokers also have an increased risk of developing head and neck cancers. Alcohol is the second

major risk factor in the etiology of tonsil cancer. Although studies have not shown a direct link between the use of alcohol alone in carcinogenesis, the combined effect of tobacco and alcohol has a synergic effect on the development of cancer cells [3].

In the last 10 years, HPV infection has been widely recognized as an important etiological factor in the development of head and neck squamous cell carcinomas. The development of PCR analysis or in situ hybridization has demonstrated the impact of HPV in oropharyngeal malignancy [1]. Gillison [4] was the first to show that HPV-positive oropharyngeal cancers have different molecular, clinical, and pathological traits than HPV-negative cancers. Although HPV is considered to play a vital role in most head and neck cancers, studies have only proven its impact in oropharyngeal cancers [5].

HPV is a double-stranded DNA oncovirus and is epitheliotropic, infecting the basal cells of the epithelium and can be found in up to 60% of squamous cell carcinomas of the oropharynx [6]. There are more than 150 isolated strains of HPV, but only two types 16 and 18 are most commonly linked to oropharyngeal cancers. The oncogenic effect of HPV is due to two proteins E6 and E7 that target the p53 and pRB (retinoblastoma) tumor suppressor genes of the infected cells making them vulnerable to mutations [7]. The loss of the pRB tumor suppressor determines the intranuclear accumulation of p16. p16 has a tumor suppressor role which normally would inhibit cell cycle but is overexpressed in HPV-positive tumors due to the action of E7. It is considered a useful marker in oropharyngeal cancers [8]. Due to the large body of evidence that suggest that HPV-positive and HPV-negative oropharyngeal cancers represent distinct subgroups of OPSCC, the National Comprehensive Cancer Network (NCCN) guidelines as of 2017 require HPV testing for all oropharyngeal tumors and that the HPV status must be included as a stratification factor [2]. The latest staging for oropharyngeal cancers takes into account the distinct groups of OPSCC, and because HPV-positive cancers tend to have a better prognosis, separate TNM staging systems are used [9, 10].

Dietary habits also play a role in carcinogenesis although harder to properly quantify. For example, iron deficiency may lead to an increased vulnerability of the oropharyngeal mucosa and decreased immune system. A diet low in fruits and vegetables can lead to a vitamin A and vitamin E deficiency that is associated with an increased risk of developing oropharyngeal malignancies. Poor oral hygiene can also be a risk factor especially for tobacco and alcohol users [11].

## 3. Symptoms and diagnosis

Oropharyngeal cancer is usually located in the tonsillar fossa, but extension to adjacent structures is common (**Figure 1**). Frequently tonsillar carcinoma extends downward to the tongue base along the glosso-tonsillar sulcus (**Figure 2**) and to the soft palate laterally. Laterally the tonsillar fossa is bounded by the superior constrictor muscle of the pharynx which offers some resistance to the spread of carcinoma. Extension past the superior constrictor muscle represents involvement of the parapharyngeal space with consecutive involvement of the pterygoid musculature or mandible locally advanced disease. Extension to the skull base is rare but possible.

Due to its rich lymphatic drainage, lymph node involvement is present in about 70% of patients. The most common lymph node levels affected are level II and level III [12].

Distant metastasis from tonsillar cancer occurs in about 15–30% of cases; the most common sites are the lung, liver, and bones [13].

Tonsillar cancer may present with a variety of signs and symptoms. In the early stages, the patient is usually asymptomatic, or it can mimic some mild diseases like sore throat or acute tonsillitis. Patients usually complain of sore throat, unilateral

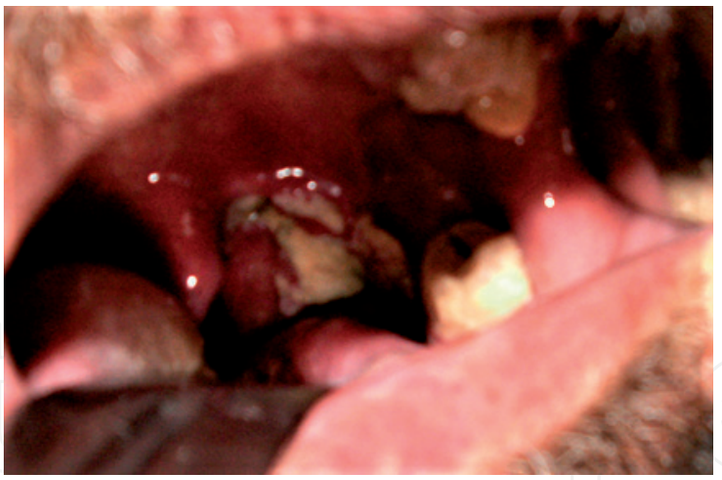

**Figure 1.**
*Oral examination of a male patient with a left oropharyngeal tumor which infiltrates and deforms the tonsillar fossa as well as part of the soft palate, with ulceration and suprainfection.*

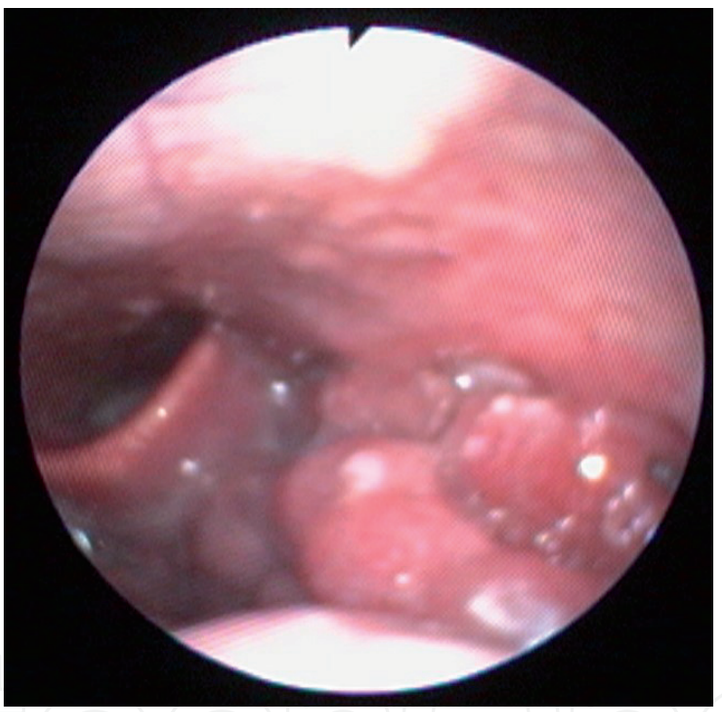

**Figure 2.**
*Fiber-optic endoscopy of a male patient showing inferior spread of a left side oropharyngeal tumor towards the tongue base.*

otalgia, or a feeling of a mass in the throat. In advanced stages it can present with dysphagia. In latter stages the patient may present with trismus or bleeding from the mouth. If the tumor has ulcerations and necrosis, patients will usually complain of bad breath. The rich lymphatic drainage could mean that the first sign of disease is enlarged lymph nodes especially in the jugulodigastric region (group II). Such patients must be asked about weight loss, hoarseness, and odynophagia. A thorough patient history about tobacco and alcohol use and other known etiological factors (including known HPV infection) may raise suspicion of a malignant tumor. HPV-positive tumors will typically appear in younger nonsmoking patients.

Patients diagnosed with a tumor involving the oral and oropharyngeal regions must undergo a full ENT examination, with neck palpation, flexible endoscopy, and biopsy. After histological confirmation of the malignancy, imaging studies must be obtained to stage the tumor. Contrast CT scans represent the standard method for

| Stage | T | N | M |
|---|---|---|---|
| I | T0-T2 | N0 | M0 |
| | T0-T2 | N1 | M0 |
| II | T0-T2 | N2 | M0 |
| | T3 | N0-N2 | M0 |
| III | T0-T3 | N3 | M0 |
| | T4 | N0-N3 | |
| IV | T Any | N Any | M1 |

**Table 1.**
*AJCC staging of HPV-positive (p16+) oropharyngeal cancer [14].*

| Tumor | Characteristics |
|---|---|
| T0 | No primary tumor identified |
| T1 | Tumor less than 2 cm in any dimension |
| T2 | Tumor between 2 and 4 cm |
| T3 | Tumor greater than 4 cm in any dimension or extension to lingual surface of the epiglottis |
| T4 | = moderately advanced local disease—tumor invades the larynx, extrinsic muscles of the tongue, medial pterygoid muscles, hard palate, mandible or beyond |

**Table 2.**
*AJCC tumor characteristics regarding HPV-positive (p16+) oropharyngeal carcinoma [14].*

| Lymph node (N) | Clinical N (cN) | Pathological N (pN) |
|---|---|---|
| Nx | Regional lymph nodes cannot be assessed | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis | No regional lymph node metastasis |
| N1 | One or more ipsilateral lymph nodes, none >6 cm | Metastasis in 4 or fewer lymph nodes |
| N2 | Contralateral or bilateral lymph nodes, none >6 cm | Metastasis in more than 4 lymph nodes |
| N3 | Lymph node(s) > 6 cm | |

**Table 3.**
*AJCC lymph node characteristics for staging of disease regarding HPV-positive (p16+) oropharyngeal cancer.*

staging and should include the skull base, cervical region, thorax, and abdomen to possibly identify secondary tumors. Contrast-enhanced MRI is superior to CT in detecting soft tissue extension and involvement but may be influenced by dental foreign materials.

Staging of the disease is done by using the AJCC cancer staging system (**Table 1**) that uses three variables—primary tumor characteristics (T), lymph node involvement (N), and the existence of metastases (M).

Starting from 1 January 2017, all patients with oropharyngeal cancer should be tested for the presence of HPV, thus classifying them in one of two possible categories—HPV positive ($p16^{INK4A}$+) and HPV negative. There is no current gold standard test, because all available testing methods were developed for cervical cancer, and not perfectly adapted for tonsillar cancer. However, p16 protein IHC is currently used for detecting HPV presence [15].

Tumor and lymph node characteristics are described in **Tables 2** and **3**, whereas the presence of distant metastases automatically stages the disease into the last and most severe stage—stage IV (**Table 1**).

## 4. Treatment and outcome

Treatment of oropharyngeal malignancy depends on the disease stage, but the principle that guides it is the same as in all cancer surgery: local disease control. Thus, with modern surgical and irradiation techniques, 5-year survival rates of almost 100% are attainable [16].

For the purpose of management protocol, oropharyngeal cancer is divided into early-stage (T1 and T2) and advanced diseases (T3 and T4). The latter are divided into resectable and non-resectable tumors. According to this, treatment for early-stage disease should be either surgery or radiation therapy with concurrent chemotherapy. Surgical treatment consists of excision of the primary tumor, either by a trans-oral approach or by external approach (lateral pharyngotomy or trans-mandibular approach by mandibular swing technique (**Figures 3–5**)).

Most oropharyngeal tumors are accessible by trans-oral approach. This is the least aggressive type of surgical approach, with the least morbidity. Auto-static mouth gags (McIver, Dingmann, etc.) permit good exposure of the surgical site, and excision by electrocautery, radiofrequency, and $CO_2$ laser, and optical augmentation either using surgical loupes or operating microscopes permit tackling most of the T1 to T3 tumors [17].

Tumors extending downward to the epiglottis and hypopharynx (pyriform sinus) require an external approach, by lateral pharyngotomy. This approach provides access to the oro- and hypopharynx, as well as control of the cervical large blood vessels and lymph nodes [18–20].

Advanced tumors (T4), tumors which involve adjacent structures (extrinsic muscles of the tongue, larynx, mandible, pterygoid muscles, or hard palate), often require an even more aggressive external approach—by lateral mandibulotomy—the so-called mandibular swing technique. This approach permits access to the

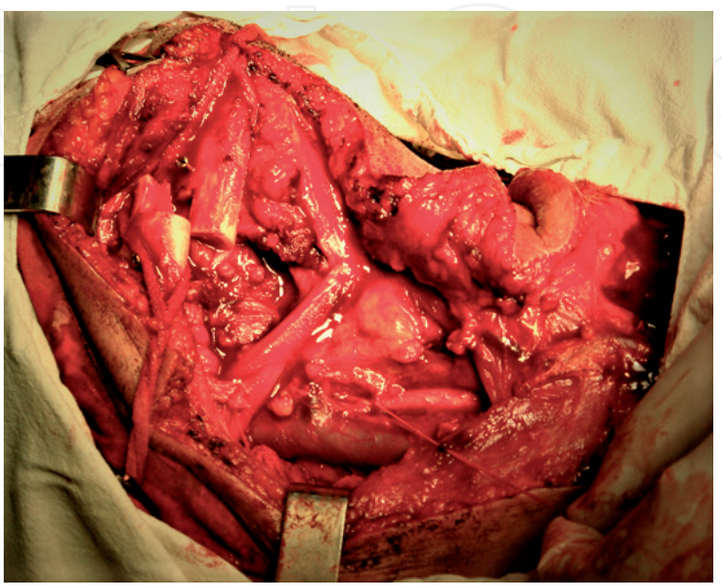

**Figure 3.**
*External approach to a right side advanced (T4) oropharyngeal cancer which shows the neck dissection, with internal jugular vein and bifurcation of the common carotid artery visible inferior to the posterior belly of the omohyoid muscle, as well as the mandibulotomy—The creation of the mandibular "swing."*

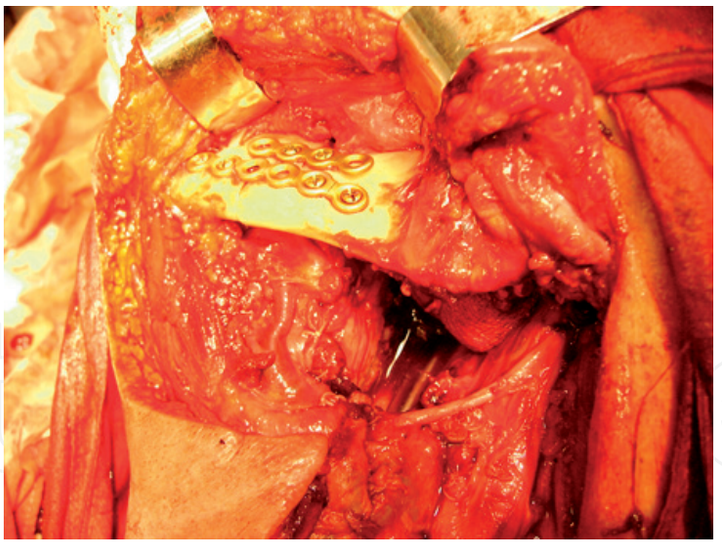

**Figure 4.**
*External approach to a left side advanced oropharyngeal tumor, via mandibular "swing" demonstrating closure of the mandibulotomy using two titanium miniplates anchored with screws.*

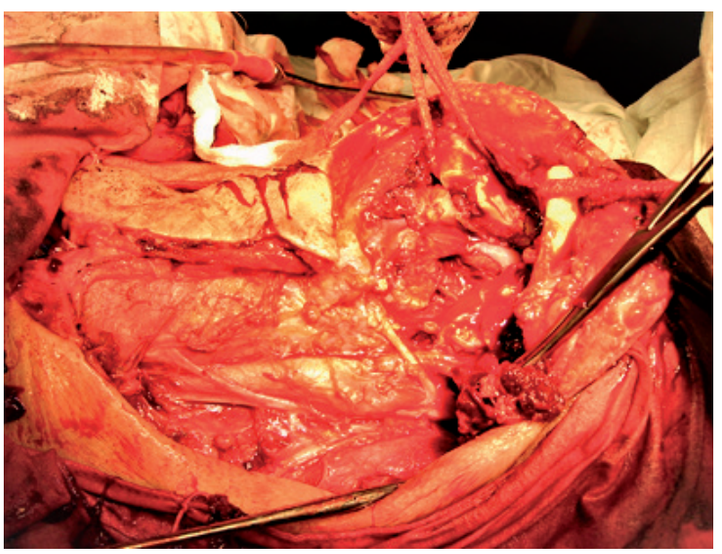

**Figure 5.**
*Extensive external approach to a left side advanced (T4) tumor of the oropharynx and hypopharynx extending to the bony cortex of the mandible—with modified radical neck dissection and lateral mandibulotomy, with the two resulting mandibular pieces being pulled apart at different angles so as to permit wider access.*

oral cavity, oropharynx, as well as hypopharynx and lateral cervical lymph nodes, parapharyngeal space, and masticator space and allows instrumentation of the entire oral cavity, making hard palate resections possible [21, 22].

Whichever surgical approach to the primary tumor the surgeon opts for, just as important as the complete excision of the tumor (the T) is the neck dissection. Tumors that do not pass the midline usually require ipsilateral lymph node dissection. However, bilateral neck dissection is sometimes required because of the vast network of lymphatics that drain the lateral pharyngeal area—most patients present with at least clinically N1 on diagnosis [23, 24].

The alternative to surgical excision of the tumor is external intensity-modulated radiation therapy (IMRT) with or without adjuvant chemotherapy. This procedure has similar outcomes compared to surgery in cases of early-stage tumors but is slightly inferior compared to surgery when addressing advanced tumors. The dose delivered to the surrounding tissues is responsible for the toxicity and late adverse

effects of radiation therapy, such as osteoradionecrosis of the mandible, radiomucositis, xerostomia, dental cavities, and teeth avulsion [25]. These have a high impact on the patients' quality of life; thus modern management of HPV-positive oropharyngeal cancer consists in trans-oral excision (with a rising trend towards robotic surgery) of the primary tumor with selective neck dissection followed by low-dose radiation therapy [25].

## 5. Conclusions

As HPV infection is a growing concern worldwide, cases of HPV-positive oral and oropharyngeal carcinoma become more frequently encountered. Treatment options for this type of malignancy follow the same principles as for non-HPV-positive squamous cell carcinoma of the oral cavity and pharynx, consisting in surgery for locoregional control of the primary tumor and regional lymph nodes and radiation therapy—either as a stand-alone option or as an adjuvant therapy following surgical excision.

However, particularities of HPV-positive oropharyngeal cancer have led to a separation of this pathologic entity from the rest of squamous cell carcinomas involving the oropharynx. These tumors have a better outcome following treatment and thus treatment options were de-escalated to offer the same outcome and 5-year survival as well as less morbidity and a better quality of life.

New perspectives in treating the chronic HPV infection as well as preventing this infection by introducing efficient vaccination programs that target girls and boys also offer a positive future perspective on reducing malignancies associated with this viral infection, including those affecting the oral cavity and pharynx.

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