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
Human Papillomavirus

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
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...
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\textsubscript{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
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

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.
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.

Author details

Șerban Vițor Gabriel Berteșteanu1,2, Raluca Grigore1,2, Alexandru Nicolaescu3, and Mihnea Cojocărița-Condeescu1

1 ENT Head and Neck Surgery Department, General Medicine Faculty, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
2 ENT Head and Neck Surgery Clinic, “Colțea” Clinical Hospital Bucharest, Bucharest, Romania

*Address all correspondence to: alexandru87nicolaescu@gmail.com

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
References

[1] Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. Journal of Clinical Oncology. 2011;29(32):4294-4301

[2] Adelstein D, Gillison ML, Pfister DG, Spencer S, Adkins D, Brizel DM, et al. NCCN guidelines insights: Head and neck cancers, version 2.2017. Journal of the National Comprehensive Cancer Network. 2017;15(6):761-770

[3] Morse DE, Psoter WJ, Cleveland D, Cohen D, Mohit-Tabatabai M, Kosis DL, et al. Smoking and drinking in relation to oral cancer and oral epithelial dysplasia. Cancer Causes & Control. 2007;18(9):919-929

[4] Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. Seminars in Oncology. 2004;31(6):744-754

[5] Stransky N, Egloff AM, Tward AD, Kostic AD, Cibulskis K, Sivachenko A, et al. The mutational landscape of head and neck squamous cell carcinoma. Science. 2011;333(6046):1157-1160

[6] Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: A systematic review. Cancer Epidemiology, Biomarkers & Prevention. 2005;14(2):467-475. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15734974 [Accessed: 3 May 2019]

[7] Hassani S, Castillo A, Ohori JI, Higashi M, Kurono Y, Akiba S, et al. Molecular pathogenesis of human papillomavirus type 16 in tonsillar squamous cell carcinoma. Anticancer Research. 2015;35(12):6633-6638. Available from: www.iiar-anticancer.org [Accessed: 10 December 2019]

[8] Oh JE, Kim JO, Shin JY, Zhang XH, Won HS, Chun SH, et al. Molecular genetic characterization of p53 mutated oropharyngeal squamous cell carcinoma cells transformed with human papillomavirus E6 and E7 oncogenes. International Journal of Oncology. 2013;43(2):383-393

[9] Oral Cavity and Oropharyngeal Cancer Stages [Internet]. Available from: https://www.cancer.org/cancer/oral-cavity-and-oropharyngeal-cancer/detection-diagnosis-staging/staging.html [Accessed: 10 December 2019]

[10] Pfister DG, Spencer S, Adelstein D, Adkins D, Brizel D. NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers [Internet]. 2.2017. Available from: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

[11] Gupta B, Bray F, Kumar N, Johnson NW. Associations between oral hygiene habits, diet, tobacco and alcohol and risk of oral cancer: A case-control study from India. Cancer Epidemiology. 2017;51:7-14

[12] Lee DJ, Kwon MJ, Nam ES, Kwon JH, Kim JH, Rho YS, et al. Histopathologic predictors of lymph node metastasis and prognosis in tonsillar squamous cell carcinoma. Korean Journal of Pathology. 2013;47(3):203-210. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3701815/ [Accessed: 17 December 2019]

[13] Chung TS, Stefani S. Distant metastases of carcinoma of tonsillar region: A study of 475 patients. Journal of Surgical Oncology. 1980;14(1):5-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7382512 [Accessed: 17 December 2019]

[14] Lydiatt W, O’Sullivan B, Patel S. Major changes in head and neck staging
for 2018. American Society of Clinical Oncology Educational Book. 2018;38(38):505-514. Available from: http://ascopubs.org/doi/10.1200/EDBK_199697 [Accessed: 17 December 2019]

[15] Kim KY, Lewis JS, Chen Z. Current status of clinical testing for human papillomavirus in oropharyngeal squamous cell carcinoma. The Journal of Pathology: Clinical Research. 2018;4:213-226. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30058293 [Accessed: 17 December 2019]

[16] Foote RL, Hilgenfeld RU, Kunselman SJ, Schaid DJ, Buskirk SJ, Grado GL, et al. Radiation therapy for squamous cell carcinoma of the tonsil. Mayo Clinic Proceedings. 1994;69(6):525-531. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8189757 [Accessed: 19 December 2019]

[17] Flint PW, Haughey BH, Lund VJ, Niparko JK, Robbins TK, Thomas RJ, et al. Cummings Otolaryngology—Head and Neck Surgery. 6th ed. Philadelphia, PA: Saunders-Elsevier; 2015. DOI: 10.1016/B978-0-323-05283-2.00009-4

[18] Bertolin A, Ghirardo G, Lionello M, Giacomelli L, Lucioni M, Rizzotto G. Lateral pharyngotomy approach in the treatment of oropharyngeal carcinoma. European Archives of Oto-Rhino-Laryngology. 2017;274(6):2573-2580

[19] Laccourreye O, Benito J, Menard M, Garcia D, Malinvaud D, Holsinger C. Lateral pharyngotomy for selected invasive squamous cell carcinoma of the lateral oropharynx—Part I: How. Laryngoscope. 2013;123(11):2712-2717

[20] Laccourreye O, Seccia V, Ménard M, Garcia D, Vacher C, Holsinger FC. Extended lateral pharyngotomy for selected squamous cell carcinomas of the lateral tongue base. The Annals of Otology, Rhinology, and Laryngology. 2009;118(6):428-434

[21] Spiro RH, Gerold FP, Strong EW. Mandibular “swing” approach for oral and oropharyngeal tumors. Head & Neck Surgery. 1981;3(5):371-378. Available from: http://doi.wiley.com/10.1002/hed.2890030505 [Accessed: 19 December 2019]

[22] Holsinger FC, Laccourreye O, Weber RS. Surgical approaches for cancer of the oropharynx. Operative Techniques in Otalaryngology-Head and Neck Surgery. 2005;16(1 Spec. Iss):40-48. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1043181005000023 [Accessed: 19 December 2019]

[23] Goudakos JK, Markou K, Nikolaou A, Themelis C, Vital V. Management of the clinically negative neck (N0) of supraglottic laryngeal carcinoma: A systematic review. European Journal of Surgical Oncology. 2009;35:223-229

[24] Zenga J, Stadler M, Massey B, Campbell B, Shukla M, Awan M, et al. Lymph node yield from neck dissection in HPV-associated oropharyngeal cancer. Laryngoscope. 2019. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31206708 [Accessed: 19 December 2019]

[25] De Felice F, Tombolini V, Valentini V, De Vincentiis M, Mezi S, Brugnoletti O, et al. Advances in the management of HPV-related oropharyngeal cancer. Journal of Oncology. 2019;2019:9173729. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31097964 [Accessed: 19 December 2019]