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Research Progress on Human Papillomavirus-Associated Oropharyngeal Cancer

Jiefan Zhao[1], Yuhui Zhao[1], Jianqi Gu[2] & Qing Dong[3]

[1] North China University of Science and Technology
[2] Hebei General Hospital
[3] Professor, School of Stomatology, North China University of Science and Technology.
Correspondence: Jianqi Gu, Hebei General Hospital; Qing Dong, Professor, School of Stomatology, North China University of Science and Technology.

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Abstract

HPV-positive oropharyngeal carcinoma is classified as a distinct clinical entity that differs substantially from other types of head and neck tumors in terms of epidemiology, morphology, molecular and clinical features, treatment, and prognosis. The research progress in the above aspects is mainly reviewed.

Keywords: human papillomavirus, oropharyngeal cancer, oropharyngeal squamous cell carcinoma

1. Introduction

Oropharyngeal cancer is a common malignant tumor in the head and neck, and the most common pathological type is squamous cell carcinoma (oropharyngeal squamous cell carcinoma, OPSCC), accounting for more than 90% (Yuan Shuoqing et al., 2021). The main risk factors for oropharyngeal cancer include genetic factors, smoking and drinking, eating habits, virus infection, etc. (Tu Xiaomin, Ren Jianjun, Zhao Yu, 2022). The incidence of oropharyngeal cancer associated with human papillomavirus (HPV) infection has increased dramatically (Buckley L, Jackett L, Clark J, et al., 2018), and HPV plays an important role in oropharyngeal cancer.

2. HPV

HPV is a circular double-stranded DNA virus composed of an 8kb genome encoding viral proteins (de Villiers E M, Fauquet C, Broker T R, et al., 2004), which mainly infects the body through damaged skin or mucous membranes. We know that there are more than 200 types of HPV viruses, which are divided into high-risk types and low-risk types, and high-risk HPV persistent infection can lead to cancer.

3. Epidemiological Manifestations

Studies worldwide have shown that the incidence of human papillomavirus-associated oropharyngeal cancer has increased dramatically in recent decades (Buckley L, Jackett L, Clark J, et al., 2018). The age of onset of HPV-positive oropharyngeal cancer tends to be younger and HPV-positive oropharyngeal cancer patients have little or no smoking history, moderate or no alcohol consumption (De Martel C, Plummer M, Vignat J, et al., 2017; Gillison M L, Chaturvedi A K, Anderson W F, et al., 2015;

National Cancer Institute, 2018; Ang K, Harris J, Wheeler R, et al., 2010; Chaturvedi A K, Engels E A, Pfeiffer R M, et al., 2011; Elwood J M, Youlden D R, Chelimo C, et al., 2014). In addition to smoking, drinking, social behavior, etc., the incidence of HPV also has a certain correlation with the region. The prevalence of HPV-positive oropharyngeal cancer varies greatly from 0% to 85% in different countries. The lowest country is India and Spain while the highest countries are South Korea and Lebanon (Carlander A F, Jakobsen K K, Bendtsen S K, et al., 2021).

In the past 10 years, the morbidity and mortality of oropharyngeal cancer in my country have also increased. The detection rate of HPV in oropharyngeal cancer patients in various places ranges from 20% to 50% (Zheng Xin & Wang Daijie, 2021), and the morbidity and mortality have shown Cities are higher than rural areas, and men are higher than women (Liu J, Yang X L, Zhang S W, et al., 2018). However, there are few domestic epidemiological data on HPV-associated oropharyngeal cancer.

4. Clinical Manifestations and Prognosis

The most common pathological type of oropharyngeal cancer is squamous cell carcinoma, and oropharyngeal squamous cell carcinoma mostly occurs in the posterior pharyngeal wall, soft palate, tonsillar complex, and base of the tongue, and the prevalence of HPV in the tonsils and the bottom of the tongue is higher than that in other parts of the pharynx, accounting for about 90% of oropharyngeal tumors (Tham T, Ahn S, Frank D, et al., 2020). The most common symptoms initially reported by patients diagnosed with HPV-positive OPSCC were neck mass, sore throat, followed by dysphagia, visible mass, bulbous sensation, odynophagia, ear pain, etc. (McIlwain W R, Sood A J, Nguyen S A, et al., 2014)

In addition to the different symptoms, the prognosis of HPV-positive OPSCC patients is better than that of HPV-negative oropharyngeal cancer patients. The survival rate and median survival time of HPV-related OPSCC patients are significantly better than those of non-related OPSCC patients, and the stage is later. The greater the difference in survival (Hengyong Li et al., 2022).

5. Pathogenic Mechanism

The currently recognized pathogenic mechanism is mainly the integration of HPV DNA into the genes of host cells, thereby exerting carcinogenesis. The most important of these is the expression of E6 and E7. The relationship between the virus and the target cells is mediated by the capsid protein, and the affinity between the capsid and the proteoglycan heparan sulfate on the basement membrane is considered to be the first step in HPV infection (Bernfield M, Gotte M, Park P W, et al., 1999). After infection, oncoproteins E6 and E7 target the cancer suppressors P53 and pRb, respectively (Babiker A Y, Eltom F M, Abdalaziz M S, et al., 2013). On the one hand, E6 protein can ubiquitinate P53, leading to the denaturation of its encoded proteosome enzyme. At the same time, E6 protein can also directly act on the active part of the P53 DNA binding site, hindering its transcription, thereby inhibiting the acetyltransferase activity of P53, destroying its stability, making it lose the ability to block the cell cycle, promote cell apoptosis, and maintain genome stability The function of (Yuan Shuoqing et al., 2021). On the other hand, E7 protein can bind and degrade retinoblastoma-related proteins, and cause the release of E2F, which eventually leads to the continuous proliferation of tumor cells, thereby causing cancer (Liu Yamin & Chen Huaihong, 2022).

6. Detection Method

The HPV status of the tumor is the main factor that determines the overall survival rate, and it is also a non-anatomical determinant that affects the risk classification and treatment selection of patients with oropharyngeal squamous cell carcinoma (Ang K, Harris J, Wheeler R, et al., 2010), so the detection of HPV is very important.

6.1 P16 Immunohistochemistry (IHC)

P16 is well accepted as a surrogate marker of HPV infection status, so p16 immunohistochemistry is the most commonly used method. However, the high-level expression of P16 protein may be affected by other factors in addition to HPV infection, which will lead to false positive results (Yang Xin & Guo Huiqin, 2022), so it is generally not used as an independent detection method but requires other methods for confirmation.

6.2 Polymerase Chain Reaction (PCR)

PCR is also a widely used detection method, which has high sensitivity and high cost performance. However, it cannot distinguish where the HPV is located, whether it is present in tumor cells or in the surrounding non-tumor

epithelium or stroma (Nuovo G J., 2011); and cannot distinguish between transcriptionally active and clinically irrelevant HPV infection (Schache A G, Liloglou T, Risk J M, et al., 2013). Therefore, the detected DNA may not be from tumor tissue.

6.3 DNA In Situ Hybridization (ISH)

DNA ISH is detected by the complementarity of DNA probes and known types of HPV DNA sequences. This method can not only directly observe whether there is HPV DNA under a high-power microscope, but also help determine the location of HPV DNA in tissues and cells, and then display the state of the virus (free or integrated), which can make up for the defects of PCR (Venuti A & Paolini F., 2012; Bray F, Ferlay J, Soerjomataram I, et al., 2018; Li Zhipeng, Fan Zhiwei, Wang Wenlong, et al., 2021). This method has high specificity, but only detecting HPV DNA cannot represent the biological activity of HPV virus. (Wu Yaping, Gao Jiamin & Sun Shuyang, 2022)

6.4 Detection of HPV RNA by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)

At present, most scholars agree that the detection of HPV oncogene E6/E7 mRNA is the gold standard for detecting the virus (Prigge E S, Arbyn M, von Knebel D M, et al., 2017). RT-PCR designed suitable primers for E6/E7 of different HPV, and then analyzed the subtype of the virus and evaluated the toxicity of the virus (Li Zhipeng, Fan Zhiwei, Wang Wenlong, et al., 2021). This method not only has high specificity and sensitivity, but also can detect the presence of transcriptionally active HPV, proving that tumorigenesis is related to HPV (Augustin J G, Lepine C, Morini A, et al., 2020). However, the requirements for the laboratory are very high, the cost is expensive, and it is rarely used clinically.

6.5 Alternative Detection Methods

In addition to the above commonly used detection methods, there are some alternative detection methods, such as the use of anti-HPV antigen serum antibodies, detection of HPV DNA in plasma and saliva, but the source of HPV-positive cells in these methods will affect the specificity of detection.

7. Treatment

There is no difference in the treatment strategies between HPV-positive oropharyngeal cancer and HPV-negative oropharyngeal cancer. Surgery, radiotherapy, chemotherapy alone or combined with targeted therapy is still the main treatment method. It has been confirmed in the literature that HPV-positive oropharyngeal cancer has a better prognosis and a higher survival rate. In the past, conventional treatment methods would bring a lot of toxic and side effects to patients and seriously reduce the quality of life of patients (Du Youqin, Mo Qiyan & Qu Song, 2022). Therefore, some scholars have suggested that patients with HPV-related oropharyngeal cancer should reduce the intensity of treatment, hoping to improve the quality of life of patients. At present, the more popular de-escalation treatment strategies mainly include cetuximab instead of cisplatin concurrent chemotherapy or removal of chemotherapy, lowering the dose of radiotherapy and chemotherapy, and oral robotic surgery.

7.1 Cetuximab Instead of Concurrent Chemotherapy with Cisplatin or Removal of Chemotherapy

Cetuximab, an epidermal growth factor receptor inhibitor, increases the radiosensitivity of oropharyngeal cancer cells by inhibiting the radiation-induced ERS signaling pathway IRE1/ATF6-GRP78. The specific mechanism may be related to down-regulation of GRP78 inhibiting radiation-induced DNA double-strand break repair and autophagy to increase apoptosis in oropharyngeal cancer (Han Chuyang, 2018), which was proposed for de-escalation therapy to reduce the toxicity of standard cisplatin therapy. However, some experiments have shown that the incidence of early, late and overall serious toxicity caused by cetuximab is not lower than that of cisplatin (although the toxicity profile is different), and the overall quality of life is also similar, contrary to experimental expectations (Mehanna H, Robinson M, Hartley A, et al., 2019). Therefore, for HPV-positive patients who can tolerate cisplatin, whether to use cetuximab instead of cisplatin remains to be discussed.

7.2 Reduce the Dose of Radiotherapy and Chemotherapy

The study found that in the treatment of HPV-positive OPSCCs with radiotherapy and chemotherapy, reducing the total dose of radiotherapy and chemotherapy did not reduce the survival rate of patients, but reduced its toxicity and improved the quality of life of patients. In the experiment of Allen M Chen et

al., the radiation dose was reduced by 15-20% compared with the standard chemoradiotherapy regimen, and the 2-year progression-free and overall survival similar to the standard chemoradiotherapy regimen was obtained, and the toxicity was acceptable. Chemotherapy doses are feasible for effective treatment of HPV-positive oropharyngeal squamous cell carcinoma (Chen A M, Felix C, Wang P C, et al., 2017).

7.3 Transoral Robotic Surgery

Due to the special location of the oropharynx, traditional surgery often causes greater trauma. However, with the popularization of the concept of functional preservation surgery and robot-assisted surgery, transoral robotic surgery has begun to be widely used in the treatment of oropharyngeal cancer. Compared with traditional radical surgery, transoral robotic surgery is more convenient to operate, less invasive, causes fewer complications, and can achieve better functional outcomes, survival outcomes, and long-term quality of life (Du Youqin, Mo Qiyan & Qu Song, 2022). Patients with early-stage oropharyngeal cancer who underwent transoral robotic surgery had improved surgical outcomes and survival compared with nonrobotic surgery (Wu Peng, Huang Qiancheng & Zhong Jialei, 2021).

8. Prevention

HPV vaccination, early screening through detection of HPVp16, and advice from healthcare professionals to patients on risk factors and preventive measures associated with this disease, as well as increasing awareness of HPV-associated oropharyngeal cancer, all contribute to the prevention of this disease. effective treatment for this disease.

9. Existing Problems and Prospects

Over time, many studies have shown that the prevalence of HPV is increasing worldwide, and HPV-associated OPSCC is an increasing health burden. The earlier the oropharyngeal cancer is detected, the smaller the tumor is, and the treatment effect is generally better; the later the tumor stage, the greater the difference in treatment effect and survival between HPV-related and non-related patients, so early detection and early treatment are very important. There are many methods for detecting human papillomavirus in oropharyngeal squamous cell carcinoma, but there are some differences, and there is no specific consensus on the best method for HPV detection in OPSCC. Currently available preventive vaccines have no therapeutic effect on acquired infections, and there are still some problems. Therapeutic vaccines have yet to be studied. In order to reduce the toxic and side effects and complications of patients after treatment and improve the quality of life of patients without reducing the treatment effect, a large number of de-escalation treatment methods have been proposed, but no unified conclusion has been drawn, further experimental research is required to provide support. Domestic research data on the epidemiology, clinical manifestations and prognosis of HPV-related oropharyngeal cancer are still relatively small, so we still need more research data to provide a basis for the clinical diagnosis and treatment of HPV-related oropharyngeal cancer.

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References

Ang K, Harris J, Wheeler R, et al. (2010). Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med, 363*(1), 24-35.

Augustin J G, Lepine C, Morini A, et al. (2020). HPV Detection in Head and Neck Squamous Cell Carcinomas: What Is the Issue? *Front Oncol, 10*, 1751.

Babiker A Y, Eltom F M, Abdalaziz M S, et al. (2013). Screening for high risk human papilloma virus (HR-HPV) subtypes, among Sudanese patients with oral lesions. *Int J Clin Exp Med, 6*(4), 275-281.

Bernfield M, Gotte M, Park P W, et al. (1999). Functions of cell surface heparan sulfate proteoglycans. *Annu Rev Biochem, 68*, 729-777.

Bray F, Ferlay J, Soerjomataram I, et al. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin, 68*(6), 394-424.

Buckley L, Jackett L, Clark J, et al. (2018). HPV-related Oropharyngeal Carcinoma: A Review of Clinical and Pathologic Features with Emphasis on Updates in Clinical and

Pathologic Staging. *Adv AnatPathol, 25*(3), 180-188.

Buckley L, Jackett L, Clark J, et al. (2018). HPV-related Oropharyngeal Carcinoma: A Review of Clinical and Pathologic Features with Emphasis on Updates in Clinical and Pathologic Staging. *Adv AnatPathol, 25*(3), 180-188.

Carlander A F, Jakobsen K K, Bendtsen S K, et al. (2021). A Contemporary Systematic Review on Repartition of HPV-Positivity in Oropharyngeal Cancer Worldwide. *Viruses, 13*(7).

Chaturvedi A K, Engels E A, Pfeiffer R M, et al. (2011). Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol, 29*(32), 4294-4301.

Chen A M, Felix C, Wang P C, et al. (2017). Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study. *Lancet Oncol, 18*(6), 803-811.

De Martel C, Plummer M, Vignat J, et al. (2017). Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer, 141*(4), 664-670.

de Villiers E M, Fauquet C, Broker T R, et al. (2004). Classification of papillomaviruses. *Virology, 324*(1), 17-27.

Du Youqin, Mo Qiyan, Qu Song. (2022). Research progress in intensity reduction therapy for HPV-positive oropharyngeal carcinoma. *Chinese Journal of Oncology Prevention and Treatment, 14*(03), 334-339.

Elwood J M, Youlden D R, Chelimo C, et al. (2014). Comparison of oropharyngeal and oral cavity squamous cell cancer incidence and trends in New Zealand and Queensland, Australia. *Cancer Epidemiol, 38*(1), 16-21.

Gillison M L, Chaturvedi A K, Anderson W F, et al. (2015). Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. *J Clin Oncol, 33*(29), 3235-3242.

Han Chuyang. (2018). Cetuximab-mediated endoplasmic reticulum stress increases radiosensitivity and its mechanism. China Medical University.

Hengyong Li, Song Yang, Kai Zhou, Yu Kong, Jieying Li, Guizhong Li, Shengyou Ge, Xiaochen Yang, Yuanyong Feng, Kai Song, Wei Shang. (2022). Survival analysis of 336 patients with HPV-related and non-correlated oropharyngeal squamous cell carcinoma. *Journal of Oral and Maxillofacial Surgery, 20*(04), 378-383. DOI:10.19438/j.cjoms.2022.04.011.

Li Zhipeng, Fan Zhiwei, Wang Wenlong, et al. (2021). Research progress on accurate detection of human papillomavirus in oropharyngeal squamous cell carcinoma. *Journal of Precision Medicine, 36*(04), 373-376.

Liu J, Yang X L, Zhang S W, et al. (2018). Incidence, mortality, and temporal patterns of oropharyngeal cancer in China: a population-based study. *Cancer Commun.,* (Lond), *38*(1), 75.

Liu Yamin, Chen Huaihong. (2022). New progress in the diagnosis and treatment of HPV-positive oropharyngeal cancer. *Journal of Clinical Otorhinolaryngology Head and Neck Surgery, 36*(10), 802-806. DOI:10.13201/j.issn.2096-7993.2022.10.015.

McIlwain W R, Sood A J, Nguyen S A, et al. (2014). Initial symptoms in patients with HPV-positive and HPV-negative oropharyngeal cancer. *JAMA Otolaryngology Head Neck Surg, 140*(5), 441-447.

Mehanna H, Robinson M, Hartley A, et al. (2019). Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase3 trial. *Lancet, 393*(10166), 51-60.

National Cancer Institute. (2018). SEER Cancer Statistics Review, 1975-2015. Noone A, Howlader N, Krapcho M, et al., editors. November 2017. SEER data submission, posted April 2018. https://seer.cancer.gov/csr/1975_2015/.

Nuovo G J. (2011). In situ detection of human papillomavirus DNA after PCR-amplification. *Methods Mol Biol, 688*, 35-46.

Prigge E S, Arbyn M, von Knebel D M, et al. (2017). Diagnostic accuracy of p16(INK4a) immunohistochemistry in oropharyngeal squamous cell carcinomas: A systematic review and meta-analysis. *Int J Cancer, 140*(5), 1186-1198.

Schache A G, Liloglou T, Risk J M, et al. (2013).

Validation of a novel diagnostic standard in HPV-positive oropharyngeal squamous cell carcinoma. *Br J Cancer, 108*(6), 1332-1339.

Tham T, Ahn S, Frank D, et al. (2020). Anatomical subsite modifies survival in oropharyngeal squamous cell carcinoma: National Cancer Database study. *Head Neck, 42*(3), 434-445.

Tu Xiaomin, Ren Jianjun, Zhao Yu. (2022). Research progress on risk factors and genetic risks of head and neck squamous cell carcinoma. *Journal of Clinical Otorhinolaryngology Head and Neck Surgery, 36*(05), 391-396. DOI:10.13201/j.issn.2096-7993.2022.05.015.

Venuti A, Paolini F. (2012). HPV detection methods in head and neck cancer. *Head Neck Pathol, 6*(Suppl 1), S63-S74.

Wu Peng, Huang Qiancheng, Zhong Jialei. (2021). Comparison of survival rates after intraoral robotic surgery and non-robotic surgery in patients with early oropharyngeal squamous cell carcinoma. *Chinese Journal of Robotic Surgery, 2*(06), 500.

Wu Yaping, Gao Jiamin, Sun Shuyang. (2022). Progress in the diagnosis and treatment of HPV-related oropharyngeal cancer. *China Journal of Oral and Maxillofacial Surgery, 20*(06), 599-606.

Yang Xin, Guo Huiqin. (2022). Recent advances in molecular pathological diagnosis of human papillomavirus-associated oropharyngeal squamous cell carcinoma. *Carcinogenesis, Teratogenesis & Mutagenesis, 34*(02), 154-157.

Yuan Shuoqing, Zhang Aobo, Dong Yanbo, Wang Zhenxiao, Liu Liangfa. (2021). Characteristics and clinical analysis of human papillomavirus-associated oropharyngeal squamous cell carcinoma. *Chinese Journal of Otorhinolaryngology-Skull Base Surgery, 27*(06), 691-697.

Zheng Xin, Wang Daijie. (2021). Research status and progress of HPV-positive oropharyngeal cancer. *Journal of Modern Oncology, 29*(04), 704-707.