American Journal of Otolaryngology and Head and Neck Surgery

Review Article
Published: 16 May, 2018

The Dynamic Change HPV has Forced onto Oropharyngeal Carcinoma

*Kamil Masood and Uttam Sinha**

Department of Otolaryngology-Head and Neck Surgery, University of Southern California, USA

Abstract

Head and neck cancer is one of the most common types of cancers in the world. However, the dynamics of the disease has changed in the past decades. A disease once characterized by smoking and drinking has more recently been associated with HPV. Additionally, prognosis for HPV associated disease seems far more improved to the non-HPV associated counterpart. Further investigations suggest the development of HPV associated oropharyngeal squamous cell carcinoma may in fact be a distinct form of cancer whose natural history needs to be pursued. Head and neck cancer and cervical cancer share characteristics in that high risk sexual behavior and exposure to and infection of HPV increases their risk however, it has been stated that HPV positive head and neck cancer has improved survival outcomes for patients. We believe that due to increased rates of HPV associated head and neck cancer yet it's receptiveness to therapy, it may be beneficial to study the natural history of HPV in its relationship with head and neck cancer in order to promote a higher quality of life in individuals with HPV positive condition.

Introduction

Head and neck cancer is one of the most common types of cancer in the world. Oropharyngeal cancer, one of the most common cancer types, has recently had a dynamic shift in the past few decades. A disease once strongly associated with smoking and drinking is now associated with HPV, a virus more commonly associated with cervical cancer. As our understanding of the disease and cancer grow, further exploration on the development of the cancer is key to understanding how to treat it correctly. Thus, by understanding the disease and exploring curative modalities, we can further improve patient survival and quality of life.

Characteristics of oropharyngeal cancer

Head and neck cancer is a term used to describe a set of different tumors that develop in the throat, larynx, nose, sinuses, and mouth. It is one of the most common cancers in the world. It has a global incidence of approximately 300,400 patients per year and global death rate of 145,400 per year [1]. In the US alone, there were an estimated 45,780 diagnoses and 8,650 deaths related to Head and Neck Cancer [2].

The most common malignancy in the head and neck region is squamous cell carcinoma. Although it has demonstrated a steady decline in nearly all subsites over the past few years, oropharyngeal squamous cell cancers have shown a distinct overall increase [3]. Oropharyngeal squamous cell carcinoma incidence increased from 1973 to 2004 in the US particularly in younger male white individuals [4, 5]. Specifically, oropharyngeal squamous cell cancer associated with HPV has increased 225% from 1988 to 2004. However, at the same time, survival has improved [3]. The increase in incidence and improving survival are attributed to the increase in HPV related disease [3-5].

Risk factors

Head and neck cancer has many established risk factors including tobacco products and alcohol use [6-9]. It has been estimated that around 30% of oropharyngeal cancer and 23% of laryngeal cancer worldwide can be attributed to alcohol consumption [10]. Although the effect of alcohol and tobacco use may vary, the combined affect of both exposures accounts for a majority of head and neck cancers [6]. It has been found that the increased alcohol and tobacco consumption trends have also increased the risk of head and neck cancer in the past 45 years [11-14]. Tobacco use appears to be a stronger risk factor for head and neck cancer than alcohol consumption. However, all who smoke and drink develop head and neck cancer thus there may be some undefined risk factor among

OPEN ACCESS

Correspondence:
Uttam Sinha, Department of Otolaryngology-Head and Neck Surgery, University of Southern California, Keck School of Medicine, Los Angeles, USA,
E-mail: Sinha@med.usc.edu

Received Date: *23 Apr 2018*
Accepted Date: *14 May 2018*
Published Date: *16 May 2018*

Citation:
Masood K, Sinha U. The Dynamic Change HPV has Forced onto Oropharyngeal Carcinoma. Am J Otolaryngol Head Neck Surg. 2018; 1(2): 1007.

women and the young [11]. It has been hypothesized that hormones may play a protective role specifically with estrogen exposure [15]. Aside from smoking and drinking, the use of betel quid and areca nut also has a strong impact on cases in India and Taiwan. Betel quid and areca nut have both been implicated in other forms of cancer as well as other impairments [16,17].

Although oropharyngeal cancer has many conventional risk factors such as smoking and drinking, there seems to be many unconventional risk factors as well. Oral hygiene and malfunctioning dentures appear to be a key factor in some cases. It is believed that this may be because certain bacteria are allowed to grow which convert ethanol into acetaldehyde a major carcinogen [18,19]. However, it was found that there is some genetic influence in the metabolism of alcohol which promotes this risk factor.

In the past few decades, there has been a dramatic shift from carcinogen-exposed mucosal transformation to malignancy to predominantly virally mediated cancer. The recent decline in HPV-negative oropharyngeal cancer parallels the declines in smoking in the United States [20]. The etiology of oropharyngeal squamous cell carcinoma has dramatically shifted over the past few decades. The gradual shift in disease etiology to that of a predominantly HPV-positive process directly manifests in the current clinical presentation of oropharyngeal patients in the care giver's office.

HPV

Most patients enrolled in therapeutic trials for squamous-cell carcinoma of the head and neck has oropharyngeal squamous cell carcinoma, which in a subgroup of these patients is caused by infection with human papillomavirus [21]. This subgroup is defined by the presence of high risk types of HPV in tumor cells, predominantly HPV type 16. The prevalence of oral HPV infection follows a bimodal curve with the first peak observed predominantly between 30 to 34 and the second peak at age 60 to 64 [22]. Men have a significantly higher prevalence than women.

The overall survival rates of HPV positive disease is high between 48% to 80% 5 year survival rates [23,24]. However, recurrence seems to be a major developing problem with regards to HPV positive disease.

Evidence over the last decade has found that a growing incidence in head and neck cancer is strongly correlated with human papilloma virus. Research thus far has identified that the biology and epidemiology of HPV positive oropharyngeal cancer is distinctly different from HPV negative cancer typically caused by tobacco and alcohol exposure [25-29].

Because of this epidemiological shift in head and neck cancer, younger white male patients with limited exposure to tobacco and alcohol have begun to manifest the disease. These individuals tend to have histories notable for increased number of sexual encounters, specifically oral sex [25]. Thus, sexual activity may be a risk factor for oropharyngeal cancer. In the past few decades, not only have causes of genital and anal cancers risen due to HPV but also a subset of head and neck cancer. HPV is responsible for an estimated 30,000 oropharyngeal cancers cases, 25% of all head and neck cancers [31]. HPV is now a major cause of oropharyngeal cancer in developed countries [31-33]. HPV has also been detected in a smaller subset of laryngeal (24%) and oral cavity (23%) cancers [31]. HPV is detected in the tumor of these oropharyngeal cancers, where it is localized to the cell nuclei, transcriptionally active, clonal, and not found in the surrounding benign tissue [34]. It has been hypothesized that the natural history of HPV in oral cancer may differ from that of cervical cancer [31] with studies indicating associations with DNA methylation in both human and viral genomes altering expression [35]. Epidemiologic evidence for the role of HPV in oropharyngeal cancer is equally strong. Case–control studies consistently show that oropharyngeal cancer patients have a higher average number of lifetime sexual partners (a surrogate for oral HPV exposure) and are more likely to have current oral HPV infection than matched controls [21,29,36].

Many believe that HPV causes a clinically unique form of oropharyngeal squamous cell carcinoma [37]. Aside from having completely different risk factors, HPV positive oropharyngeal cancer appears to have better survival when compared to HPV negative patients whether they were treated with radiotherapy alone, induction chemotherapy, or radiation with concurrent cisplatin chemotherapy [34,34,38]. Although the mechanism is unclear, clearly HPV plays a key role in the development of HPV positive cancer. At least 90% of HPV-positive cancers are associated with high risk or oncogenic HPV type 16 [31], and oral infection confers an approximate 50-fold increase in the risk of HPV-positive cancer [39]. HPV has been identified as an independent prognostic factor for survival and progression-free survival among patients with oropharyngeal cancer which may be consistent with hypothesis that HPV-positive and HPV negative oropharyngeal squamous cell carcinomas are distinct and have different causes [34] risk factor profiles [21] and survival outcomes.

Risk factors for oral HPV and transmission

The main prevalence sites of HPV include the epithelium of the vagina, vulva, penis, anal canal, cervix, perianal region, crypts of the tonsil, and oropharynx. There exist multiple pathways for HPV transmission to the oral cavity including sexual transmission, Autoinfection, and rarely through perinatal transmission of the neonate during its passage through an infected birth canal of the mother [5,40]. Oral HPV acquisition was found to be more positively associated with number of recent oral sex and open mouth kissing partners than with the number of vaginal sex partners [5,41]. Sexual behavior has consistently been associated with increased oral HPV prevalence.

It is unclear whether HPV can be casually transmitted to the oral cavity. A study showed there was some association between open mouth-kissing in a small study size however the prospect needs to be further evaluated [42]. Oral HPV in children is incredibly rare [43]. Concordant oral and cervical is also rare which indicates auto inoculation from one area to another is uncommon [44-46]. It has been shown that oral HPV infection in one spouse was associated with a fourfold increase of Oral HPV in the other spouse in a study of pregnant women and tenfold increased risk of persistent infection in the other spouse [47].

Other risk factors have consistently been associated with increased odds of prevalent oral HPV. HIV infection is associated with significantly increased oral HPV prevalence suggesting that immunosuppression may impact oral HPV. Even with adjusting for sexual behavior, Oral HPV prevalence appears higher than men than in women [48]. Oral HPV appears to also increase with age however the reason behind this unusual age-related prevalence pattern remains unclear.

HPV effect on cancer development (Angiogenesis/ metastasis)

Once HPV has come into contact with tissue within the throat and mouth, it forces its way into individual cells. Smoking and drinking also increase the likelihood of cancer however it appears upon entering cell tissue the virus promotes viral oncogenes [49].

HPV is a small DNA based virus that infects keratinocytes of the skin and mucous. Of the greater than 100 types of HPV, HPV 16 comprises 90% of all infections [31]. HPV 16 is not the only form of HPV that is a potential risk factor for head and neck cancer. Non-HPV 16 genotypes account for 9% of HPV related Oropharyngeal carcinoma [46]. The main key HPV types aside from 16 implicated with head and neck cancer are 18, 33, and 52 [47]. The clinical characteristics are largely similar to HPV 16 and thus the favorable prognosis is also applicable to these cases. HPV itself encodes for many genes that induce tumorigenesis including E6 and E7. The E6 oncoprotein causes ubiquitin mediated degradation of p53, a key gene that functions in regulating the cell cycle and tumor suppression. E7 inhibits the ability of retinoblastoma tumor-suppressor genes, thus inhibiting its ability to repress the expression of replication enzyme genes.

Of the major head and neck cancers HPV seems to be affecting most prevalently in Oral and Oropharyngeal Cancer. In a study done in the Czech Republic, it was found that 51.5% of samples tested had some trace of HPV with 80% of these cases specifically being HPV 16 [3]. In addition, it appears that the rate of HPV prevalence is different depending on the location 25% in oral cases and 57% in oropharyngeal and distinctly higher in nonsmokers and nondrinkers. HPV 16 has previously been implicated in the development of cervical cancer along with HPV 18 [4]. Studies have shown that HPV positive oropharyngeal cancer has distinctly better outcomes given the same treatment [50-52].

It has been known that HPV infection has led to virtually all cases of cervical cancer [26,40]. Molecular evidence also provides evidence that supports that HPV is involved in the pathogenesis of a sect of squamous cell carcinomas of head and neck cancer. Genomic data of oncogenic HPV is detected in at least 26% of all squamous cell carcinomas of head and neck cancer worldwide. However molecular evidence of oropharyngeal squamous cell carcinoma is more rigorous in which viral integration and expression of viral oncogenes (E6 and E7) have been shown [47].

Head and neck cancer and cervical cancer share characteristics in that high risk sexual behavior and exposure to and infection of HPV increases risk [53]. Although high risk sexual behavior, exposure to, and infection of HPV have all been strongly associated with squamous cell carcinomas of head and neck, there has been no studies indicated the association of all three with head and neck cancer.

It has been confirmed that HPV positive head and neck cancer has improved survival outcomes for patients in both single and multicenter clinical trials [54]. The risk factors and demographic and tumor characteristics of HPV-positive patients differ from those of HPV negative patients. HPV-positive tumors were more likely than HPV-negative tumors to arise from the oropharynx, to be poorly differentiated, and to have basaloid features.

The complex effect of HPV on prognosis and treatment

Several studies have shown that patients with oropharyngeal cell carcinoma with HPV-positive tumors have a better prognosis than patients with HPV negative tumors [55]. Patients tend to have better overall and disease specific survival rates [56]. Significant prognostic factors were the presence of HPV, extracapsular spread and tumor size with HPV being the most significant prognostic factor. It was also found that HPV status was associated with positive therapeutic response and survival. Patients with head and neck cancer of the oropharynx or larynx had improved overall survival and after adjusting for age, tumor stage and ECOG performance status, lower risks of progression and death.

Several case series have supported an inverse association between tumor HPV status and the presence of p53-inactivating mutations in head and neck cancers [34,57]. There appears to be a clearly better response to chemotherapy and radiation in HPV positive cancer patients compared to HPV negative ones [34,57]. This is likely due to an intact p53 which would not necessarily exist in HPV negative cancer. This intact p53 would then be activated leading to apoptosis due to the chemotherapy induced stress. However, it has been shown that HPV positive oropharyngeal cancer still showed improved prognosis relative to HPV negative patients both with and without p53 mutations which appears to be enigmatic [58]. The biological basis for improved survivability is unclear.

In the largest retrospective analysis of the impact of HPV on outcome, the 3-year overall survival was 82.4 % (77.2 to 87.6) in the HPV positive subgroup and 57.1% (48.1 to 66.1) in the HPV negative subgroup and the three-year progression free survival was 73.7% (67.7 to 79.8) and 43.4% (34.4 to 52.4) respectively [34]. Tobacco use had a distinct negative impact on prognosis, independent of HPV.

In another studying using E6 to E7 PCR methods, it was found that 82% of HPV positive patients were alive after 5 years while only 35% of HPV negative patients [59].

In a prospective study, it was found that HPV positive head and neck cancer had a 61% lower risk of death and a 62% lower risk of progression when compared to HPV negative patients after adjusting for age, tumor stage, and ECOG performance status [38].

Recurrence

The most common site for recurrence is the neck and the pharynx [39,60]. Standard therapy for patients with recurrence consists of surgical resection although success rates are not generally high for this form of treatment. Reirradiation is also possible, but due to toxicity of treatment and treatment related deaths the dangers of the treatment greatly outweigh the benefits so many clinicians avoid this modality. The majority of patients with recurrence are treated with chemotherapy regiments [22,61,62]. Thus, these patients are treated with palliative chemotherapy. For these patients, survival is between 6 and 10 months [63,64].

Few studies have reported on outcomes of patients with metastatic or recurrent HPV positive head and neck cancer [65,66]. Because HPV positive patients are more susceptible to treatment it can be suggested that recurrent cancer may not be as susceptible and require more aggressive treatment. Some clinical trials suggest a median overall survival with recurrent HPV ranging from 11 months to 12 months [67]. Of the few studies on metastatic/recurrent HPV positive head and neck cancer, one study indicates that HPV positive head and neck cancer appears to have favorable prognosis after recurrent/metastatic cancer. Systemic treatment leads to a prolonged disease-free period even after metastasis [68]. Studies suggest more aggressive treatment may improve overall survival however parallel

comparisons are difficult. The potential benefit of a multimodality approach compared to using chemotherapy alone in the metastatic or recurrent setting may greatly improve overall survival [69].

Treatment

Treatment of head and neck cancer mainly focuses on surgical resection, radiation therapy, and/or chemo therapy. Primary treatment strongly varies with the anatomic site and stage of disease. For most early cancers, surgical resection is the cornerstone of treatment [70]. The main goal of surgery is the removal of all cancerous tumors and some surrounding tissue. This is to reduce the risk of recurrence. Certain anatomic sites such as tonsils, base of tongue, and floor of the mouth maybe treated with radiotherapy instead. An early stage of head and neck cancer is associated with excellent prognosis, thus surgical resection or radiation alone is considered sufficient treatment [71].

Several multimodality treatments exist for later staged cancer. Patients with later stage disease are treated with a combined therapy due to nodal metastasis. Patients are usually diagnosed at later stages and thus require multiple levels of treatment. Chemotherapy may be used in conjunction with radiation therapy. The efficacy of chemo radiotherapy in head and neck cancer has been well established, irrespective of HPV status [72]. Chemotherapy can be given either prior to or concurrently with radiotherapy. The addition of chemotherapy leads to greater improvements in survival with concurrent chemo radiotherapy proving superior to induction chemotherapy [73]. The standard treatment in head and neck cancer is currently high-dose cisplatin in conjunction with radiation therapy.

Those with HPV positive head and neck cancer had a higher baseline and post treatment overall quality of life compared to HPV negative patients. These scores were not affected by the primary treatment modality [74]. Later stage cancer may require reconstructive surgery. This can be necessary if portions of the jaw, skin, pharynx, or tongue are required to be removed due to infection of the tumor. Usually this type of operation is to help restore the person's appearance and function.

Side effects of surgery depend on the type and location of the surgery. Common side effects include temporary or permanent loss of normal voice impaired speech, and hearing loss. Difficulty with oral motor functions including chewing and swallowing after surgery may also be a problem.

The most common type of radiation therapy is external beam radiation therapy. Radiation therapy is optimal when given at 1.8 Gy per day with a dose level of approximately 60 Gy [75]. Intensity-modulated radiation therapy uses advanced technology to more accurately direct the beams of radiation at the tumor thus reducing damage the surround tissues. Early on optimization of radiation therapy was experimented on determining there was no survival advantage over standard once-daily fractionation [73,76]. Patients going through radiation therapy may experience difficulties swallowing, skin irritation, dry mouth, bone pain, nausea, fatigue, mouth sores and damage to salivary glands as well as fibrosis of the surrounding tissue.

Chemotherapy is the use of drugs to destroy cancer cells. These drugs focus on reducing the cell's ability to divide and grow as well as promoting apoptosis. The most common form of treatment is combination drug therapy TPF, docetaxel, cisplatin, and fluorouracil. Bleomycin, docetaxel alone, hydroxyurea, and methotrexate are also prescribed for head and neck cancer. Chemotherapy is commonly given either intravenously or orally. Chemotherapy regimens usually consist of a specific number of cycles given over a set period.

Targeted therapy is when specific genes, proteins, and tissue environment are targeted to reduce the growth and survival of cancer cells. EGFR has shown exceptional prowess as a primary target for head and neck cancer however targeted therapy is often expensive however [77]. Targeting EGFR has been a proven method of treating head and neck cancer through the drug Cetuximab. Cetuximab, an EGFR inhibitor, is the only targeted therapy approved for head and neck cancer. Many other targets have been identified in recent years including PIK3CA, Notch 1, ALK 1, and hedgehog however all require additional research. PIK3CA maybe a new target for targeted therapies as it would appear that there is some increase in mutation of PIK3CA in HPV positive patients [78-81]. In fact, several reports indicate that mutations in PIK3CA ranging between 6 and 20% of head and neck cancers.

Following diagnosis of the oral cavity and pharynx cancer, the 5-year relative survival is close to 40% in the United States and in Europe, although it varies substantially from country to country. Moreover, the prognosis is generally better for women and malignancies arising from the hypopharynx.

There has been some debate in the level of treatment necessary to treat HPV positive head and neck cancer as although traditionally multi-modality therapy is used it does not appear to be a necessity. HPV positive head and neck cancer prognosis is generally favorable, independent of treatment modality [59]. It can be suggested that reducing the aggressiveness of treatment may still produce similar. Currently treatment is defined by stage and site of disease and is independent of HPV status.

Conclusion

The incidence of HPV related head and neck cancer appears to be growing specifically in younger patients. With unique risk profiles, factors, and presentation, HPV positive disease acts distinctly different with an apparently better prognosis compared with the HPV negative counterpart. Further investigation on treatment modality is necessary not only for primary infection but recurrent disease as well. Advancements in treatment information will be able to guide treatment methodology and enhance our understanding of disease.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5-29.
3. 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. J Clin Oncol. 2011;29(32):4294-301.
4. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and-unrelated oral squamous cell carcinomas in the United States. J Clin Oncol. 2008;26(4):612-9.
5. Ryerson AB, Peters ES, Coughlin SS, Chen VW, Gillison ML, Reichman ME, et al. Burden of potentially human papillomavirus-associated cancers of the oropharynx and oral cavity in the US, 1998–2003. Cancer. 2008;113(10):2901-9.
6. Boyle P, Levin B. World Cancer Report 2008. IARC. 2008;510.
7. Boyle P, Levin B. World Cancer Report. Lyon: International Agency for

Research on Cancer (IARC). World Health Organization. 2008.

8. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F,et al. A review of human carcinogens-Part B: biological agents. Lancet Oncol. 2009;10(4):321-2.

9. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. Lancet Onco. 2010;11(8):781-9.

10. Boffetta P, Hashibe M, La Vecchia C, Zatonski W, Rehm J. The burden of cancer attributable to alcohol drinking. Int J Cancer. 2006;119(4):884-7.

11. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev. 2009;18(2):541-50.

12. De Andrade M, Amos CI, Foulkes WD. Segregation analysis of squamous cell carcinoma of the head and neck: evidence for a major gene determining risk. Ann Hum Genet. 1998;62(6):505-10.

13. Centers for Disease Control and Prevention (CDC. (2011). Quitting smoking among adults--United States, 2001-2010. MMWR Morb Mortal wkly Rep. 2011;60(44):1513-9.

14. Centers for Disease Control and Prevention (CDC). Current cigarette smoking among adults-United States, 2011. MMWR. Morbidity and mortality weekly report. 2012;61(44):889-94.

15. Hashim D, Sartori S, Vecchia CL, Serraino D, Maso LD, Negri E, et al. Hormone factors play a favorable role in female head and neck cancer risk. Cancer Med. 2017;6(8):1998-2007.

16. Ko YC, Huang YL, Lee CH, Chen MJ, Lin LM, Tsai CC. Betel quid chewing, cigarette smoking and alcohol consumption related to oral cancer in Taiwan. J Oral Pathol Med. 1995;24(10):450-3.

17. Chen YJ, Chang JTC, Liao CT, Wang HM, Yen TC, Chiu CC, et al. Head and neck cancer in the betel quid chewing area: recent advances in molecular carcinogenesis. Cancer Sci. 2008;99(8):1507-14.

18. Tsai ST, Wong TY, Ou CY, Fang SY, Chen KC, Hsiao JR, et al. The interplay between alcohol consumption, oral hygiene, ALDH2 and ADH1B in the risk of head and neck cancer. Int J Cancer. 2014;135(10):2424-36.

19. Rosenquist K. Risk factors in oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. Swed Dent J Suppl. 2005;(179):1-66.

20. Centers for Disease Control and Prevention (CDC). Cigarette smoking among adults--United States, 2006. MMWR Morb Mortal wkly Rep. 2007;56(44):1157-61.

21. Gillison ML, D'souza G, Westra W, Sugar E, Xiao W, Begum S, et al. Distinct risk factor profiles for human papillomavirus type 16–positive and human papillomavirus type 16–negative head and neck cancers. J Natl Cancer Inst. 2008;100(6):407-20.

22. Langer CJ, Harris J, Horwitz EM, Nicolaou N, Kies M, Curran W, et al. Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. J Clin Oncol. 2007;25(30):4800-5.

23. Gillison ML, Zhang Q, Jordan R, Xiao W, Westra WH, Trotti A, et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. J Clin Oncol. 2012;30(17):2102-11.

24. Settle K, Posner MR, Schumaker LM, Tan M, Suntharalingam M, Goloubeva O, et al. Racial survival disparity in head and neck cancer results from low prevalence of human papillomavirus infection in black oropharyngeal cancer patients. Cancer Prev Res(Phila). 2009;2(9):776-81.

25. D'souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, et al. Case–control study of human papillomavirus and oropharyngeal cancer. N Engl J Med. 2007;356(19):1944-56.

26. Herrero R, Castellsagué X, Pawlita M, Lissowska J, Kee F, Balaram P, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst. 2003;95(23):1772-83.

27. Applebaum KM, Furniss CS, Zeka A, Posner MR, Smith JF, Bryan J, et al. Lack of association of alcohol and tobacco with HPV16-associated head and neck cancer. J Natl Cancer Inst. 2007;99(23):1801-10.

28. Smith EM, Ritchie JM, Summersgill KF, Hoffman HT, Wang DH, Haugen TH, et al. Human papillomavirus in oral exfoliated cells and risk of head and neck cancer. J Natl Cancer Inst. 2004;96(6):449-55.

29. Schwartz SM, Daling JR, Madeleine MM, Doody DR, Fitzgibbons ED, Wipf GC, et al. Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. J Natl Cancer Inst. 1998;90(21):1626-36.

30. Zhang Y, Wang R, Miao L, Zhu L, Jiang H, Yuan H. Different levels in alcohol and tobacco consumption in head and neck cancer patients from 1957 to 2013. PloS One. 2015;10(4):e0124045.

31. D'souza G, Fakhry C, Sugar EA, Seaberg EC, Weber K, Minkoff HL, et al. Six-month natural history of oral versus cervical human papillomavirus infection. Int J Cancer. 2007;121:143-50.

32. Näsman A, Attner P, Hammarstedt L, Du J, Eriksson M, Giraud G, e al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: An epidemic of viral-induced carcinoma? Int J Cancer. 2009;125(2):362-6.

33. Heck JE, Berthiller J, Vaccarella S, Winn DM, Smith EM, Shan'gina O, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol. 2010;39:166-81.

34. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363:24-35.

35. Parfenov M, Pedamallu CS, Gehlenborg N, Freeman SS, Danilova L, Bristow CA, et al. Characterization of HPV and host genome interactions in primary head and neck cancers. Proc Natl Acad Sci USA. 2014;111(43):15544-9.

36. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev. 2005;14(2):467-75.

37. Gillison ML, D'souza G, Westra W, Sugar E, Xiao W, Begum S, et al. Distinct risk factor profiles for human papillomavirus type 16–positive and human papillomavirus type 16–negative head and neck cancers. J Natl Cancer Inst. 2008;100(6):407-20.

38. Rischin D, Young RJ, Fisher R, Fox SB, Le QT, Peters LJ, et al. Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. J Clin Oncol. 2010;28(27):4142-8.

39. Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst. 2000;92(9):709-20.

40. Pigott K, Dische S, Saunders MI. Where exactly does failure occur after radiation in head and neck cancer?. Radiother Oncol. 1995;37(1):17-9.

41. Adelstein DJ, Ridge JA, Gillison ML, Chaturvedi AK, D'Souza G, Gravitt PE, et al. Head and neck squamous cell cancer and the human papillomavirus: summary of a National Cancer Institute State of the Science Meeting, November 9–10, 2008, Washington, DC. Head Neck. 209;31(11):1393-422.

42. D'Souza G, Agrawal Y, Halpern J, Bodison S, Gillison ML. Oral sexual behaviors associated with prevalent oral human papillomavirus infection. J Infect Dis. 2009;199(9):1263-9.

43. Smith EM, Swarnavel S, Ritchie JM, Wang D, Haugen TH, Turek LP. Prevalence of human papillomavirus in the oral cavity/oropharynx in a large population of children and adolescents. Pediatr Infect Dis J. 2007;26(9):836-40.

44. Fakhry C, D'souza G, Sugar E, Weber K, Goshu E, Minkoff H, et al. Relationship between Prevalent Oral and Cervical Human Papillomavirus Infections in Human Immunodeficiency Virus-Positive and-Negative Women. J Clinical Microbiol. 2006;44(12):4479-85.

45. Smith EM, Ritchie JM, Yankowitz J, Wang D, Turek LP, Haugen TH. HPV prevalence and concordance in the cervix and oral cavity of pregnant women. Infect Dis Obstet Gynecol. 2004;12:45-56.

46. Termine N, Giovannelli L, Matranga D, Caleca MP, Bellavia C, Perino A, et al. Oral human papillomavirus infection in women with cervical HPV infection: new data from an Italian cohort and a metanalysis of the literature. Oral Oncol. 2011;47(4):244-50.

47. Rintala M, Grénman S, Puranen M, Syrjänen S. Natural history of oral papillomavirus infections in spouses: a prospective Finish HPV Family Study. L Clin Virol. 2006;35:89-94.

48. Klein SL. The effects of hormones on sex differences in infection: from genes to behavior. Neurosci Biobehav Rev. 2000;24(6):627-38.

49. Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. Semin Oncol. 2004;31(6):744-54.

50. Varier I, Keeley BR, Krupar R, Patsias A, Dong J, Gupta N, et al. Clinical characteristics and outcomes of oropharyngeal carcinoma related to high-risk non–human papillomavirus16 viral subtypes. Head Neck. 2016;38(9):1330-7.

51. Michaud DS, Langevin SM, Eliot M, Nelson HH, Pawlita M, McClean MD, et al. High-risk HPV types and head and neck cancer. Int J Cancer. 2014;135(7):1653-61.

52. Haughey BH, Sinha P. Prognostic factors and survival unique to surgically treated p16+ oropharyngeal cancer. Laryngoscope. 2012;122:13-33.

53. Gillison ML, Shah KV. Chapter 9: Role of mucosal human papillomavirus in nongenital cancers. J Natl Cancer Inst Monogr. 2003;(31):57-65.

54. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus–positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008;100(4):261-69.

55. Ragin CC, Taioli E. Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: Review and meta-analysis. Int J Cancer. 2007;121(8):1813-20.

56. Greenberg JS, Fowler R, Gomez J, Mo V, Roberts D, El Naggar AK, et al. Extent of extracapsular spread: a critical prognosticator in oral toungue cancer. Cancer. 2003;97(6):1464-70.

57. Dai M, Clifford GM, Le Calvez F, Castellsagué X, Snijders PJ, Pawlita M, et al. Human papillomavirus type 16 and TP53 mutation in oral cancer: matched analysis of the IARC multicenter study. Cancer Res. 2004;64(2):468-71.

58. Licitra L, Perrone F, Bossi P, Suardi S, Mariani L, Artusi R, et al. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. J Clin Oncol. 2006;24(36):5630-6.

59. Posner MR, Lorch JH, Goloubeva O, Tan M, Schumaker LM, Sarlis NJ, et al. Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial. Ann Oncol. 2011;22(5):1071-7.

60. Kotwall C, Sako K, Razack MS, Rao U, Bakamjian V, Shedd DP. Metastatic patterns in squamous cell cancer of the head and neck. Am J Surg. 1987;154(4):439-42.

61. Langlois D, Eschwege F, Kramar A, Richard JM. Reirradiation of head and neck cancers. Presentation of 35 cases treated at the Gustave Roussy Institute. Radiother Oncol. 1985;3:27-33.

62. Spencer SA, Harris J, Wheeler RH, Machtay M, Schultz C, Spanos W, et al. Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck. Head Neck. 2008;30(3):281-8.

63. Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol. 2006;24(17):2644-52.

64. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359(11):1116-27.

65. Price KAR, Okuno SH, Garcia JJ, Molina JR, Olsen KD, Kasperbauer JC, et al. Survival in patients with HPV-positive oropharynx squamous cell carcinoma with distant metastases. J Clin Oncol. 2013;31(15):6095.

66. Mehra R, Egloff AM, Li S, Yang D, Wang L, Zhu F, et al. Analysis of HPV and ERCC1 in recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). J Clin Oncol. 2013;31(15):6006.

67. Williams JS, Villanueva C, Foa P, Rottey S, Winquist E, Licitra LF, et al. Safety and efficacy of panitumumab (pmab) in HPV-positive (+) and HPV-negative (-) recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): Analysis of the global phase III SPECTRUM trial. J Clin Oncol. 2012;30(15):5504.

68. Dang RP, Le VH, Miles BA, Teng MS, Genden EM, Bakst RL, et al. Clinical outcomes in patients with recurrent or metastatic human papilloma virus-positive head and neck cancer. Anticancer Res. 2016;36(4):1703-19.

69. Deeken JF, Newkirk K, Harter KW, Marshall MB, Banovac F, Johnson L, et al. Effect of multimodality treatment on overall survival for patients with metastatic or recurrent HPV-positive head and neck squamous cell carcinoma. Head Neck. 2015;37(5):630-5.

70. Iyer NG, Dogan S, Palmer F, Rahmati R, Nixon IJ, Lee N, et al. Detailed Analysis Of Clinicopathologic Factors Demonstrate Distinct Difference in Outcome and Prognostic Factors Between Surgically Treated HPV-Positive and Negative Oropharyngeal Cancer. Ann Surg Oncol. 2015;22(13):4411-21.

71. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol. 2011;100(1):33-40.

72. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol. 2011;100:33-40.

73. Beitler JJ, Zhang Q, Fu KK, Trotti A, Spencer SA, Jones CU, et al. Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. Int J Radiat Oncol Biol Phys. 2014;89:13-20.

74. Maxwell JH, Mehta V, Wang H, Cunningham D, Duvvuri U, Kim S, et al. Quality of life in head and neck cancer patients: impact of HPV and primary treatment modality. Laryngoscope. 2014;124(7):1592-7.

75. Peters LJ, Goepfert H, Ang KK, Byers RM, Maor MH, Guillamondegui O, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. Int J Radiat Oncol Biol Phys. 1993;26:3-11.

76. Nguyen-Tan PF, Zhang Q, Ang KK, Weber RS, Rosenthal DI, Soulieres D, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck

carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. J Clin Oncol. 2014;32(34):3858-66.

77. Psyrri A, Seiwert TY, Jimeno A. Molecular pathways in head and neck cancer: EGFR, PI3K, and more. In American Society of Clinical Oncology educational book. Am Soc Clin Oncol Educ Book. 2013:246-55.

78. Seiwert TY, Keck MK, Zuo Z, Khattri A, Brown C, Stricker T, et al. Genomic profiling of a clinically annotated cohort of locoregionally advanced head and neck cancers (HNC) treated with definitive chemoradiotherapy. J Clin Oncol. 2012;30(15):5517.

79. Agrawal N, Frederick MJ, Pickering CR, Bettegowda C, Chang K, Li RJ, et al. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. Science. 2011;333(6046):1154-7.

80. Morris LG, Taylor BS, Bivona TG, Gong Y, Eng S, Brennan CW, et al. Genomic dissection of the epidermal growth factor receptor (EGFR)/PI3K pathway reveals frequent deletion of the EGFR phosphatase PTPRS in head and neck cancers. Proc Natl Acad Sci USA. 2011;108(47):19024-9.

81. 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):1157-60.