

**PROGNOSTIC ROLE OF HUMAN PAPILLOMA VIRUS IN ORAL SQUAMOUS CELL
CARCINOMA: A REVIEW**Dr. Sareh Farhadi*¹ and Maryam Kakuinejad²¹Assistant Professor, Oral & Maxillofacial pathology Dept., Dental Branch of Tehran, Islamic Azad University, Tehran, Iran.²Student of Dentistry, Dental Branch of Tehran, Islamic Azad University, Tehran, Iran.***Corresponding Author: Dr. Sareh Farhadi**

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Article Received on 02/09/2017

Article Revised on 23/09/2017

Article Accepted on 13/10/2017

ABSTRACT

Aim & background: In spite of increase in the incidence of oral squamous cell carcinoma, there are not serious achievements gained in related treatment modalities and survival rates. Hence, through identifying the etiologic factors and the prognostic parameters, it is hoped that it would be possible to cure the lesions and reduce patients' suffering and ailments. Human Papilloma Virus (HPV) might be one of the most important prognostic factors in oral cavity cancers. This study is an attempt to investigate & review of HPV prognostic role in oral squamous cell carcinoma. **Methods & Materials:** The investigated articles have been collected and studied meticulously using the data bases of PubMed, Medline, Scopus and Google Scholar through keywords of HPV, prognosis, survival rate, clinical outcome, oral cancer and OSCC during years of 2000 to 2015. **Results:** After scrutinizing and considering 23 articles, it was clarified that HPV-positive tumors can be treated easier. It can be related to some reasons such as more sensitiveness to therapies including chemotherapy and chemo radiation therapy. Furthermore, according to 12 articles, it was concluded that patients with HPV-positive tumors had higher survival rates compared with the HPV-negative ones, HPV-positive characteristic can be a significant prognostic factor. **Conclusion:** OSCC Patients presenting with HPV, have better prognosis and therapeutic response compared to those HPV-negative patients.

KEYWORDS: HPV, prognosis, survival rate, clinical outcome, oral cancer, OSCC.**INTRODUCTION**

Nowadays, there is a considerable occurrence of oral squamous cell carcinoma (SCC) worldwide. It has been notable especially in the tonsil and tongue base, in patients who were between 40-55 years old.^[1]

The small non-enveloped DNA viruses which infect squamous epithelial cells are known as human papilloma viruses (HPVs). Above 200 kinds of them have been distinguished. Yet, definitely there are further kinds that have not been known yet. HPVs cause a considerable range of epithelial lesions, mostly the benign hyperplasia, such as wart or papilloma that have less potential to cause cancer.

There is a subgroup of HPVs-which are called high risk HPV- and are related to precancerous lesions. A small number of people become infected with high risk HPVs and develop cancers after several years from the first stage of infection.

According to the documents from epidemiologic and molecular studies in 1995, the international agency for research on cancer distinguished that the types 16 and 18 of high risk HPVs were responsible for human cancer.^[2] These two HPV types also cause roughly 70% of cervical cancer incidents. Whereas, the other high risk HPV types are responsible for all of the 30 percent remained cases of the disease.^[3]

Around 60% of squamous cell cancers of mouth and larynx are positive for HPV16 in USA. HPV-positive tumors seem to be clinically and biologically different sorts in comparison with HPV-negative ones. Moreover, it is likely that they are more sensitive to chemotherapy and radiation therapy. Hence, the chance of treatment and survival is higher. HPV is one of the pathogenic factors in a portion of mouth and larynx squamous cell carcinomas. Though, it should be noticed that the biological and natural history of HPV infection of mouth and larynx has not been fully recognized. Neither has the ideal clinical control of such cases been completely clarified. So, we conducted a review of related reports to achieve a better understanding of the issue.

Research method

The investigated articles have been collected and studied meticulously using the data bases of PubMed, Medline, Scopus and Google Scholar through keywords of HPV, prognosis, survival rate, clinical outcome, oral cancer and OSCC (oral squamous cell carcinoma) during years of 2000 to 2015.

RESULTS

Among 23 articles which were reviewed in the present study, 12 articles had explicitly pointed out that patients with HPV-positive tumors, had higher survival rates.^[20,34,40,42,45,46,48,49,51,52,55,57] Moreover, it should be mentioned that in one of these articles, it was reported that there is a relationship between the type of sexuality and the survival rate in HPV-positive HNSCC(head and neck squamous cell carcinoma). Hence, it was shown that the survival rate among men is higher than in women.^[34]

Another important finding, was pointed out in 12 articles which had demonstrated that HPV infection of tumors was an important prognostic factor.^[11,13,39,44-47,50,51,54,55,57]

Hence, the HPV-positive patients had a better prognosis rather than the HPV negative ones. The reason for the improvement in prognosis and survival rates can be due to the better response and higher sensitivity to radiotherapy and chemotherapy upon these tumors. It should be added that this issue had been reported in 7 articles among the all of the reviewed ones.^[40,43,46,49,51,52,54]

It was stated in one of the articles that the better outcome can also be related to the absence of field cancerization beside the higher sensitivity and response to chemo radiation therapy in HPV-positive tumors.^[51] Also, it was mentioned in one of the articles that HPV-positive tumors have less probability of relapse and subsequent secondary tumors.^[56] In addition, it was stated in another article that, HPV-positive tumors have less aggressive property in comparison to the HPV-negative ones.^[36]

No.	First author	country	year	Participants	Findings
1	Riaboshapka AN ^[42]	Russia	2014	60, patients with locally advanced HPV-associated squamous cell carcinoma of oral cavity and oropharynx.	Koilocytosis and expression of E6 HPV 16/18 types have no predictive value. Median of overall survival correlated with koilocytosis, expression of E6 HPV types 16/18 and p16INK4a.
2	Lindel K ^[43]	Switzerland	2001	99, squamous cell carcinoma of the oropharynx	Human papillomavirus positivity have a favorable outcome attributable to an increased sensitivity toward radiotherapy.
3	De Petrini M ^[44]	Italy	2006	47,squamous cell carcinomas of the oropharynx and the oral cavity	HPV-positive oropharyngeal cancers comprise a distinct disease entity with an improved prognosis.
4	Gillison ML ^[11]	USA	2000	253, patients with newly diagnosed or recurrent HNSCC	HPV-positive oropharyngeal cancers have a markedly improved prognosis
5	Ritchie JM ^[34]	USA	2003	139, oral and oropharyngeal cancer	HPV infected patients had better overall survival than those with HPV-negative tumors.(There was an interaction between gender and HPV for overall and disease-specific survival that suggested that HPV infected males had better prognosis than HPV-negative males, but this was not the case among females.)
6	Jan Klozar ^[45]	Czech	2007	81,patients treated by surgery for oral or oropharyngeal squamous cell cancer	HPV-positive patients had significantly better both overall and disease-specific survival rates than HPV-negative patients. No significant differences were found in the pN classification, in the number of positive nodes and the presence of extracapsular spread in the involved nodes between HPV positive and HPV-negative tumors. Multivariate analysis showed that significant prognostic factors of survival were the

					presence of HPV in the tumor, extracapsular spread and tumor size. HPV was the most significant prognostic factor in the studied group of patients with oropharyngeal tumors and possibly should be considered in treatment decisions
7	Shanthi Marur ^[46]	USA	2010		HPV-positive oropharyngeal cancer seems to be more responsive to chemotherapy and radiation than HPV-negative disease. HPV 16 is a prognostic marker for enhanced overall and disease-free survival, but its use as a predictive marker has not yet been proven.
8	Seth R. Schwartz ^[47]	USA	2001	254, patients diagnosed with primary oral cancer	The presence of HPV type 16 DNA is independently associated with a favorable prognosis in patients with oral squamous cell carcinoma.
9	Dahlgren L ^[48]	Sweden	2004	110, patients with tongue cancer	HPV is significantly more common in base of tongue cancer than in mobile tongue cancer, and has a positive impact on disease-specific survival in patients with base of tongue cancer.
10	Farshid Dayyani ^[49]	USA	2010	5681, head and neck squamous cell carcinomas (HNSCC)	HPV-related HNSCC comprise about 25% of all HNSCC. They are predominantly tumors of the oropharynx, and exhibit a separate biologic behavior including improved response to (chemo)-radiation and survival compared to HPV-negative HNSCC.
11	Niklas Reimers ^[50]	Germany	2007	106, newly diagnosed OSCC	HPV+/p16+ tumors tended to have decreased EGFR expression, but using both immunohistological markers has significant prognostic implications
12	Carole Fakhry ^[40]	USA	2008	96, patients with stage III or IV HNSCC of the oropharynx or larynx	patients with HPV-positive tumors had higher response rates after induction chemotherapy and after chemoradiation treatment. Patients with HPV-positive tumors had improved overall survival, lower risks of and death from any cause than those with HPV-negative tumors. In Conclusion For patients with HNSCC of the oropharynx, tumor HPV status is strongly associated with therapeutic response and survival
13	Giuseppina Campisi ^[51]	Italy	2009		HPV has been found to be the most significant positive prognostic factor in patients with oro-pharyngeal tumors. The favorable outcome of HPV-induced oropharyngeal cancers might be attributable to the absence of field cancerization or enhanced radiation sensitivity. Taking this into consideration, the diagnosis of HPV infection should be determined in all oropharyngeal cancers, considering its presence as a key factor in the

					decision-making process of treatment. However, we are unable to make the same suggestion for the OSCC. HPV 16 has been positively associated with a response to chemo-radiation in oropharyngeal cancer and with overall and disease-specific survival.
14	Kumar B ^[52]	USA	2007	42 oropharyngeal cancer patients (30 men and 12 women)	HPV16 copy number was positively associated with response to therapy and with overall and disease specific survival
15	Kumar B ^[53]	USA	2008	66 patients with stage III to IV squamous cell carcinoma of the oropharynx (SCCOP)	Low EGFR and high p16 (or higher HPV titer) expression are markers of good response to organ-sparing therapy and outcome
16	Danny Rischin ^[54]	Canada	2009	465, Patients with stage III or IV head and neck squamous cell cancer	HPV-associated oropharyngeal cancer is a distinct entity with a favorable prognosis compared with HPV-negative oropharyngeal cancer when treated with cisplatin-based chemoradiotherapy
17	Ang KK ^[55]	USA	2010	323, oropharyngeal squamous-cell carcinoma	Tumor HPV status is a strong and independent prognostic factor for survival among patients with oropharyngeal cancer.
18	Stina Syrjänen ^[20]	Finland	2005	422, cases of tonsillar carcinoma	patients with HPV 16-positive tumors seem to have a better overall- and disease-specific survival, as compared with the HPV-negative group.
19	Paul M. Weinberger ^[13]	USA	2006	79 OSCCs	HPV_/p16 high types of OSCC, showed favorable prognosis
20	Lisa Licitra ^[56]	Italy	2005	90 oropharyngeal cancer patients	reduced risk of relapse and second tumors associated with HR-HPV positivity of oropharyngeal cancer
21	Wei LI ^[36]	Australia	2003	86 tonsil cancers	HPV-positive tonsil cancers may be a distinct biological group with less aggressive characteristics. Screening of tonsil cancers for HPV DNA may help optimise treatment and provide more accurate prognostic information
22	David Lindquist ^[39]	Sweden	2007	203 patients with tonsillar cancer	The presence of HPV-16, but not viral load, in tonsillar cancer was shown to be a favorable prognostic factor for clinical outcome.
23	J. B. Vermorken ^[57]	Belgium	2014	tumor samples from 416 patients	p16 positivity and HPV positivity were associated with prolonged survival compared with p16 negativity and HPV negativity. The results from this analysis suggest that p16 and HPV status have prognostic value in recurrent and/or metastatic SCCHN.

DISCUSSION

HPV genome is a double stranded circular DNA molecule of 8000 base protein (bp) which encodes ten proteins. HPV genome is made up of three important parts. First, a 4000bp part that encodes proteins

participating in DNA replicating and cell transformations. Second, a 3000bp which encodes structural proteins of virus, and third, a 1000 bp that doesn't encode any protein, but contains regulatory elements of viruses life cycle including its replication.^[4]

If an injury causes wounds, HPVs enter to the basal cells of epithelium. Papilloma viruses DNAs remain in these basal cells as a low- copy DNA .But during the differentiation of these cells and migrating to the upper layers of the epithelium, the HPV DNA also replicates and as a result we will have a high numbers of copies of viruses DNA.^[5,6] HPVs encode two important proteins; E6 and E7. E6 interferes with the P53 tumor suppressor protein and suppresses its function, while E7 also binds to retinoblastoma (Rb) tumor suppressor protein. These two proteins together cause increased DNA replication of papilloma viruses in Keratinocytes.^[7,10]

There is a high relationship between HPV infection and cervical carcinoma. Though the epidemiological, molecular and clinical findings show that in some cases who have not used tobacco and/or alcohol, high risk HPVs, particularly HPV16 are the reason for development of head and neck tumors.^[11,15] Finding a connection between HPV and a subtype of OSCC isn't an easy task due to different types of OSCC and also, because only a minority of patients are HPV-related. The primary clue that showed the relevance of HPV with the pathogenesis of a subcategory of HNSCC was recognized by Syrjanen *et al.*^[20] HPV-16 DNA was initially distinguished in an invasive HNSCC in 1985.^[21] This is why HPVs genomes have been frequently distinguished in a wide range of HNSCC.^[22] The difference of range may be due to different anatomic sites of malignancies and the procedures used to distinguish HPV-DNA.

The most frequently found genotype both in cervical malignancies and HPV-type in HNSCC is HPV-16. It could be detected in more than 90% of HPV-positive patients.^[11,13] There are some researches that demonstrate that the HPV subclasses related to OSCC look like the ones detected in cervical malignancies but they are not exactly the same as each other.^[23,25]

In HPV associated head and neck carcinomas, the amount of p16 is very high, because the p16 tumor suppressor gene(CKDN2A)is negatively regulated by Rb protein.^[26,27] Many clinical evidences suggest that HPV-associated OSCC and classic OSCC could have completely different entities.^[13,28] Risk of incidence of HPV tobacco associated OSCC is higher in males rather than females, However the incidence of HPV associated OSCC is the same for both sexualities. In addition most of the HPV associated OSCC patients are nonsmokers and nondrinkers and on average 5 years younger than their tobacco-use-associated counterparts.^[29]

It should be noted that the mere existence of HPV-DNA in an OSCC cannot prove that the carcinoma is the HPV-associated type .The carcinoma with active HPV-DNA transcription is the only type which is associated with it clinically and histologically. Regarding the studies done, it can be concluded that the status of p16 expression can clarify the biologically related cases. According to

studies, there are 3 distinct of OSCC: class I, HPV-negative/p16 no expressing; class II, HPV-positive/p16 no expressing; and class III, HPV-positive/p16 expressing oropharyngeal tumors.^[30]

HPV associated OSCC are related with better prognosis than HPV-negative tumors in the most of the studies.^[11,31,36] Moreover, According to the results of retrospective analyses, the patients with HPV-positive oropharyngeal cancer have higher response rates to chemotherapy and radiation and increased survival.^[35,37,39] In addition , in 2008 , a prospective clinical trial , in patients with head and neck squamous cell carcinoma showed that the response to treatment , survival rate and other related outcomes were better in HPV positive types versus HPV negative ones.^[40] The good survival rates imply the increased sensitivity to chemotherapy and radiotherapy in HPV- positive patients.

The positive result of HPV-associated oropharyngeal malignancies can be due to the non-existence of field cancerization or it can be because of increased sensitivity to radiation therapy.^[35] “ Field cancerization” is a phrase applied to explain whether cancers associated early genetic modifications are present in the epithelium that multiple independent lesions are produced. They can cause the formation of multifocal malignancies.^[41]

CONCLUSION

OSCC Patients presenting with HPV, have better prognosis and therapeutic response compared to those HPV-negative patients. It is notable that the molecular categorization of malignancies could supply new outstanding information which helps the prognosis to be calculated more accurately. Hence, it can well affect alternative therapeutic choices.

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