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Review Article

ROLE OF HUMAN PAPILLOMA VIRUS IN HEAD & NECK MALIGNANCY

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ABSTRACT

Human papilloma virus has been routinely implicated in the carcinogenesis of uterine cervix, vagina, vulva and anal region. Recently over the past two decades, it has been found that HPV virus is also responsible for the carcinoma of tonsil and base tongue region in the oropharynx. Interestingly the main viral strain that is involved in carcinogenesis of uterine cervix and oropharyngeal region is HPV 16. Currently, the incidence of oropharyngeal malignancy is increasing alarmingly and more than 80% of such malignancies are due to high risk HPV virus infection. So a literature review was done to analyse data on disease prevalence, disease behaviour and treatment outcome of HPV positive Head & Neck malignancy. It was found that unlike non HPV related Head & Neck carcinoma which usually affects older age group, HPV positive head and neck malignancy tend to affect younger age group. Individuals with HPV positive oropharyngeal malignancy tend to have oral sex and have multiple sexual partners. Such sexual practice, explains the reason for the confinement of HPV positive malignancy mainly to the oropharyngeal region in head and neck. Tumour has less aggressive course and they show better response to treatment. Overall the tumour affects younger individuals and shows better treatment response. All these favourable factors have opened up scope for treatment de-intensification, targeted therapy and cancer prevention using HPV vaccine.

Keywords*: Oropharyngeal carcinoma, HPV virus*

INTRODUCTION

Human papilloma virus (HPV) especially the strain 16 and 18 has been known to cause carcinoma of the uterine cervix. However, in the last two decades, various studies have demonstrated the role of HPV virus in carcinoma of head and neck region, especially in oropharynx. In the Head and Neck region, HPV positive squamous cell carcinoma (SCC) commonly affects tonsil and base of tongue region in orophrayngx [1].

All over the world, tobacco products and alcohol remain the leading cause for Head and Neck malignancy. As the public awareness increases, the incidence of tobacco and alcohol related Head & Neck cancer has reduced tremendously especially in the western world. But it is associated with an increasing trend of oropharyngeal malignancy involving tonsil and base of tongue region. More than 90% of such oropharyngeal malignancies are caused by HPV virus [2]. Such rising trend in HPV related oropharyngeal malignancy is attributed to increasing practice of oral sex in the affected individuals. HPV positive oropharyngeal malignancy is increasing alarmingly so knowledge and understanding of HPV positive head and neck squamous cell carcinoma (SCC) have become very essential now.

Human papilloma virus.

Human papilloma virus belongs to the heterogeneous group of small DNA virus of the family Papillomaviridae. They usually affect the basal cells of the stratified epithelium at mucosal or cutaneous sites. More than 90 types of HPV virus have been sequenced so far of which type 16 and 18 is more carcinogenic. This virus has been implicated in the carcinogenesis of cervix, vagina, vulva, penis and anal region [3]. HPV infections are mainly sexually transmitted through direct skin or mucosa contact and represent the most common sexually transmitted infection worldwide. Majority of infections clear spontaneously in 12 to 24 months and clinical progression to invasive carcinoma is a very rare event and occurs only in high grade lesions [4].

HPV induced carcinogenesis.

HPV virus genome has three regions such as a non-coding region (LCR), and two protein coding regions namely early (E) and late (L) region. Genes in the E region especially E6 and E7 are mainly implicated in the carcinogenesis. E6 gene of HPV 16 virus causes degradation of p53 gene in host cell [5]. p53 is considered as a molecular policeman, it induces the cell cycle arrest/apoptosis in response to cellular stress or DNA damage. HPV 16 virus induces carcinogenesis by attacking p53 protein. E7 gene of HPV 16 binds to pRb (retinoblastoma gene), which is in control of G1-S phase transition in cell cycle. Inactivation of pRb leads to uncontrolled cell cycle progression resulting in carcinogenesis [6].

Clinical profile of HPV positive HNSCC.

The demographic profile of HPV positive oropharyngeal SCC is entirely different when compared to the non-HPV related one. Unlike non-HPV related HNSCC, patients with HPV positive oropharyngeal SCC usually belongs to younger age group. They are more likely to

have better dentition, less or no tobacco or alcohol use, a greater marijuana use and greater number of oral sex partners than HPV non related group [7]. They have better performance status and belong to higher socioeconomic status. They can tolerate the treatment better because of less co-morbid factors.

Characteristics of HPV positive HNSCC.

HPV positive oropharyngeal malignancies tend to behave less aggressively when compared to the non-HPV related malignancy. They usually arise from the tonsillar crypts unlike the environment related SCC which usually arise from the surface epithelium [8]. HPV-induced HNSCCs are often described as non-keratinizing, poorly differentiated or basaloid carcinomas, and are diagnosed in earlier T-category with a trend for a more advanced N-category, with cystic degeneration than the HPV-unrelated carcinomas. HPV positivity is associated with better response to treatment and modality-independent survival benefit [3] Thus it becomes very essential to differentiate between HPV positive and non- HPV positive head and neck malignancy.

Management of HPV positive HNSCC.

Standard treatment for oropharyngeal malignancy includes radiotherapy/surgery for stage 1 and stage 2 lesions and concurrent chemo-radiotherapy for stage 3 and stage 4 lesions. The same protocol is being followed for HPV positive oropharyngeal SCC. Many times such an aggressive treatment is often associated with significant long term morbidity in the form of severe swallowing difficulty. It alters the post-treatment quality of life (QOL) significantly [9]. Such QOL issues are undesirable for cancer which is less aggressive with better prognosis and when the affected persons are of relatively younger age group. All these issues have created a scope for treatment de-intensification.

In treatment de-intensification, the focus is to make the treatment less aggressive but without compromising the oncological outcome. Treatment de-intensification is the need of the hour, as the overall treatment related morbidity can be drastically reduced. Treatment de-intensification involves reducing the dose of radiotherapy from the standard 70Gy to 54Gy dosage and substitution of EGFR inhibitor (cetuximab) instead of cisplatin in chemotherapy [10]. Among the surgically treated group, treatment de-intensification involves replacement of routine open surgery by trans-oral robotic surgery (TORS). TORS provides better survival outcome than standard open surgery and causes lesser treatment related morbidity [11]. Some studies show that there is no significant difference between radiotherapy versus surgery in HPV positive oropharyngeal SCC [12]. However, we still need a lot of evidence to recommend treatment de-escalation for HPV positive oropharyngeal SCC at this stage, as we have quite a number of on-going trials on treatment de-intensification which are yet to complete at this time [13].

Prognosis of HPV positive HNSCC:

The better overall survival of HPV-positive patients may depend on their younger age at diagnosis, superior performance status, lower smoking and alcohol related morbidity, the distinct biology of cancer, reduced risk of second primary tumours or a more aggressive treatment strategy. The favourable outcome of HPV-induced SCC may be attributable to enhanced sensitivity to treatment due to a wild-type TP53, allowing an apoptotic response of cancer cells to radiation and chemo-radiation [14].

The role of HPV vaccine.

Two types of HPV vaccines are currently available for protection against cervical and ano-genital cancer namely HPV 4 (protects against HPV 6, 11, 16, 18 strains) and HPV 2 (protects against HPV 16, 18 strains). The quadrivalent HPV 4 vaccine has demonstrated very high vaccine efficacy (>98%) for the prevention of anal, cervical, vaginal and vulvar pre-cancers among vaccine-type-naïve individual [15]. Like HPV4, HPV2 vaccine has very high efficacy (>97%) in the prevention of vaccine-type HPV-related cervical pre-cancers among HPV naïve individuals [16]. The effectiveness of both the vaccines is reduced when the vaccination is given to individuals who are already infected with the vaccine strains. HPV vaccine gives definitive protection against cancer of uterine cervix and ano-genital regions in vaccinated individuals but, it is not sure that whether the same vaccine will give similar protection against oropharyngeal carcinoma. It is also very difficult to study the effectiveness of HPV vaccine in oropharyngeal carcinoma as a lot of other carcinogens and social behaviours have an influence on the outcome.

CONCLUSION

The incidence of HPV positive oropharyngeal malignancy is increasing tremendously. HPV positive malignancy tends to affect a relatively younger age group and has a better prognosis. The disease shows a better response to the currently available standard treatment modalities. Better treatment outcome has created a scope for treatment de-intensification in HPV positive malignancy. The role of HPV vaccine in prevention of HPV related oropharyngeal malignancy is very difficult to understand at this point.

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