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Human Papilloma Virus as the Largest Prognostic Factor of Oropharyngeal Squamous Cell Carcinoma

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Abstract

Past studies focusing on the developments of head and neck oncology have established that HPV mediated oropharyngeal patients have greatly improved clinical outcomes in association to HPV-negative oropahryngeal carcinomas. Over the past several years there has been a greater change on the primary site allocation of oropharyngeal carcinomas on western countries with a constant increase in OPC. Over several years HPV has increased significantly particularly among oropharyngeal cancer and has evolved into an extra risk. Up to today. OPSCC symbolize one of the large scale health issues, with about 200000 new cases noted internationally every year.

OPC has been noted to be on the rise while head and neck cancer decreases. HPV- positive has an high value a increased incidence in youthful married men superior socioeconomic position and mostly tend to have high-risk sexual practices.

Keywords: Oropharyngeal; Oncology; HPV; Pidemiology

Introduction

The most common location of HPV related OPSCC is palatine tonsils and base of tongue [1]. The oropharynx is an extremely funtional area, consists of broad mucosal related lymphoid tissue, this build up a more lenient environment for HPV infection. Even though demonstrating at more advanced stage, HPV OPC is identified with good survival outcomes and decreased recurrence rates compared to HPV-negative OPC [2]. Past studies have shown that HPV positive has a less risk of death than HPV negative. HPV detection is an important standard care of pharyngeal malignancy [3]. There are more than 200 HPV serotypes, and the most common in OPSCC is 80%–95% and in anogenital cancers is 52%–58% and it is a high risk HPV subtype [4]. HPV types such as HPV 18, 31, 33 and 33 are barely found in OPSCC. OPSCC's are generally named as HPV-positive or HPV-negative tumors, according to World Health Organization (WHO) on the 2017 new classification of head and neck tumors [5-7].

Literature Review

Among all, the high prevalence is reported in males other than females. Previous estimations have shown that HPV differs significantly with race and age and gender. Most affected tend to be Caucasians of age range 20 years-24 years old, even though they have less to non-exposure to alcohol, tobacco and high education [8]. Authors on the prevalence of OPSCC in the united states found high incidence rate but relatively low rate of HPV vaccination in teenagers than country wide. This was significant for initiating policy changes in order to boost HPV vaccination in children and heighten perception of its benefits [9]. Worldwide incidence of head and neck cancers is reducing but HPV related head and neck incidence is promptly increasing in the last decades [10].

HPV-positive OPSCC has a positive prognosis in comparison to HPV-negative tumors. Patients with advanced stage HPV (+) have a 5 year survival rate of about 75% –80% compared with rates of less than 50% for patients with HPV(−)tumors. The survival rate of patients with HPV (+) tumors can partly credited to their outstanding treatment sensitivity which responds more positively to chemotherapy and radiation than HPV (−) tumors. Establishing prognostic biomarkers of HPV-associated OPC has arised from the need to lower treatment morbidity while keeping high cure rates [11]. It is significant to note why HPV OPSCC inflates concurrently with the last decades of life. Least cross-sectional reports are made accessible, but minority are broadcasted on the momentary dynamics. HPV (+) OPSCC has been found to have an enhanced prognosis and decreased rates of unfavourable events, while HPV-has poor results if treated with radiation in comparison with surgery [12]. Moreover, histologic classification, clinical phase, its metastasis and its status of HPV16 were found to be liberated prognostic factors. Women with clinical stage I-II, histologic classification I, hpv16 and NO metastasis demonstrated good prognosis.

Results

Human papillomaviruses are microscopic non enveloped double-stranded DNA viruses. Which consists of over 170 types. A lot of HPV (+) tumors are a result of HPV which is high risk, more particularly type 16. Type 16 is accountable for additional 90% of cases. Tumorigenesis is persuaded by HPV which is related to transformation activity of viral E6 and E7 oncoproteins. Additional mechanisms such as deregulation of immune inflammatory mediators and gene expression control by specific microRNAs expression can be significant in the series of transformation [13]. HPV may encourage initial transformation in cells which afterwards are deprived of the

HPV. DNA sequences concurrently with carcinogeneis. Nonetheless this is exceedingly not likely since steadfastness of oncoproteins E6, E7 on the high risk HPV genotypes seem to be necessary for the preservation of HPV-associated malignancy, as is apparent from existence of HPV DNA on cells [14]. E6 and E7 oncoproteins are significant in maintaining of the resultant neoplastic growth [15]. The transformation of cellualar ensured by compound interaction of the oncogenesis with multiple cellular factors of cell cycle regulation along with p53, Rb, p21, p27 and cyclin-CDK complexes. All these infections with HPV genotypes are related with elevated risk of HPV-related squamous cell carcinoma [16].

Recent research has validated that HPV has a close relationship with subset of head and neck OPSCC. Human papilloma virus 16 is the most frequent strain found in majority of tumors. Patients with HPV virus were found to have better prognosis, most likely because they engage in risky sexual behaviors, even though they have low history of smoking and alcohol abuse than patients with HPV negative tumors. Moreover, not every study has confirmed these findings because even with high risk to HPV 16, 18 and 33 strains can be found in healthy human beings [17]. Head and Neck Cancers (HNC's) are known as heterogeneous diseases which are initiated by two carcinogens mainly HPV infection and tobacco/alcohol. p16INK4A and p53 expression levels was found through IHC analysis as possible diagnostic markers. Even though patients with HNC's were at a greater advantage of anti-EGFR therapy more especially cetuximab the predictors were not fully defined. Positive expression of P16INK4A was discovered to be highly corresponding with HPV [18].

Testing of HPV

There is still no agreement to which is the best testing technique, besides many non-invasive tests and clinical tests approaches. All recently diagnosed OPSCC need to go through testing for HPV infection. This assists in guiding description of primary site and therapeutic choices [19]. The WHO has officially recommended direct molecular HPV testing. The generally known HPV testings were identified as HPV Polymerase Chain Reaction (PCR), HPV DNA *in situ* hybridization, p16 Immuno Histo Chemistry (IHC). IHC results assist in identifying p16 positivity in oropharyngeal carcinoma, even though there is no numerical relationship of p16 positivity of HPV with gender, age or site. IHC-based discovery of p16 gives a substandard prognostic facts if not linked with the detection of HPV DNA. Even though p16 expression and HPV DNA infection are associated with OPSCC nor yet of the tests alone is the excellent strategy for HPV detection of status [20]. These tests help to determine HPV testing. While HPV DNA ISH is more specific, p16 IHC and HPV DNA PCR were found to be highly sensitive. These tests in particular requires surgical biopsies [21]. The efficiency and the implementation of HPV vaccination and screening remains a huge challenge worldwide [22]. The only available HPV testing in practice includes Paraffin-Embedded (FFPE) biopsy specimens and formalin-fixed. In some studies patients with primary tumor and metastatic lymph nodes has proved HPV status whereby they were subjected to pretreatment Contrast-Enhanced CT (CECT). Large dissimilarities were discovered in heterogeneity parameters by texture analysis of pretreatment CECT, confered to HPV status. This texture analysis can be utilized as collateral tool to diagnose HPV status in clinic [23]. Circulating Tumor DNA (ctDNA) test can be used to detect plasma Epstein-Barr viral DNA by screening for initial nasopharyngeal cancers, nonetheless the announced sensitivity for viral ctDNA tests to discover HPV-associated cancers is prudent. With this modernized perceptive of HPV subtypes and its variations ddPCR through HPV ctDNA is extremely sensitive and quite specific. Recognizing HPV16 and HPV 33 subtypes in a comparable description as stated in extensice genomic profilling studies. This would conclude that by identifying small tumors HPV16 and HPV33 ctDNA ddPCR can be effortlessly utilised in immediate screening detection trials and help disease reaction monitoring, corresponding to Epstein-Barr virus DNA [24].

TNM staging of HPV-related oropharyngeal carcinoma

There are mainly 2 different staging system for p16 negative and p16 positive OPSCC. The World Health Organisation has classified OPSCC based on HPV status, therefore direct molecular HPV testing was highly recommended [25]. A new clinical stage classification of OPC has been acknowledge 8th edition AJCC TNM (ICON-S model) after the previous 7th edition TNM, but it is imprecise that HPV-relatedness is interpreted with good diagnostic certainty and prognostic worth. The effect p16INK4A status in TNM-8 on the classification of OPSCC pin-points that fundamental evidence is rare, its phase grouping particularly has prognostic goal, and a non demanding application of TNM-8 can contradictory affect patient's survival rate as the understanding of TNM 8 as bearing therapeutic goal can result into de-escalating treatment regimens p16INK4A-positive reports, more exclusively when arranged within stage I regardless the existence of neck metastasis [26]. The International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S) has initiated a TNM classification aimed for HPV (+) OPSCC. These stage classifications were rated based on survival performance. The ICON-S classification is stage I (T1–T2N0–N1), stage II (T1–T2N2 or T3N0–N2), and stage III (T4 or N3) respectively. Stage IV is Metastatic disease (M1) according to ICON-S. 8th edition TNM staging system gives exceptional oropharyngeal carcinoma stratification following actual chemo-radiotherapy other that the 7th edition. Other variables in clinic like thorough response in 3 months, smoking and tobacco must be advised in forthcoming studies as they are known to give extra risk stratification data in HPV-positive disease [27]. Various studies done in communities an increased incidence of HPV infection have discovered no prognostic scope for nodal involvement among patients with HPV (+) oropharyngeal carcinomas, as a result at a pace of diagnosis, regional involvement should not be a prognostic factor HPV-positive oropharyngeal carcinoma patients [28]. The studies have explained that lower lymph node neck involvement had an important effect on the survival of ICON-S stage III. Unfortunately these are no effect on the survival stage III ICON-S. After all the survival was the same for patients with less than <5 lymph nodes; 5 lymph nodes and those with>lymph nodes on all ICON-S stages [29-33].

Differential diagnosis of oropharyngeal carcinoma in HPV (+) related

Leukoplakia: It is previously reported that OPSCC is known with a presence of potentially malignant disorders of 15%-48% cases. A more frequent malignant disorder in oral mucosa is Oral Leukoplakia (OL). WHO has described it as a white patch or plaque which can't be fully defined clinically or pathologically. There is a less HPV prevalence (OL). The significance of etiopathogenesis of HPV in oral malignant lesions is still vague. An applicable detecting technique is still a controvert issue. Other studies have shown that p16 over-expression in leukoplakia does not correspond to existing clinical

temperaments. Such as malignant site, age,smoking or abuse of alcohol. Nonetheless, a negative correlation between dysplasia and the expression of p16 was found to be present.

Tonsillar hypertrophy: The existence of HPV was investigated in 146 tonsil cases out 104 Chinese children which was done using flow-through hybridization gene-chip technology. This was done to analyze the relationship between predominance of the virus and other clinical aspects of tonsilar. As a result patients had no HPV DNA. The smooth access of tonsillar crypts and friendly micro environment factors can help cause high prevalence of HPV on nongenital environments. On normal oral mucosa the prevalence of HPV ranges from 0.6% to 81%. Multiple warty appearances can also appear on bilateral Grade III tonsillar enlargement on top of tonsils [34].

Necrotic nodal cervical metastases: The existence of HPV DNA, its physical status with its genotype were found to be consistent amongst primary tumor and node metastasis. Nodal cervical metastases are known to be associated with p-16 negative and p-16 positive OPSCC respectively. Patients initially are at an increased risk of regional deterioration. According to CT and MRI, cystic node metastasis is specific of OPSCC and it's linked with HPV positivity, related to solid metastasis or necrotic metastasis. The study has enacted that the status of HPV stay consistent after metastasis.

Pathological anatomy of HPV (+) oropharyngeal carcinoma

There have been reported elevated incidences of HPV-related oropharyngeal squamous cell carcinomas mostly on tonsillars and toungue. This is noted in age group 20 years-44 years old respectively between year 1973 to 2004. This figure has increased among men 3.9% to 2.1%. The preference is related to special transitional mucosa on the oropharynx. It is mostly present on tonsilar tissue and shows likeness on cervical mucosa. The penetration of the mucosal surface may facilitate the virus capture by advancing access to basal cells. This can be slightly confirmed by the fact that when you collect oral samples through oral rinsing, detection rate of HPV can be very high than using swabs.

Current treatment approaches for HPV (+)

The preferred choice of therapy is not necessarily dependent of HPV, but instead is subject to the patient's condition, its local preference and its anatomic characteristics. The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN, USA) managed to isolate treatment pathways p16 positive and p16 negative OPSCC. Their recommendations are the same, the only difference is that Radiation Therapy (RT) treatment is recommended for T1 N1 p16-negative tumors meanwhile it's not the same case for p16-positive tumors. The preferred treatment for early stage tumors remain RT or surgery. In China, RT is considered as a standard treatment for all OPSCC case, but some studies have suggested that it is not a recommended therapy for high risk patients with OPSCC because of increased estimates of late and acute toxicity so these patients need to choose other options. Recent reports on impact of tumor HPV on RT impartiality must be weighted in radiation dose with agreed standard approach even though each person has exclusive treatment which is still unclear. For advanced stages the preferred treatment is combined therapy. Induction chemotherapy is still being studied, but recent demonstration has shown there is no advantage of survival in induction induction Chemotherapy (CRT) [37]. CRT is known with enhanced survival in senior patients with HPV-positive OPSCC analogous in consequence to the advantage in HPV- negative patients. Additional studies are vital to search excellent therapeautic methods in old society [38]. The choice to involve the vaccine in youth adults vaccination arrangement was introduced as feedback rising evidence displaying efficiency in decreasing HPV infections and associated diseases [39]. Prophylactic vaccination positively work by reducing HPV-related disease, likewise OPSCC. Even though the prerequisite is currently not sufficient, it is a high rate of vaccination. This results in reduction of incidence increase because of low vaccination rates and the prolonged time in-between HPV-induced carcinogenesis and initial infection. Therefore the prevalence of HPV-induced oropharyngeal carcinoma is not much conventional in near future [40]. Vaccine programmes have been useful in lowering the morbidity and mortality of infectious diseases.

Discussion

A prophylactic HPV vaccine has been introduced recently by the national immunization programmes directed for developed countries but soon to be introduced in developing countries. The main goal is to prevent HPV related cancers. Food and Drug Administration (FDA) has approved HPV prophylactic vaccines which is currently being used. Epithelial Growth Factor Receptor (EGFR) as a targeted therapy which is highly expressed in head and neck cancer patients is being evaluated. Its over-expression is found to be related with reduced survival in previous studies. The idea of Multi Disciplinary Team (MDT) has always been gold standard. Due to increasing incidence of disease burgeoning research on HPV-related OPC, amended UK management guidelines are currently pulished. Considering management choices with patiets earlier ease decision implementation as these options can likely change after consulting the patient. Improvments and advances are still necessary in HPV testing. Customarily, OPSCC needs hostile treatment which is related with high morbidity and destitute functional and quality living outcomes. Human Papilloma Virus (HPV)-mediated Oro Pharyngeal Cancer (OPC) is correlated with adequately adavnced survival in contrast to with HPV-negative OPC and may be favorabe surgically and nonsurgicaly treated. The adoption of surgical treatment has decreased mainly in 2010 to 2014. Many hospitals displayed a powerful reverse interrelationship with the estimate of positive surgical margins. The instinctive treatment approach does not only depend on staging but furthermore on geographic, patient and hospital distinct factors. Previous 10 years-15 years have observed considerable advances in surgery, therapy and RT. As of recently minimal invasive surgery has taken over. With laser microsurgery and transoral robotic procedures. Intensity-Modulated RT (IMRT) and new proton-beam RT has complemented RT to an exeedingly fair and precise treatment tool with convinient tool to save swallowing structures and salivary glands. Targeted therapies like cetuximab and immunotherapy are included in apparatus of systemic therapy. Exceptional prognosis of HPV related OPSCC with its morbidity correlated with treatment, de-escalation of therapy through different methods is in research.

Conclusion

The aspect of high-risk HPV infection particularly p16 with its oncogenesis is determined. Overexpression of p16 is determined, strong and backup biomarker for HPV mediated carcinogenesis in oropharyngeal location only. HPV testing for high risk is recommended for all new oropharyngeal cancer patients. This includes primary tumor or cervical nodal metastases, administering

immunohistochemistry, but this is not commonly recommended for other HNC's. Approaches against HPV infection such as frequent vacciantion vaccination on genders, teenagers and adults (9 years-26 years old) can avoid further incidence of HPV-positive oropharyngeal carcinomas. More research is needed to better enlighten non-classical components of transmission together with exposure.

Conflicts of Interest

There are no conflicts of interest

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