

Human Papillomavirus and Oropharyngeal Cancer: An Overview

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ABSTRACT

Human papillomavirus (HPV) is a known aetiological factor in the development of oropharyngeal squamous cell carcinomas (OPSCC), however it is a distinct disease to HPV-negative OPSCC. It is more prevalent in younger patients with fewer comorbidities and HPV status is most commonly detected by p16 immunohistochemistry, which acts as a surrogate marker. Until recently, the TNM staging model was wrongly predicting a poor prognosis for many patients by determining an imperfect overall stage, however this has been resolved by an updated edition. Current management of OPSCC is not determined by HPV-status but there are ongoing trials into treatment deintensification to reduce side effects but maintain OS. Furthermore, prognosis is drastically improved in HPV-positive OPSCC.

INTRODUCTION

Oropharyngeal squamous cell carcinomas (OPSCCs) are one of the most common types of head and neck cancer (HNC) worldwide. They accounted for approximately 25% of new HNC cases in 2012¹ and from 1990-2010 the incidence of OPSCC in the UK quadrupled.² OPSCC develops from the squamous epithelium of the oropharynx which comprises the tongue base, tonsils and soft palate.² OPSCCs were traditionally associated with alcohol and tobacco use however due to a decline in smoking prevalence a high percentage of OPSCCs are now increasingly associated with human papillomavirus (HPV) infection.³

HPV is the most common sexually transmitted infection² and the majority of adults engaging in sexual activity have been exposed to it. Although 7% of people are thought to have an oral HPV infection at any one time, most of these will clear the infection whilst remaining asymptomatic, and it will not develop into OPSCC.⁴ Several types of HPV have been discovered, but most are not carcinogenic. Those that are, including HPV 16 and 18, are considered high-risk.⁵ Of these, HPV-16 is most prevalent in HPV-positive OPSCC and is present in approximately 90% of cases.^{3, 6} It is currently the only high-risk HPV that the International Agency for Research on Cancer considers to be oncogenic in OPSCC.

HPV, a small double-stranded DNA virus, infects basal keratinocytes of the mucosa through micro abrasions on the cell surface.⁶ Once HPV has entered the basal cells its DNA enters the host cell nucleus and in high-risk HPV infection this causes the expression of oncoproteins E6 and E7. Malignancy at this stage is not absolute, and its risk is relative to the expressed proportion of these oncoproteins.⁷ These affect p53, however, the inhibition of retinoblastoma by E7 also increases the expression of p16, another tumour-suppressor gene and it is suggested that this is the reason HPV-positive OPSCC has better outcomes.⁷ The overexpression of p16 is not present in HPV-negative OPSCC, thus it is often used as a surrogate marker for HPV infection.

HPV-positive OPSCCs are clinically unique and have a different epidemiology, presentation, and prognosis and are often considered a different disease entity^{2,8}. Patients with HPV-positive OPSCC are usually younger, of higher socioeconomic class, and have been less exposed to tobacco and alcohol than those with HPV-negative disease.^{6, 2} Furthermore, within the subsites of the oropharynx, HPV-positive cancers are most prevalent at the tongue base and tonsils, and initial presentation is usually at a more advanced stage.²

RESULTS AND DISCUSSION

Epidemiology

The incidence of OPSCC has increased despite the overall incidence of HNC decreasing.¹⁰ There is evidence proposing that HPV-positive OPSCC has increased in incidence dramatically, whereas the incidence of HPV-negative OPSCC has declined.^{11, 12} In support of this, one study in the UK found that although OPSCCs have risen in incidence, the percentage of HPV-positive and HPV-negative OPSCCs have risen proportionally.³ This study was a case-controlled, cross-centre study that had a sample size of 1474 patients and used three different investigations for HPV testing; HPV gene expression detected by p16 immunohistochemistry (IHC) and HPV DNA detected by polymerase chain reaction (PCR) and/or in situ hybridisation (ISH).¹³

The large sample size and use of widely accepted tests to assess HPV status are major strengths of this study but these findings are only applicable to the UK as it was not an international multi-centre study. As HPV is not the causative factor, the increase in OPSCC may be due to a rise in alcohol consumption. In spite of this evidence, it is widely accepted that HPV-positive OPSCCs account for the vast majority of OPSCCs in most of the western world.² HPV-positive OPSCC is most common in white men, of middle-age and high socioeconomic class, who don't drink or smoke.^{14, 15} One of the explanations for the increased prevalence in males is that oral HPV infection, which is considered to be the precursor of HPV-positive OPSCC,^{14, 16} is more common in men. Despite this, one study found that women were equally affected by HPV-positive OPSCCs.¹⁷ Changing attitudes towards sexual activity have driven the increase in oral HPV infection. Increasing numbers of genital and oral sex partners, and earlier onset sexual activity increase the risk of infection.

Diagnosis and HPV status

Accurate diagnosis of OPSCC, requires multiple stages of investigation.¹ These include clinical examination with flexible direct endoscopy, cross sectional imaging, and panendoscopy or examination under anaesthesia. A biopsy is required to determine the histopathology of the primary tumour.² Biopsies can be taken using fine needle aspiration in some cases, but most require an incision under local or general anaesthetic. It is imperative that all biopsies undergo HPV testing to ensure appropriate

treatment.^{2, 18} HPV testing is not uniform across the board and there are multiple methods used. HPV E6 mRNA PCR is considered gold standard.¹⁹ The most frequently used tests are p16 IHC, HPV DNA PCR, and HPV DNA ISH. These are usually performed on formalin-fixed paraffin embedded samples.²⁰ p16 IHC tests are considered a surrogate marker for HPV infection and are only considered positive if over 70% of sample cells show “strong nuclear and cytoplasmic staining”.^{20, 21} They found however that a combination of p16 IHC and HPV DNA PCR had a sensitivity and specificity of 97% and 94% respectively, which is appropriate for clinical use and comparable to the gold standard test. However, National Institute for Health and Care Excellence (NICE) account for this reduction in specificity by recommending that all OPSCC samples should be tested by p16 IHC and those that are positive should subsequently be tested for HPV DNA using PCR.²² This means that false positives would likely be picked up by PCR. This is a less invasive method and could be researched further.

Staging

Like most cancers, OPSCCs are staged to decide on appropriate treatment and assess prognosis. A tumour, node, metastasis (TNM) model is typically used to stage the cancers and the ‘N’ category was previously considered to be most indicative of prognosis in OPSCCs.^{21, 22} In HPV-positive cancers, primary tumour stage is a superior prognostic indicator. The American Joint Committee on Cancer’s (AJCC’s) 7th edition TNM staging for OPSCC was not stratified according to HPV-status, and overall stage, representing prognosis and mortality, was more dependent on nodal, rather than tumour stage. Thus, many proposed an improved method of staging or recommendations for subsequent editions. As of January 2018, a new 8th edition (TNM-8) came into effect.²² This is stratified by HPV-status and has different staging based on clinical and pathological findings, responding to many of the shortfalls of the previous edition and increasing its prognostic value in HPV-positive OPSCCs. Although, TNM-8 is a vast improvement on its predecessor, it fails to account for certain significant prognostic factors. Tobacco use has long been known to worsen outcomes in HPV-negative disease but it also has a negative impact on prognosis in HPV-positive OPSCC, thus a more holistic tool to assess prognosis may be more useful. One such tool, a nomogram, has already been developed and externally validated (see Appendix 1), and prognostic predictions using this tool were superior to TNM or HPV status alone.²³ However, it is important to recognise that this tool was developed before the release of TNM-8 and so it cannot be compared to this. The tool combines smoking status, tumour stage and HPV status, among other factors to determine prognosis in OPSCC. The C-statistic for the tool is 0.82 and 0.8 for overall and progression-free survival respectively, both of which indicate a strong model for prediction.

Treatment

Current guidelines on treatment of OPSCC suggest combinations of various treatments and do not differentiate between HPV status. NICE guidelines recommend

offering patients with early stage disease (T1-2 N0) a choice between transoral surgical resection and primary radiotherapy.²³ Transoral surgical resection is preferred to open surgery as it has comparable outcomes, but with reduced morbidity and loss of function,² and can be accomplished using two methods: transoral laser surgery (TLS) or transoral robotic surgery (TORS).² Adjuvant treatments of postoperative radiotherapy, with or without chemotherapy, are only recommended if low prognosis risk factors are present.

Locoregionally advanced disease (T3-4 or N1+) is treated with a variety of combinations of surgery, radiotherapy, and chemotherapy,^{2, 12} and across the UK there is no consensus on the preferred treatment.¹ Treatment decision is dependent on individual presentation, NHS trust facilities, and patient preference. Trials have also been conducted to assess the use of monoclonal antibodies that target epidermal growth factor receptor as an adjuvant treatment for advanced OPSCC, but the results are not unanimous.²³ One study found that the addition of cetuximab to induction chemotherapy (IC) and chemoradiation improved long term disease control. In contrast, another found that cetuximab and radiotherapy were not comparable to cisplatin and radiotherapy when assessing locoregional control and overall survival (OS).²³ It is worth noting this study had a small sample size and so its results did not reach statistical significance.²⁰

It is well recognised that HPV-positive OPSCC has a better response to treatment and improved prognosis,¹⁴ due to its increased sensitivity to chemotherapy and radiation.¹² For this reason, many argue HPV-positive OPSCC should be managed differently, and that treatment should be deintensified to reduce the debilitating side effects. There are ongoing trials looking at treatment deintensification to assess whether OS can be maintained, while reducing toxicity and improving quality of life (QOL). These studies are researching different methods of deintensification including comparing TORS with radiotherapy,²⁰ reduced dose radiotherapy⁵ and cetuximab compared to chemoradiotherapy.²³ One completed trial on HPV-positive OPSCC used IC first and assessed complete clinical response before stratifying patients into high and low-risk groups based on this. The low-risk group were given intensity-modulated radiotherapy 54Gy, whereas the high-risk group were given 69.3Gy radiotherapy. Both groups received weekly cetuximab. This trial found that for HPV-positive OPSCCs that respond well to IC, reduced intensity treatment has suitable progression-free survival but with reduced swallowing and nutritional status difficulties.^{17, 19, 20}

Prognosis

HPV-positive OPSCC has distinct epidemiology, clinical presentation and molecular characteristics.¹⁸ Several studies and meta-analyses have been conducted to assess its prognosis in comparison to its HPV-negative counterpart, and there is overwhelming evidence to suggest prognosis is significantly improved in HPV-positive OPSCC.^{1, 24, 25} Risk of overall death in HPV-positive disease was reduced by 74% in one particular study.²⁶ This was echoed in a recent meta-analysis which found that OS and progression-free survival at three years were both better in HPV-positive

OPSCC, at 82% and 73% respectively, compared with 57% and 43% in HPV-negative disease. Tumour status is also a good prognostic indicator following disease progression, and median survival in one study was 2.6 years in HPV-positive OPSCC compared to 0.8 years in HPV-negative OPSCC. HPV tumour status also has a prolonging effect on the time to recurrence and O’Sullivan et al. discovered that risk of distant metastasis continued up to five years, so OS and disease-free progression should be assessed long-term.²⁷

The mechanisms behind improved outcomes in HPV-positive OPSCC are unclear but patient factors are thought to contribute, including reduced comorbidities, younger age, and low exposure to tobacco. In HPV-positive disease tumour suppressor proteins, retinoblastoma and p53, are inhibited but do not harbour mutations and p16, another tumour suppressor gene which is linked with superior outcomes, is overexpressed. This is possibly a further reason for improved prognosis. Another explanation could be an increased sensitivity to radiotherapy. This is likely due to reduced tobacco exposure and increased numbers of wild-type p53, which assists effective apoptosis.¹²

Further Discussion

Prevention of HPV-positive OPSCC is an important area for further research. HPV is a sexually transmitted infection and educating patients about its role in the development of OPSCCs and encouraging safe sex by advocating the use of condoms and dental dams could decrease its transmission.¹⁶ HPV vaccinations are another key area for prevention. There are currently two on the market and both protect against HPV-16/18 which are the most prevalent high-risk HPV types in HPV-positive OPSCCs.¹⁴ Many developed countries have a routine HPV vaccination programme for young girls to protect against cervical cancer, including the UK, who started routinely vaccinating 12-13-year-old girls in 2008.¹⁶ However, most countries do not vaccinate boys even though HPV-16/18 are known carcinogens in penile and oropharyngeal

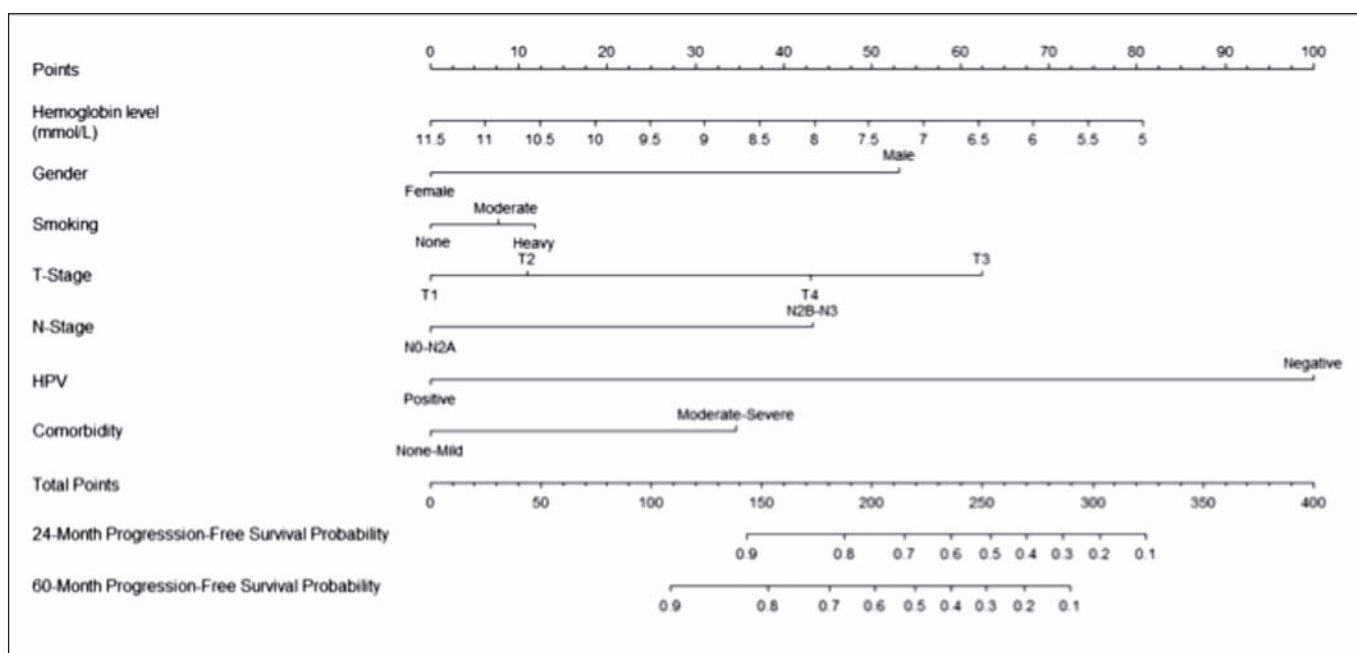
cancers. It was assumed that vaccinating girls would provide herd immunity for boys, however this has not been the case given the increased incidence of HPV-positive OPSCC in young men. There has been much debate on the routine vaccination of boys and whether it could be deemed cost-effective but there is little research into the efficacy of HPV vaccination in OPSCC.¹⁴ In light of this, clinical trials need to be conducted to assess the efficacy of routine HPV vaccination in the prevention of HPV-positive OPSCC.

CONCLUSION

HPV-positive OPSCC is still a relatively new diagnosis and is not yet entirely distinct from its HPV-negative counterpart. The epidemiology of the disease is now more clearly understood and recent updates to the TNM model have improved the overall stage allocated to patients, meaning they are given a more accurate prognosis. Management is complex but there has been a move to deintensify treatment in an attempt to improve QOL while maintaining OS, and there are many ongoing trials to identify an optimal treatment. There is overwhelming evidence suggesting prognosis is better than in HPV-negative disease but the mechanism behind this is poorly understood and further research needs to be conducted to identify prognostic factors within HPV-positive OPSCC. There is a need for future trials to assess the effect of HPV vaccination on HPV-positive OPSCCs and prospective studies should be conducted to determine the efficacy of routinely vaccinating young boys.

APPENDIX 1

Graphic nomogram for prediction of overall survival in oropharyngeal squamous cell carcinomas – using a combination of factors including HPV status, smoking status and gender – reprinted from predictcancer.org, created by Rios Velazquez et al.²⁸



APPENDIX 2

Method and search details

I used the database PUBMED to do my literature search. I initially searched different variations of “human papillomavirus” AND “oropharyngeal squamous cell carcinoma”. I then narrowed down by adding search terms depending on which section of my SSM I was researching for. These search terms included “epidemiology”, “diagnosis”, “staging”, “TNM”, “treatment”, “management”, “prognosis”, “survival” and “outcomes”. I only reviewed recent articles that were published from 2008 onwards.

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