The role of the pathologist in the multidisciplinary management of human papilloma virus-associated head and neck cancer

Tim Helliwell

Abstract

The recognition of a subset of oropharyngeal carcinomas in which the neoplastic process is driven by human papillomaviruses (HPV) has important implications for patients and clinicians. The increasing incidence challenges clinical services at a time when smoking and alcohol related malignancies are becoming fewer. For patients, HPV-associated carcinomas have a relatively good prognosis and there is the prospect that treatment may be less intensive without compromising the outcome. The use of individually targeted therapies is determined by the availability of tumour-specific biomarkers. The challenge for pathologists is to ensure that testing protocols provide accurate, reproducible and timely advice for clinicians and patients to make informed decisions. A combination of immunocytochemical assessment of p16 expression and in situ hybridisation for high risk HPV DNA provides acceptable sensitivity and specificity. Recruitment to clinical trials for oropharyngeal carcinomas requires assessment of HPV status using routine methodologies but, in future, other molecular methods may be required.

Keywords diagnosis; human papillomavirus; immunocytochemistry; in situ hybridisation; multidisciplinary management; oropharynx; p16; prognosis; squamous cell carcinoma

Introduction

Squamous cell carcinoma, worldwide, is a common malignancy of the head and neck region and has traditionally been associated with exposure to the carcinogenic effects of tobacco and alcohol. The rapidly increasing incident of carcinomas of the tonsils and base of tongue in the last 20–30 years has led to the recognition of high risk human papillomaviruses (HPV16 and HPV18) as important drivers for a subset of squamous cell carcinomas typically, but not exclusively, affecting younger, male patients who have not been exposed to other carcinogens. In most populations studied, HPV16 is the main carcinogen in over 70% of oropharyngeal carcinomas.[1] At other sites in the head and neck region, very few (less than 5%) carcinomas are thought to be caused by HPV.[1,2] The full clinical impact of recognising the presence of HPV in oropharyngeal carcinomas has yet to be realised. While HPV-associated carcinomas undoubtedly have a better prognosis than non-HPV carcinomas, largely as a result of a better response to radiotherapy, the rate of distant metastasis is similar for HPV-associated and other carcinomas.[3] The impact on prognosis of the de-intensification of therapeutic regimes (with a reduction in the side effects of chemoradiotherapy) is the subject of clinical trials and, in the context of personalised approaches to treatment, the appropriate balance between primary minimally invasive surgery and primary radiotherapy has yet to be determined. Novel therapeutic strategies based on immunotherapy to HPV are being considered and entering trials. The pathologist therefore currently has a key role in advising patients on the prognosis of their carcinomas and recruitment to clinical trials and, in future, working in the multidisciplinary setting to determine the optimal therapeutic pathway for each patient.

Prognostic implications of HPV-associated oropharyngeal carcinomas

Overall, HPV-associated carcinomas have a 53% improvement in overall survival and 30% improvement in disease free survival compared with HPV-negative carcinomas.[4] The study by Ang et al. was the first to show conclusively that HPV-positive oropharyngeal carcinomas have a relatively good prognosis regardless of treatment modality and also showed that the risk of death increased for each additional pack year of cigarettes smoked, supporting the previous study of Lindquist et al.[3,5] Studies in Liverpool and elsewhere,[6] reinforce the previous reports of a more favourable outcome for patients with p16 and/or HPV-positive carcinomas regardless of treatment modality. HPV-associated carcinomas tend to have smaller primary tumours and more advanced nodal disease than HPV-negative tumours but, stage-for-stage, the beneficial prognostic effects are primarily through a reduction in the risk of loco-regional recurrence, as the rates of distant metastasis are similar in HPV-positive and HPV-negative carcinomas.

Reviews of major trials[7,8] have shown that HPV-positive tumours differ from HPV-negative tumours in their responses to treatment, although the methodologies used to identify HPV-associated carcinomas vary, with some studies using molecular methods and others implying the presence of HPV from overexpression of p16 protein. Retrospective reviews of material include the DAHANCA and TROG 02.02 studies using p16 evaluation have shown that radiosensitisation using hypoxic modification is beneficial in patients with HPV-negative tumours but HPV-positive tumours showed no benefit. HPV DNA evaluation in the TAX 324 study suggested that it might be possible to reduce long term toxicity while maintaining survival in HPV-positive tumours by reducing the intensity of radiotherapy in sequential treatment regimens[9] and further studies are in progress to confirm this. The improved prognosis for patients with HPV-positive carcinomas may also be seen in patients with recurrent disease, but evidence is limited.[8]

The relationship between HPV and smoking is complex. Experimental studies suggest that HPV-positive tumours are not more inherently sensitive to radiotherapy or cisplatin, but that treatment induces a more intense immune response in the HPV-positive tumours.[10] The extent to which HPV infection is beneficial to the outcome of smoking-induced carcinomas or smoking reduces the immune response to HPV-induced tumours is open to debate.

Tim Helliwell *M.D. M.B. B.Chir. F.R.C.Path. Department of Cellular Pathology, Liverpool Clinical Laboratories, Liverpool, UK.* *Conflicts of interest: none declared.*

Several reasons probably account for the better prognosis of HPV-associated carcinomas compared with those in which smoking and alcohol are implicated as carcinogens, but the mechanisms are not fully understood. Possible factors include fewer molecular changes, particularly to p53-related pathways and immune surveillance reacting to HPV antigens. HPV-associated carcinomas are associated with far fewer second primary tumours compared to HPV-negative carcinomas, suggesting that field cancerisation does not occur to the same extent. Furthermore, HPV-positive carcinomas show lower levels of adverse prognostic markers such as the Epidermal Growth Factor Receptor [EGFR,[11]]. However, once HPV status has been established, further predictive biomarker testing is currently not routinely undertaken in diagnostic practice. Nevertheless, as targeted therapy becomes more established, specific biomarker testing may further refine the management of HPV-positive carcinomas.

Therapeutic implications

In the past, the therapeutic options for the treatment of head and neck cancers through induction chemotherapy, hyperfractionated radiotherapy, surgery and molecularly targeted agents has led to an intensification of treatment with an increase in the severity and duration of side effects such as swallowing and speech impairment, dry mouth and osteonecrosis. Patients and their clinicians have a major interest in considering whether patients are getting the treatment that maximises their chances of disease control and minimises the side effects.

In clinical practice, the introduction of HPV testing is currently justifiable in order to provide a more accurate prognosis for patients. Recruitment to clinical trials may require stratification by HPV status and, for trials aimed at de-escalation of toxic therapies, the risks to patients of inaccurately attributing HPV-negative patients to the HPV-positive group may carry real risk.

The UK national guidance is that early stage (T1-2, N0,M0) oropharyngeal carcinomas may be treated either by surgery or radiotherapy (with surgical salvage) resulting in five year survival rates of between 81 and 100% for primary surgery and 77−89% for radiotherapy.[12] Surgery is usually transoral laser resection but open operations may be performed. As 10−30% patients who are clinically T1-2, N0 will have occult nodal disease, an ipsilateral selective neck dissection is recommended. For advanced (T3-4, N0-3) oropharyngeal carcinomas, surgery may be offered (with postoperative radio and/or chemotherapy), but most patients who are medically fit will be treated by primary chemoradiotherapy using cisplatin in combination with radiotherapy. The guideline recommends that treatment should only be modified according to HPV status in the context of a clinical trial, but regular experience of tumour board meetings suggests that p16/HPV ISH data are increasingly being used, to moderate treatment within an agreed therapeutic range, either to justify radical chemoradiotherapy in advanced disease with the anticipation of good outcome, or to de-escalate treatment in order to reduce the potential side effects of adjuvant treatment.

Importance of clinical trials − risk stratification

HPV is now recognised as an independent risk factor for oropharyngeal carcinomas and, given the impact on prognosis, knowledge of the HPV status is essential when assessing the outcomes of clinical trials. Strategies targeted at the different molecular phenotype seen in HPV-associated carcinomas are also being developed. A detailed review of current clinical trials indicates that most studies are looking at the potential to de-intensify treatment regimens and therefore reduce the impact of the side effects of treatment (see article by Powell and Evans in this issue). Immunological strategies directed against HPV are also being developed,[13,14] for example, the REALISTIC trial is a phase 1 study being run from Liverpool to investigate the tolerability and immunogenicity of a modified Listeria monocytogenes vaccine expressing HPV16 E7.

Morphologic terminology of HPV-associated carcinomas

The sites of predilection for HPV-associated carcinomas are the palatine and lingual tonsils and the base of tongue. The normal reticulated epithelium of the epithelial crypts at these sites is closely associated with lymphocytes and typically lacks keratinisation. The HPV-associated carcinomas in these areas also tend to have a non-keratinising, basaloid phenotype and often show lymphocytic infiltration.[15] The terminology used by pathologists to describe HPV-associated carcinomas has changed in recent years and is potentially a source of confusion, with terms such as basaloid, nasopharyngeal-like, transitional-type and poorly-differentiated carcinomas being used. These terms may be misleading as they are also used for morphologically distinctive variants of squamous cell carcinoma in other parts of the upper aerodigestive tract (Figure 1).

In 1998 Wilczynski[16] described three patterns of tonsillar squamous cell carcinoma in a small series of 21 patients:

- Well-keratinised carcinomas with central keratin pearls and more peripheral angulated cells with basal-type cells at the periphery of the islands, particularly in areas of infiltration.
- Poorly-keratinised carcinomas composed of sheets of small ovoid to spindled cells with a high nucleocytoplasmic ratio, indistinct borders, minimal or no keratinisation and small areas of central necrosis.
- An intermediate group with predominantly basal-type cells but with more keratinisation than the poorly differentiated group.

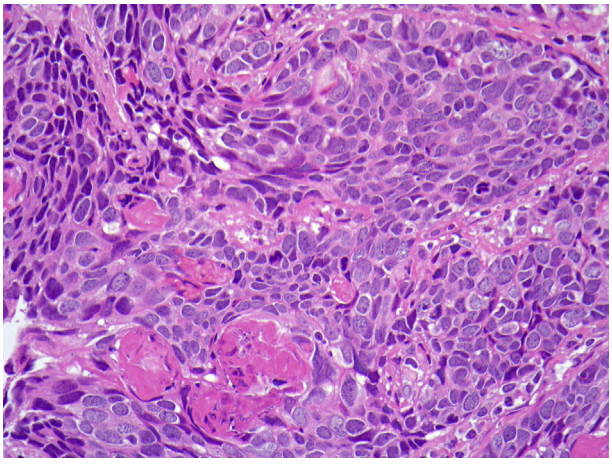

Figure 1 Non-keratinising squamous cell carcinoma of the tonsil. This carcinoma was positive for p16 and HPV16. H&E.