HPV-associated Head and Neck Cancers – an update

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Epidemiology

- Increasing incidence of oropharyngeal carcinoma over the last 30 years
  - United States and Europe
  - Survival rates improving

Molecular profile of HPV-associated cancers

- High risk HPV types (HPV-16/18)
- E6 and E7 viral proteins inactivate p53 and pRb
- Removal of negative feedback by pRb allows overexpression of p16

Other sites (clinical significance uncertain)

- Sinonasal carcinomas (~20%)
- Oral cavity, laryngeal carcinomas (~5%)

HPV-16 and cancers
- A probable cause for oral, tonsil, pharynx
- A cause for larynx

HPV-18 and cancers
- A probable cause for oral

Epidemiology

- Associated with changing patterns of sexual activity
  - Number of lifetime sexual partners
  - Number of oral-genital sexual partners
- 18-82% oropharyngeal carcinomas related to HPV infection (geography and methodology)
  - UK data suggest 70-80%
- Other sites (clinical significance uncertain)
  - Sinonasal carcinomas possibly 20%
  - Oral cavity, laryngeal carcinomas ~5%
**Morphology of Oropharyngeal HPV-associated Carcinomas**

Varied terminology
- Non-keratinising
- Basaloid
- Poorly-differentiated

- Arises from reticulated epithelium of tonsillar crypts
- Non-keratinising SCC
  - May show focal maturation (eosinophilia, keratin whorls)
  - Not really poorly differentiated (fewer genetic changes, better prognosis)
- However
  - Not all non-keratinising SCC are HPV related
  - Some keratinising SCC are HPV related
  - Some basaloid squamous carcinomas are HPV-positive (non-HPV basaloid SCC are more aggressive)
  - Some small cell carcinomas are HPV positive

**Laboratory diagnosis**

- **Research**
  - Fresh frozen tissue, or
  - Optimally preserved tissue, quality assured
- **Clinical setting**
  - Formalin-fixed paraffin embedded tissue
  - Limited access to molecular technology
  - Prognosis and management influenced by many factors other than viral presence
  - What is an acceptable level of specificity and sensitivity?

**Methodologies**

- Prognostic value relates to carcinomas where proliferation and progression are driven by HPV and not by mere presence of virus
- A gold standard in research setting is taken as identification of HPV mRNA by qPCR
- Other PCR-based methods for HPV DNA
- In situ hybridisation (DNA or RNA)
- p16 immunocytochemistry, reporter for functionally active HPV infection

**Schache et al. (2011)**

<table>
<thead>
<tr>
<th>HPV Diagnostic Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>RNA-qPCR (&quot;gold standard&quot;)</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td><strong>p16 IHC</strong></td>
<td>94%</td>
<td>82%</td>
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<tr>
<td>HR HPV ISH</td>
<td>88%</td>
<td>88%</td>
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<tr>
<td><strong>Combined p16/HR HPV ISH</strong></td>
<td>88%</td>
<td>90%</td>
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<tr>
<td>DNA qPCR</td>
<td>97%</td>
<td>87%</td>
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<tr>
<td>Combined p16/DNA qPCR</td>
<td>94%</td>
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Prognostic Discrimination of Tests
Kaplan-Meier estimates of survival by HPV status (RNA / DNA)

Diagnostic practice and HPV
- Improved prognostication of neck nodes with unknown primary
  - HPV/EBV assessment may point to primaries in oropharynx or nasopharynx respectively
- WHO Blue Book Classification of Oropharyngeal Carcinomas in changes between 2015 and 2017 editions
- TNM staging in UICC, AJCC in changes in v8

HPV-related SCC — cystic nodal metastasis

WHO Classification 3rd Edition

WHO Classification 4th Edition

p16 Positive Oropharynx - Definition of Primary Tumour (T)

T0 No primary identified, but p16 positive cervical node(s) involved
T1 Tumour 2 cm or smaller in greatest dimension
T3 Tumour larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4 Moderately advanced or very advanced local disease

p16 Negative Oropharynx - Definition of Primary Tumour (T)

Tis Carcinoma in situ
T1 Tumour 2 cm or smaller in greatest dimension
T3 Tumour larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4 Moderately advanced or very advanced local disease

HPV-positive carcinoma
HPV-negative carcinoma
(p16 as acceptable surrogate)
Impact on management

• Stratification of patients by HPV status is a useful guide to prognosis using standard therapies
• Extranodal extension may be of less importance in HPV-related carcinomas needs confirmation
• HPV+ SCC with small cell component highly malignant
• Should HPV status be used to modify treatment?
  - Results of clinical trials are awaited
  - Should we treat advanced disease more aggressively if know prognosis is better
  - Should de-escalate treatment to reduce side effects

Impact on prognosis

• HPV+ oropharyngeal carcinomas have a relatively good prognosis regardless of treatment
• Cancers are not inherently more sensitive for radiotherapy or cisplatin; these treatments result in a more intense immune response in HPV+ cancers
• HPV and smoking
  - Patients with HPV+ carcinoma and who were smokers tend to have intermediate prognosis
  - HPV improves outcome of smoking induced cancers
  - Smoking reduce immune response to HPV-induced cancers

Summary

• The UK shares the world-wide increasing incidence of HPV- associated carcinomas of the oropharynx
• Squamous cell carcinomas are now even more interesting to surgeons and oncologists
• HPV carcinomas often have a better prognosis and may provide an opportunity to modify standard treatment
• Challenge for laboratories
  - Identify HPV associated cases in routine material for informed decisions on patient management
  - Varied morphology, but predominantly non-keratinising this is probably not sufficient evidence on which to base treatment
  - Other tests need to be accurate, reproducible and timely
• Currently, p16 immunocytochemistry and HPV-16 DNA ISH are favoured