Chemoradiotherapy for HPV-associated oropharyngeal cancer

Dr Mererid Evans
Velindre Cancer Centre, Cardiff University
Increased 2-3 fold in Wales over 10 years

2001-06: 55% of cases HPV positive

2010-12: 75% of cases p16 positive
HPV-positive OPC

- HPV-positive and negative OPC are different diseases but are treated similarly

- Need to revisit the principles used for management of HNSCC when dealing with HPV-positive OPC (like NPC)

- Patient (younger, fitter, less likely to smoke) and tumour/clinical differences as well as molecular differences are relevant to treatment decision making
The Mutational Landscape of Head and Neck Squamous Cell Carcinoma

Nicolas Stransky, 1* Ann Marie Egloff, 2* Aaron D. Tward, 1,3,4* Aleksandar D. Kostic, 1,5 Kristian Cibulskis, 1 Andrey Sivachenko, 1 Gregory V. Kryukov, 1,5 Michael S. Lawrence, 1 Carrie Sougnez, 1 Aaron McKenna, 1 Erica Shefler, 1 Alex H. Ramos, 1 Petar Stojanov, 1 Scott L. Carter, 1 Douglas Voet, 1 Maria L. Cortés, 1 Daniel Auclair, 1 Michael F. Berger, 1 Gordon Saksena, 1 Candace Guiducci, 1 Robert C. Onofrio, 1 Melissa Parkin, 1 Marjorie Romkes, 6 Joel L. Weissfeld, 7 Raja R. Seethala, 8 Lin Wang, 8 Claudia Rangel-Escareño, 9 Juan Carlos Fernandez-Lopez, 9 Alfredo Hidalgo-Miranda, 9 Jorge Melendez-Zajgla, 9 Wendy Winkler, 1 Kristin Ardlie, 1 Stacey B. Gabriel, 1 Matthew Meyerson, 1,5,10,11 Eric S. Lander, 1,5,12 Gad Getz, 1 Todd R. Golub, 1,5,11,13,14† Levi A. Garraway, 1,5,10,11†† Jennifer R. Grandis 2,15††

74 HNSCCs, whole-exome sequencing
Diverse mutational aetiology - 39 genes high statistical chance mutation

Science 2011;333:1157-1160
Less p53 mutations in HPV positives (p=0.001)

Mutation rate of HPV positives ~50% of HPV negatives (mean 2.28 mutations/Mb vs 4.83 mutations/Mb, p=0.004)
HPV oncogenesis

HPV E6 and E7 proteins ‘switch off’ cellular tumour suppressor genes p53 and Rb. Deregulation of cell cycle can lead to rapid proliferation → genetic instability →→→→ cancer.
Molecular differences between HPV-positive and negative tumours

<table>
<thead>
<tr>
<th></th>
<th>HPV positive</th>
<th>HPV negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation burden</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>p53 mutation (what about expression)</td>
<td>p53 wild type (E6 degrades)</td>
<td>p53 mutation (60%)</td>
</tr>
<tr>
<td>P16 expression</td>
<td>Overexpression (not inactivated)</td>
<td>p16 inactivation (low expression)</td>
</tr>
<tr>
<td>EGFR (what about mutation)</td>
<td>Low expression</td>
<td>High expression</td>
</tr>
</tbody>
</table>

Treatment options

• Primary radiotherapy/chemoradiotherapy (CRT)

• Surgery +/- post-operative RT/CRT (33% OPCs in E&W are treated surgically, DAHNO 2011)

• Recurrent/distant metastatic disease – palliative systemic therapy
Influence of HPV on response to RT in HNSCC

DAHANCA 5 (N=156, 47% OPC)

Greater benefit in more advanced disease (N+, stage III-IV)

Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC).
Pignon JP et al. on behalf of the Meta-Analysis of the MACH-NC Collaborative Group

..An Update on 93 randomised trials and 17,346 patients.
*Radiother. Oncology* 2009;92:4-14. (>3000 OPC patients)

Absolute survival benefit of chemotherapy = 4.5% at 5yrs (p<0.0001)
Greatest benefit from **concurrent** chemotherapy = 6.5% at 5yrs (p<0.0001)
No significant survival advantage from induction or adjuvant chemotherapy
Concurrent chemotherapy also reduced loco-regional failure
Decreasing effect of chemotherapy with age (>70yrs)

Approx. 17% had oropharyngeal cancer, <40% HPV-positivity rate (pre 2000), ~6% overall
Tumor HPV status and survival

Two-year overall survival

Log-rank test, $p=0.005$

95%

62%

33% survival difference

Overall survival based on tumour HPV status (chemoradiotherapy)

3yr OS **82.4%** HPV positive vs **57.1%** HPV negative (p<0.001)

25% survival difference

Radiotherapy - health warning!

Major deviations from the radiotherapy protocol:

- **reduce survival by 20%**
  (2y OS 50% vs 70%)

- **reduce locoregional control rates by 24%**
  (2y LRC 54% vs 78%)

Late Toxicity of chemoRT

- Late toxicity worse after CRT than RT alone (Denis IJROBP 2003, Caudell IJROBP 2009)

- 43% of patients develop Grade 3-4 late toxicity (Machtay JCO 2008)

- Swallowing dysfunction major impact on QOL (Langendijk 2008); 24% feeding tube dependence at 1y (Caudell IJROBP 2009), 13% >2y (Machtay JCO 2008)

- 88% have reduced MDADI score 3m after treatment for H&N cancer; 80% at 12m. (Jo Patterson, personal communication)
IMRT reduces Late Toxicity

Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial

Christopher M Nutting, James P Morden, Kevin J Harrington, Teresa Guerrero Urbano, Shreerang A Bhide, Catharine Clark, Elizabeth A Miles, Aisha B Miah, Kate Newbold, Mary Anne Tanay, Fawzi Adab, Sarah J Jefferies, Christopher Scrase, Beng K Yap, Roger P A’Hern, Mark A Sydenham, Marie Emson, Emma Hall, on behalf of the PARSPORT trial management group*


Severe xerostomia (dry mouth) reduced after IMRT vs conv. RT

- from 74% to 34% at 12 months (p=0.0027)
- from 83% to 29% at 24 months (p=0.0001)
Original Article

Target Volume Definition for Intensity-modulated Radiotherapy after Induction Chemotherapy and Patterns of Treatment Failure after Sequential Chemoradiotherapy in Locoregionally Advanced Oropharyngeal Squamous Cell Carcinoma

S.W. Loo*, K. Geropantas*, P. Wilson†, W.M.C. Martin*, T.W. Roques*
Outstanding questions/controversies

1. Do HPV-positive patients develop distant metastases?

2. Can we omit chemotherapy/modify systemic therapy?

3. How should we manage HPV-positive smokers?

4. What is the role of neck dissection after CRT?

5. What is the optimum adjuvant treatment after surgery for OPC?
Do HPV-positive cancers metastasize?

• **Yes.** HPV positive/negatives have similar rates of distant mets (Ang *NEJM* 2010, O’Sullivan *JCO* 2013); may occur late and in unusual sites (Huang *IJROBP* 2012).

• Advanced nodal disease increases the rate of mets in OPC (11% N1-N2a vs 28% N2b/c/N3, p<0.001) (Garden et al, *Cancer* 2004)
Deintensification Candidate Subgroups in Human Papillomavirus–Related Oropharyngeal Cancer According to Minimal Risk of Distant Metastasis

Brian O’Sullivan, Shao Hui Huang, Lillian L. Siu, John Waldron, Helen Zhao, Bayardo Perez-Ordóñez, Ilan Weinreb, John Kim, Jolie Ringash, Andrew Bayley, Laura A. Dawson, Andrew Hope, John Cho, Jonathan Irisk, Ralph Gilbert, Patrick Gullane, Angela Hui, Fei-Fei Liu, Eric Chen, and Wei Xu

HPV-positive patients with T4 +/- N3 disease have a lower distant control rate than other HPV-positive patients (76% vs 93%)

Distant control rate for HPV-positive N2c disease (73% vs 92%, p=0.02) is lower with RT than (concurrent) chemoradiotherapy; possibly also for N2b heavy smokers.
De-intensification subgroups?

• Induction chemo has a greater effect on distant metastases than concurrent chemotherapy (Pignon meta-analysis *Radiother Oncol* 2009); ↓ by 11% at 5y (p=0.04) (*Oral Oncology* 2012)

• HPV-positives have a higher response rate to IC than HPV-negatives (82% vs 55%, p=0.01, Fakhry *JNCI* 2008)

• Consider induction chemotherapy for T4 or N3 disease

• Concurrent CRT appears necessary for N2c disease and possibly also N2b heavy smokers

Consider RT alone for T1-T3 N0-N2a (N2b) OPC?
De-ESCALaTE HPV

Control Arm
RT (70Gy in 35#) + concurrent Cisplatin (x3)

Treatment Arm
RT (70Gy in 35#) + concurrent Cetuximab (x8)

Primary endpoint = late severe toxicity

Target no. 304

Cl: Hisham Mehanna, Coventry

Determination of EGFR-inhibitor versus Standard CRT early And Late Toxicity Events in HPV – positive Oropharyngeal SCC

SCC oropharynx Stage III/IV

P16 IHC Positive

Randomisation 1:1

T3N0-T4N0, T1N1-T4N3 Not IVc (metastatic) Excludes smokers >10pack/yrs with N2b,N2c, N3 disease
Vaccine studies: REALISTIC

- Liverpool, Marsden, Cardiff
- Phase I: safety, immunogenicity
- Therapeutic HPV vaccine

**ADXS11-001**

*Listeria monocytogenes* (Lm) vector

HPV16 E7 fusion protein

CI: Professor Terry Jones
Smoking and HPV

Smoking may alter behaviour/treatment response of HPV+OPC

Overall Survival According to Tumor HPV Status

- Low risk 93% at 3 yrs
- Intermediate risk 70.8%
- High risk 46.2%

Hazard ratio for death, 0.38 (0.26–0.55); P<0.001

HPV positive patients with N2b-N3 disease with 10 pack-yr smoking history= ‘intermediate’
Smoking and HPV-questions

- Does smoking affect disease-specific survival/loco-regional failure in HPV-positive patients? .....or are smokers dying of other smoking-induced diseases?

B. O’Sullivan JCO 2013: smoking >10pack/yrs reduced OS (HR 1.72, 1.1-2.7) but not RFS (HR 1.1, 0.7-1.9) in 382 HPV-positive OPC patients.

Gillison JCO 2012: smokers >10 pack/yrs (in RTOG 0129) had higher LRF rate, even after adjustment for p16 (p=0.04)

..........suggests a possible direct effect on treatment response and/or disease control.
Smoking and HPV-questions

• **What constitutes a smoker?** (is self-reporting accurate?): mean pack/yr smoking history 34 (former = 27; current = 45) (Garden, *Radiation Oncology* 2013)

  Risk of progression and death from OPC increase directly as a function of tobacco exposure – by **1% per pack/yr**; independent of p16 (Gillison 2012)

• **Is timing of smoking important?**

  Former and never smokers may have similar outcomes (Garden 2013, South Wales data)

  Smoking during RT doubles risk of death (after accounting for pack/ys) (Gillison 2013)
Smoking and HPV - conclusions

• Need to further refine classification of a ‘smoker’ and ‘non-smoker’ and investigate what it is about smoking that affects prognosis

• Identify molecular biomarkers to stratify smokers (and non-smokers) into risk groups – likely to be more reliable than self-reported pack/yr smoking history

• Ongoing RCTs will give us valuable information .......
  RTOG 1016 (USA) and De-Escalate HPV (UK).
Elective (planned) neck dissection 6-12 weeks after CRT

Response assessment 4-12 weeks after CRT

Neck dissection if less than complete response
Role of neck dissection after CRT

- 5 yr regional control rate in patients with nodal complete response to CRT = **92%** (Weber et al, *IJROBP* 2012)

- For patients without a complete response, regional control rate = 84%; better with ND (90%) than without (76%, p<0.001). Only 30% had viable tumour (associated with worse prognosis).

- When/how should response assessment be carried out? (PET-Neck)
Role of ND in HPV-positive OPC

- Huang ICHNO 2013: 493 HNSCC patients with N2/N3 disease (50% HPV-positive). CT scan 8-10 weeks after RT

- Similar nodal complete response rate (~50%) in HPV-positives and negatives

- But, residual nodes in HPV-positive patients continued to regress >24 weeks after RT and had a higher rate of ultimate regression, even without neck dissection. HPV positives had a low rate of locoregional failure.

- Conclusion: may need to modify treatment response assessment protocols for HPV-positive disease
tonsil primary
p16-positive

Left retropharyngeal lymph node
Retropharyngeal lymph nodes

• Incidence in surgical series: 0 to >30%. Independent predictor for higher recurrence and worse Disease Specific Survival

• In a study of 205 patients with stage III/IV OPC (88% HPV-positive) (Spector et al, JAMA 2012), 18% had radiologic evidence of RPLN involvement (CT>1cm or FDG-avid on FDG-PET): 13% BOT, 22% tonsil cancers, 14% other OPCs.

• Higher in patients with multinodal disease

• Must be considered when planning RT and/or surgery
Adjuvant treatment of HPV-positive OPC

• Role for transoral surgery for T1-3 N0-N2b HPV-positive OPC

• Excellent results local control/survival (Haughey 2011)

• Compelling data on function (vs CRT)

• But role is questionable if adjuvant (high dose) RT and/or chemoRT is routinely given afterwards.....
PATHOS trial: post-operative adjuvant treatment for HPV-positive tumours

- HPV positive OPC T1-3 N1-N2b
- Transoral surgery + neck dissection
- Pathology risk assessment
  - Low risk
  - Intermediate risk
    - >1 LN, LN>3cm, T3, PNI
  - High risk
    - ECS, +ve margin
- Endpoints:
  - Phase II – swallowing function; phase III – survival

Randomized, multi-centre phase II

Endpoints: phase II – swallowing function; phase III – survival

° Test arm, #comparator
Recurrent/metastatic HPV-positive OPC

• 5-18% of HPV-positives develop locoregional recurrence and 7-24% develop distant metastases within 3yrs.

• **EXTREME study**: median survival R/M HNSCC **10.1m** (Cis+5-FU +Cetuximab) **vs** 7.4m (Cis+5-FU alone) (Vermoken, *NEJM* 2008)

• **SPECTRUM study**: median survival R/M HNSCC **11.1m** (Cis+5-FU+Panitumumab) **vs** 9.0m (Cis+5-FU alone) (Vermoken, *ICHNO* 2013)

• What is the effect of HPV status?
Recurrent/metastatic HPV-positive OPC

• Vermoken, _ICHNO_ 2013

**EXTREME** (Median Overall Survival, months)

C+Cetux  

12.6m HPV+  vs  

9.7m HPV-  (p=0.09)

**SPECTRUM**

C only  

12.6m HPV+  vs  

8.6m HPV-  (HR 0.7; 0.47-1.04)

• p16 positive and negative patients benefitted from Cetuximab in EXTREME (ORR HPV positives 50% vs 21%, p=0.06) (greater in HPV negatives); only HPV negatives benefitted from Panitumumab in SPECTRUM
Recurrent/metastatic HPV-positive OPC

- p16 status may be a positive prognostic factor in R/M HNSCC

- p16 status may be predictive.

- Outcomes (OS, PFS, ORR) of HPV-positive patients with recurrent/metastatic disease remain poor and new strategies are needed to improve outcomes in future.
Conclusions

• HPV-positive OPC is a distinct disease entity. Treatment protocols must maintain high survival rates whilst minimizing toxicity.

• RT alone may be sufficient for T1-T3 N2a (N2b) HPV-positive OPC. IMRT quality is paramount.

• Alternative is transoral resection and modified (de-intensified) adjuvant treatment.

• For stage III/IV disease, chemolMRT is standard of care. Concurrent chemotherapy may be replaced by Cetuximab (RCTs). Induction chemotherapy may be needed for T4/N3 disease.

• New strategies are needed for recurrent/metastatic HPV-positive oropharyngeal cancer.