HPV POSITIVE OROPHARYNGEAL CARCINOMA
the radiation oncologist point of view

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DISCLOSURE OF INTEREST

Nothing to declare
HEAD AND NECK CANCER - HPV

Change in incidence:

A

B

- Cigarettes
- Cigars
- Pipe/roll your own
- Chewing
- Snuff

- Larynx
- Floor, gum, and other mouth
- Tongue
- Oropharynx/tonsil
HEAD AND NECK CANCER - HPV

Change in incidence:

Chaturvedi AK J Clin Oncol 2011
## TWO DISTINCT HEAD AND NECK CANCERS

<table>
<thead>
<tr>
<th></th>
<th>HPV-Positive</th>
<th>HPV-Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomic site</strong></td>
<td>Tonsil / BOT</td>
<td>All sites</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Basaloid</td>
<td>Keratinized</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>3:1 men</td>
<td>3:1 men</td>
</tr>
<tr>
<td><strong>SE status</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td>Sexual behavior</td>
<td>Alcohol / tobacco</td>
</tr>
<tr>
<td><strong>Cofactors</strong></td>
<td>Marijuana, immunosuppression</td>
<td>Diet, hygiene</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>p53WT, p16+</td>
<td>p53Mu, p16-</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>Increasing</td>
<td>Decreasing</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>High</td>
<td>Worse</td>
</tr>
</tbody>
</table>

### Overall Survival by HPV Status in Prospective Phase III RT Trials

<table>
<thead>
<tr>
<th>Clinical trial (PI, year)</th>
<th>N eval. for HPV</th>
<th>N HPV+</th>
<th>Prognostic biomarker</th>
<th>Treatment</th>
<th>OS HR HPV+ versus HPV- (follow-up years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAHANCA5 (Lassen, 2009)</td>
<td>156</td>
<td>35</td>
<td>p16^{NK4a} + versus p16^{NK4a} (p16^{NK4a} IHC)</td>
<td>RT +/- Nimorazole</td>
<td>0.22 (0.08–0.56) (5y)</td>
</tr>
<tr>
<td>RTOG 0129 (Ang, 2010)</td>
<td>323</td>
<td>206</td>
<td>HPV+ versus HPV− (DNA ISH and p16^{NK4a} IHC)</td>
<td>Accelerated-RT and CDDP Versus RT and CDDP</td>
<td>0.42 (0.27–0.66) (3y)</td>
</tr>
<tr>
<td>RTOG 9003 (Gillison, 2010)</td>
<td>190</td>
<td>74</td>
<td>p16^{NK4a} + versus p16^{NK4a} (p16^{NK4a} IHC)</td>
<td>RT versus hyper-FX RT versus AFX with split versus AFX-CBDCA</td>
<td>0.44 (0.31–0.61) (5y)</td>
</tr>
<tr>
<td>TAX 324 (Posner, 2011)</td>
<td>111</td>
<td>56</td>
<td>HPV+ versus HPV− (F6/E7 HPV DNA PCR)</td>
<td>TPF versus PF ICT followed by weekly CBDCA and RT</td>
<td>0.2 (0.1–0.38) (5y)</td>
</tr>
<tr>
<td>TROG 0202 (Rischin, 2012)</td>
<td>185</td>
<td>106</td>
<td>p16^{NK4a} + versus p16^{NK4a} (p16^{NK4a} IHC and DNA PCR/ISH)</td>
<td>CDDP and RT +/- Tirapazamine</td>
<td>0.43 (0.2–0.93) (2y)</td>
</tr>
<tr>
<td>IMCL-9815 (Bonner, 2014)</td>
<td>182</td>
<td>75</td>
<td>p16^{NK4a} + versus p16^{NK4a} (p16^{NK4a} IHC)</td>
<td>RT versus RT and Cetuximab</td>
<td>0.27 (0.15–0.51) (5y)</td>
</tr>
<tr>
<td>RTOG 0522 (Ang, 2014)</td>
<td>321</td>
<td>235</td>
<td>p16^{NK4a} + versus p16^{NK4a} (p16^{NK4a} IHC)</td>
<td>CDDP and RT +/- Cetuximab</td>
<td>85.6% versus 60.1%; P&lt;0.001 (3y)</td>
</tr>
</tbody>
</table>

AFX, accelerated fractionation; CBDCA, carboplatin; CDDP, cisplatin; Eval, evaluable samples; FX, fractionation; HR, Hazard Ratio; ISH, in situ hybridization; HPV, Human papillomavirus; OS, Overall survival; PF ICT, Induction chemotherapy with Cisplatin and 5-Fluorouracil; PI, principal investigator; RDT, radiotherapy; TPF, Taxotere, Cisplatin, 5-Fluorouracil.
INFLUENCE OF HPV AFTER CONVENTIONAL RADIOTHERAPY IN HNSCC (5FX/WEEK)

DAHANCA 5 (N=156)

HPV/p16-positivity is a favourable and strong independent prognostic factor in head and neck cancer radiotherapy

Lassen P J Clin Oncol 2009
CHEMORADIOThERAPY: RTOG 0129

93% 3y DFS

<50% 3y DFS

Ang KK New Eng J Med 2010
POSTOPERATIVE RADIOCHEMOTHERAPY

**Figure B:**

- **Pts. with oropharyngeal carcinoma**
- **Loco-regional control**
- **Months after begin of treatment**
- **HPV16 DNA +**
- **HPV16 DNA -**

- **p=0.02**

Data points:

<table>
<thead>
<tr>
<th>Months</th>
<th>HPV16 DNA +</th>
<th>HPV16 DNA -</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>24</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>36</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>48</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>60</td>
<td>21</td>
<td>33</td>
</tr>
</tbody>
</table>

Lohaus F. Radiother Oncol 2014
Influence of HPV for all HNC?

OS by p16 status stage III-IV **OPC** (E) versus st III-IV **non-OPC** (F) after (chemo)RT

![Graphs showing survival rates for OPC and non-OPC](image)

Lassen P et al Radiother Oncol 2014
NEED FOR NEW CLASSIFICATION

HPV+  HPV-

Huang C et al JCO 2015
**Clinical and Pathological T categories**

- **T1** Tumour 2 cm or less in greatest dimension
- **T2** Tumour more than 2 cm but not more than 4 cm
- **T3** Tumour more than 4 cm in or extension to lingual surface of epiglottis
- **T4** Tumour invades any of the following: larynx, deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, mandible*, lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases carotid artery

**Clinical N categories**

<table>
<thead>
<tr>
<th>N0</th>
<th>No regional lymph node metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Unilateral metastasis, in lymph node(s), all 6 cm or less</td>
</tr>
<tr>
<td>N2</td>
<td>Contralateral or bilateral metastasis in lymph node(s), all 6 cm or less in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in lymph node(s) greater than 6 cm in dimension</td>
</tr>
</tbody>
</table>

**Clinical**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1, T2</td>
<td>N0, 1</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T1, T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0, N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T1-T4</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
WHY BETTER PROGNOSIS?

Higher locoregional control:

- HPV-positive tumors may harbor fewer or different genetic alterations, which can be associated with better response to therapy

Cancer Genome Atlas Network Nature 2015

Figure 3 | Candidate therapeutic targets and driver oncogenic events. Alteration events for key genes are displayed by sample (n = 279). TSG, tumour suppressor gene.
WHY BETTER PROGNOSIS?

Higher locoregional control:

- HPV-positive tumors may harbor fewer or different genetic alterations, which can be associated with better response to therapy.
- HPV-positive tumors have higher radiosensitivity, due to compromised DNA repair capacity.
  - In vitro data suggest high number of residual DNA double strand breaks after irradiation.
UNDERLYING BIOLOGY
WHY BETTER PROGNOSIS?

Higher locoregional control:
- HPV-positive tumors may harbor fewer or different genetic alterations, which can be associated with better response to therapy
- HPV-positive tumors have higher radiosensitivity, probably due to intact apoptotic response to radiation
- Immunologic response may play a role in the improved response to radio- and chemotherapy in HPV-positive tumors

Reduced rates secondary tumors
- Less field cancerization

Reduced frequency of poor prognostic factors
- Performance status, T-stage, younger age, reduced smoking
HEAD AND NECK CANCER AND HPV

Observed Associations Between HPV and HNC

Sexual behaviors → HPV infection → HPV in tumor

Head and neck cancer
### HEAD AND NECK CANCER - HPV

**Risicofactoren**

**Risk Models for HPV+ and HPV− HNC¹a**

<table>
<thead>
<tr>
<th></th>
<th>Tobacco</th>
<th>Alcohol</th>
<th>Dentition</th>
<th>Oral Sex</th>
<th>Marijuana</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjusted odds ratios for HPV positive cancer</strong></td>
<td><img src="chart" alt="" /></td>
<td><img src="chart" alt="" /></td>
<td><img src="chart" alt="" /></td>
<td><img src="chart" alt="" /></td>
<td><img src="chart" alt="" /></td>
</tr>
<tr>
<td><strong>Adjusted odds ratios for HPV negative cancer</strong></td>
<td><img src="chart" alt="" /></td>
<td><img src="chart" alt="" /></td>
<td><img src="chart" alt="" /></td>
<td><img src="chart" alt="" /></td>
<td><img src="chart" alt="" /></td>
</tr>
</tbody>
</table>

¹ Odds ratios adjusted for age, gender, race, tobacco, alcohol, oral hygiene, marijuana, and oral sex, as appropriate.
RISK FACTORS FOR HEAD AND NECK CANCERS

HPV-
- Smoking
- Drinking

HPV+
- High number of oral sex partners
- High number of open mouth kissing partners
- Young age of first sexual experience
# HPV AND OROPHARYNGEAL CANCER

<table>
<thead>
<tr>
<th></th>
<th>HPV Positive</th>
<th>HPV Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td>• 5 years younger</td>
<td>• Typical ages</td>
</tr>
<tr>
<td></td>
<td>• Non-smokers/non-drinkers</td>
<td>• Tobacco and alcohol</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>Tonsil &amp; Tongue base</td>
<td>All locations</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Poorly differentiated, non-keratinizing, basaloid</td>
<td>Keratinizing SCC</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>• p53 inactivated by E6</td>
<td>• p53 inactivated by mutation</td>
</tr>
<tr>
<td></td>
<td>• Rb inactivated by E7</td>
<td>• Rb inactivated by cyclin D1 amplification</td>
</tr>
<tr>
<td></td>
<td>• p16 over-expressed</td>
<td>• Inactivation of p16</td>
</tr>
</tbody>
</table>
HPV POSITIVE DISEASE

Clinical observations: HPV positive tumors tend to respond better to radiotherapy
- RT alone
- Radiochemotherapy
- Postoperative radio(chemo)therapy

UNDERLYING BIOLOGY

A

0Gy  2Gy 4h

C

SQD9

SCCO90

SCC154

P16−
P16−
P16+
P16+

% of cells with >10 RAD51 foci

SQD9  SCC090  SCC154

*p<0.001

Dok R Cancer Res 2014
CANCER OF THE OROPHARYNX (NCCN 2014)

Base of tongue/tonsil/posterior pharyngeal wall/soft palate: any T, N2-3

Treatment of Primary and Neck

Concurrent systemic therapy/RT or Induction CT (cat. 3) → RT or CRT

OR

Transoral or open resection: primary and neck

OR

Multimodality clinical trials

Primary Site

Complete clinical response

Residual tumor

Adjuvant Treatment

Residual tumor in neck

Complete clinical response of neck

Salvage surgery + neck dissection as indicated

Neck dissection

If negative post-treatment evaluation, observe

If positive post-treatment evaluation, neck dissection

Adverse Features

N1, N2a-b, N3

Resection of primary, ipsilateral, or bilateral neck dissection

If extracapsular spread and/or positive margin, consider CRT (cat. 1)

N2c

Resection of primary and bilateral neck dissection

If other risk features, RT or consider CRT

## Survival rates by tumor HPV status

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Time</th>
<th>HPV+</th>
<th>HPV-</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I + C-XRT (E2399)</td>
<td>2-year</td>
<td>95%</td>
<td>62%</td>
<td>0.005</td>
</tr>
<tr>
<td>C-XRT</td>
<td>3-year</td>
<td>~90%</td>
<td>~60%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>XRT+/-S</td>
<td>5-year</td>
<td>81%</td>
<td>36%</td>
<td>0.005</td>
</tr>
<tr>
<td>S+/-XRT</td>
<td>5-year</td>
<td>79%</td>
<td>46%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Hammarstedt Mol Oncol; Licitra JCO; Fakhry JNCI; Gillison
Figure 1: Acute toxicity relative risk values ($T_{rel}$) and relative max-grade values for 13 head and neck treatment groups ranked by increasing relative risk.

$P$ = platinum, $H$ = hydroxyurea, 5-FU = fluorouracil, PA = paclitaxel.
### De-intensification trials in HPV-associated OPSCC.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>N</th>
<th>Inclusion criteria</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy de-intensification trials</td>
<td>III</td>
<td>706</td>
<td>T1–2, N2a–3, or T3–4, any N, HPV-positive OPSCC</td>
<td>Cetuximab versus high-dose cisplatin concurrent with accelerated IMRT (70 Gy in 6 weeks)</td>
</tr>
<tr>
<td>De-ESCALaTE HPV (NCT01874171)</td>
<td>III</td>
<td>304</td>
<td>Stage III–IVA HPV-positive OPSCC (T3N0–T4N0, T1N1–T4N3). Excludes &gt; N2b, &gt;10 PY</td>
<td>Cetuximab versus high-dose cisplatin concurrent with RT (70 Gy)</td>
</tr>
<tr>
<td>TROG 12.01 (NCT01855451)</td>
<td>III</td>
<td>200</td>
<td>Stage III (excluding T1–2, N1) or IV (excluding T4, N3, or M1) HPV-positive OPSCC if ≤10 PY. If &gt;10 PY, only N0−3a</td>
<td>Cetuximab versus weekly cisplatin concurrent with RT (70 Gy) once per week</td>
</tr>
<tr>
<td>Radiotherapy de-intensification trials</td>
<td>II</td>
<td>296</td>
<td>T1–2, N1–2b, or T3, N0–2b disease and &lt;10 PY HPV-positive OPC</td>
<td>Reduced-dose IMRT (60 Gy) with/ without weekly cisplatin</td>
</tr>
<tr>
<td>NCT01530997</td>
<td>II</td>
<td>40</td>
<td>T1–3, N0–2c HPV-positive OPSCC if &lt;10 PY or &gt;5 years of abstinence</td>
<td>IMRT (54–60 Gy) with weekly cisplatin (30 mg/m²)</td>
</tr>
<tr>
<td>ECOG 1308 (NCT01084083)</td>
<td>II</td>
<td>80</td>
<td>Resectable stages II/IIIb and IVA/IVA HPV-positive OPSCC (p16-high or HPV-16 ISH positive)</td>
<td>IC, then response-adapted RT (54 or 66–70 Gy) with cetuximab</td>
</tr>
<tr>
<td>The Quarterback Trial (NCT01706939)</td>
<td>III</td>
<td>365</td>
<td>Stage III/IV (M0) HPV-associated OPSCC/unknown primary/hyperpharynx. Excludes active smokers&gt; 20 PY</td>
<td>IC with TPF: patients with CR/PR randomly assigned 2:1 to carboplatin with RT (56 versus 70 Gy) per week. Non-responders receive standard RT.</td>
</tr>
<tr>
<td>De-intensification of surgery/adjunct therapy</td>
<td>II</td>
<td>377</td>
<td>Resectable stage III–IVA p16-positive OPSCC</td>
<td>TORS then risk-adapted post-operative treatment (observation/50 versus 60/66 Gy with weekly platinum)</td>
</tr>
<tr>
<td>ECOG 3311 (NCT01267832)</td>
<td>II/III</td>
<td>242</td>
<td>Resectable T1–T3, N0–2b HPV-positive OPSCC. Excludes active smokers with N2b disease</td>
<td>TORS then re-adapted post-operative treatment (observation/50 versus 60/60 Gy with or without weekly cisplatin)</td>
</tr>
<tr>
<td>PATHOS trial (NCT02215265)</td>
<td>II/III</td>
<td>500</td>
<td>Transoral resected p16-positive OPSCC (R0 margin), T1–4a, pN positive with ECE</td>
<td>Post-operative adjuvant 60-Gy RT with or without weekly cisplatin</td>
</tr>
<tr>
<td>ADEPT (NCT01687413)</td>
<td>III</td>
<td>500</td>
<td>P16-positive OPSCC (R0 margin), stage I–IVB. Excludes ≥10 PY or smoking within 5 years</td>
<td>Surgery followed by hyperfractionated IMRT (36 Gy/20 fractions BID) + weekly docetaxel</td>
</tr>
</tbody>
</table>
WHAT’S NEXT?

Separate trials for HPV+ and HPV- disease

Can we de-intensify treatment in low risk HPV+/nonsmokers while maintaining overall survival

- What are the means to customize radiotherapy?

- Reduce dose
- Reduce volumes
- Follow up
- Fractionation schedules
- Concomitant therapies

Customize radiotherapy
## 1. Dose Reduction

### Radiotherapy de-intensification trials

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Stage</th>
<th>N</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRG HN-002 (NCT02254278)</td>
<td>II</td>
<td>296</td>
<td>T1–2, N1–2b, or T3, N0–2b disease and &lt;10 PY HPV-positive OPC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T1–3, N0–2c HPV-positive OPSCC if &lt;10 PY or &gt;5 years of abstinence</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>IC with TPF: patients with CR/PR randomly assigned 2:1 to</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>carboplatin with RT (56 versus 70 Gy) per week. Non-responders</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>receive standard RT.</td>
</tr>
</tbody>
</table>
1. DOSE REDUCTION

HN002: randomized Phase 2 trial for patients with p16+, non-smoking associated, locoregionally advanced OPC

**Eligibility**
- OP SCCA
- ≤10 pack-year
- T1-T2 N1-N2b
- T3 N0-N2b

**Registration**
- Central review
- p16+ IHC

**Stratification Factors**
- Declare intent
- Unilat vs Bilat
- Neck XRT

60 Gy XRT (2Gy/fx) in 6 weeks + cisplatin 40 mg/m² weekly x 6 cycles

60 Gy XRT (2 Gy/fx) at 6 fractions/week for 5 weeks
DOSE REDUCTION

ECOG 1308: randomized Phase 2 trial

- Estimated N = 83
- No prior therapy for HNC
- Only HPV+ disease
- PS 0-1
- Resectable or potentially resectable

Induction
- Cetuximab + cisplatin/paclitaxel Q3W x 3 cycles

Group 1
Cetuximab + low-dose IMRT
- CR
- PR
- SD
- 54 Gy

Group 2
Cetuximab + standard-dose IMRT
- 70 Gy

- Primary endpoint: 2-year PFS rate 85%
- Secondary endpoints: OS, QOL, overall response, toxicity, biomarkers

Cmelak A ASCO 2014, abstract LBA6006
DOSE REDUCTION

ECOG 1308

Cmelak A ASCO 2014, abstract LBA6006
Marur JCO 2017
DOSE REDUCTION

Quarterback

HPV+ Oropharynx Phase III: Reduced Dose Chemoradiotherapy for Induction PR/CR
The Quarterback Trial

- Docetaxel
- Cisplatin
- 5-FU Reduced 25%
- 3 Cycles

Primary End Points
1. 3-yr LRC, PFS
2. Toxicity/Function
3. Patterns of Failure
4. Stage IV, HPV 16, P16+
5. Stratify: < 20 pack yrs smoking

CLINICAL and PET PR/CR
Randomize 2:1
Daily Radiotherapy 5600 cGy
Reduced 20%

CLINICAL and PET SD/NR

C/E

Daily Radiotherapy 7000 cGy

Follow up

Reduce dose
Fractionation schedules
Concomitant therapies
Reduce volumes
POSTOP DOSE REDUCTION
POSTOP DOSE REDUCTION

PATHOS

- Phase II trial
  242 pts
  - P16+ OPSCC
  - T1T3N0N2b
  - transoral surgery to primary + neck dissection

Low risk: no adjuvant therapy

Intermediate risk:
T3 tumours (or T1T2 tumours with additional risk factors)
N2a or N2b
perineural and/or vascular invasion or close margins (15mm)

High risk
positive (<1mm) margins and/or evidence of cervical lymph node extracapsular spread

PORT 60Gy 6 wks
PORT 50Gy 5 wks
POCRT 60Gy 6 wks + cisplat
PORT 60Gy 6 wks
POSTOP DOSE REDUCTION

ADEPT

-P16+ OPSCC
-Transoral resection T1-T4a primary negative margin
-Neck dissection: ECE in nodal metastasis

IMRT 60Gy/2Gy

IMRT 60Gy/2Gy + cisplatinum 40mg/m2 weekly
2. CONCOMITANT THERAPIES

SUBSTITUTE CETUXIMAB FOR CISPLATIN?

Bonner JA Lancet Oncol 2010
P16 is a strong prognostic factor in locally advanced oropharyngeal cancer: overall survival

Rosenthal D ASCO 2014 Abstract 6001
SUBSTITUTE CETUXIMAB FOR CISPLATIN?

LRC interaction test $P = \text{NS}$

Number at risk OPC p16 evaluable ($n = 182$)

<table>
<thead>
<tr>
<th>Category</th>
<th>RT p16 negative</th>
<th>RT p16 positive</th>
<th>RT + cet p16 negative</th>
<th>RT + cet p16 positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRC, months</td>
<td>$n$</td>
<td>$n$</td>
<td>$n$</td>
<td>$n$</td>
</tr>
<tr>
<td>0</td>
<td>64</td>
<td>34</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>12</td>
<td>31</td>
<td>24</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td>24</td>
<td>17</td>
<td>20</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>36</td>
<td>3</td>
<td>12</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>48</td>
<td>0</td>
<td>6</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Rosenthal D ASCO 2014 Abstract 6001
SUBSTITUTE CETUXIMAB FOR CISPLATIN?

Biological rationale to use cetuximab in HPV+ disease?

Controversial

- Inverse correlation EGFR gene copy number, EGFR protein expression and HPV status or p16 expression
- Immune stimulatory effect of C225 could potentiate the cytotoxic T-Cell base antitumor immune response already present in HPV+ OPSCC
- EXTREME trial: cetuximab beneficial independent of p16 status, SPECTRUM trial: panitumumab only effect in p16- disease

Clinical rationale to use cetuximab in HPV+ disease?

Controversial

- Tremplin study JCO 2013, Hitt ASCO 2013: toxicity difference cetuximab/CDDP??
SUBSTITUTE CETUXIMAB FOR CISPLATIN?

RTOG 1016: phase 3 trial in HPV-associated Oropharyngeal Cancer

Stratification Factors
- Oropharyngeal cancer
- Selected stage III-IV
- p16+ (HPV+)
- Any smoking history

Accelerated IMRT + cisplatin
100 mg/m² Q3 weeks x 2

Accelerated IMRT + cetuximab weekly x 8

- Required sample size: 706 patients
SUBSTITUTE CETUXIMAB FOR CISPLATIN?

RTOG 1016

Stratification Factors
- Oropharyngeal cancer
- Selected stage III-IV
- p16+ (HPV+)
- Any smoking history

Accelerated IMRT + cisplatin 100 mg/m² Q3 weeks x 2

Accelerated IMRT + cetuximab weekly x 8

TROG 12.01

- p16+ OPSCC
- st III (excl T1-2N1) or IV (excl T4, N3 and distant M+)
- if smoking history > 10 pack years: nodal disease must be N0-N2a

RT 70Gy 7 wks+ weekly cisplatin

RT 70Gy 7 wks + weekly cetuximab

De-ESCALaTE

HPV+OPSCC Stage III/IVb

Standard RCT

Standard RT + Cetuximab
3. REDUCE IRRADIATED VOLUMES

Unilateral-only IMRT

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>N</th>
<th>N0-1, %</th>
<th>T1-2, %</th>
<th>Contralateral Neck failure, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson, 1999</td>
<td>178</td>
<td>87</td>
<td>65</td>
<td>3</td>
</tr>
<tr>
<td>Kagei, 2000</td>
<td>32</td>
<td>84</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>O’Sullivan, 2001</td>
<td>228</td>
<td>83</td>
<td>84</td>
<td>3</td>
</tr>
<tr>
<td>Rusthoven, 2009</td>
<td>20</td>
<td>20</td>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>Chronowski, 2012</td>
<td>102</td>
<td>56</td>
<td>100</td>
<td>2</td>
</tr>
</tbody>
</table>
3. REDUCE IRRADIATED VOLUMES

PROTON 1

FIGURE 1. Effect of human papillomavirus (HPV) status on the response of head and neck squamous cell carcinoma cells to photon or proton irradiation. HPV-negative cells (HN5, SqCC/Y1, and MDA686Tu) and HPV-positive cells (UMSCC-47, UPCI-SCC-154, and UPCI-SCC-152) were exposed to single doses of photons (6 MV X-ray, panel A) or protons (200 MeV, panel B) at 2 Gy, 4 Gy, or 6 Gy, and colonies were stained and counted 10 to 17 days later. Values shown are means ± SEM from at least 3 independent experiments. [Color figure can be viewed at wileyonlinelibrary.com]

Sio et al
Int J Radiat Oncol Biol Phys 2016

Wang et al
Head&Neck 2016
3. REDUCE IRRADIATED VOLUMES

PROTON therapy

Widesott L Int J Radiat Oncol Biol Phys 2008
4. HYPOXIA MODIFICATION?

- Excellent radiotherapy response (Rishin JCO 2010; Ang NJEM 2010)
- No benefit from hypoxia targeted therapy (Lassen 2010 R&O; Rishin JCO 2010)
- Hypoxia seems not to affect prognosis (Toustrup, R&O 2012)

Adapted from Toustrup K et al., R&O 2012
5. ALTERED FRACTIONATION?

Fig. 4. Primary loco-regional tumour control as a function of number of fractions per week in p16-positive tumours and p16-negative tumours.
## 6. IMMUNOTHERAPY?

**Table 1. Human papillomavirus-targeted therapies**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism of action</th>
<th>Example</th>
<th>HNSCC development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA vaccines</td>
<td>Non-living antigens able to induce CTL, Th and B-cell immunity</td>
<td>pNGVL4a-CRT/E7 (Detox)</td>
<td>Phase I</td>
</tr>
<tr>
<td>Peptide vaccines</td>
<td>Incorporation of amino acid sequences that form an immunogenic peptide molecule representing the specific epitope of a TAA that binds onto HLA molecules</td>
<td>P16_37-63</td>
<td>Phase I and II</td>
</tr>
<tr>
<td>DC vaccination</td>
<td><em>Ex vivo</em> culture of DCs derived from HPV + patients; re-injection of DCs after maturation and activation</td>
<td></td>
<td>Phase I withdrawn</td>
</tr>
<tr>
<td>Bacterial vaccines</td>
<td>Live attenuated bacteria (e.g. Listeria monocytogenes) bioengineered to secrete an HPV16-E7 fusion protein targeting HPV-transformed cells. Infection of APCs by bacterial vector stimulates MHC class I and II pathways resulting in specific T-cell immunity</td>
<td>ADXS11-001</td>
<td>Phase II</td>
</tr>
<tr>
<td>Adoptive T-cell transfer</td>
<td>Harvesting and <em>ex vivo</em> expansion of the patient’s own tumor antigen-specific T cells, followed by re-infusion to the patient</td>
<td></td>
<td>Phase I/II</td>
</tr>
<tr>
<td>TCR gene transfer</td>
<td>Isolation a high-affinity HLA-A2-restricted TCR against the HPV16 E6 oncoprotein derived by a T cell clone against E6 epitope; gene sequencing of the TCR and generation of a retroviral expression vector encoding the TCR followed by transduction of T cells expressing the TCR</td>
<td>E6-TCR</td>
<td>Phase I/II</td>
</tr>
</tbody>
</table>

APC, antigen-presenting cell; CTL, cytotoxic T-lymphocyte; DC, dendritic cell; HLA, human leukocyte antigen; HPV, human papillomavirus; MHC, major histocompatibility complex; TCR, T-cell receptor; TTA, tumor-associated antigen; Th, T-helper cell.

Economopoulou P et al
Ann Oncol 2016
ROLE OF FOLLOW UP AFTER RT

1. lymph node regression
2. metastasis

→ both show distinct pattern in HPV+ versus HPV- disease
FOLLOW UP AFTER RT

1. Lymph node regression

During RT, enlargement of cystic lymph nodes has been described, with need for replanning.
FOLLOW UP AFTER RT

1, lymph node regression

After RT, lymph nodes involute more quickly, but undergo a prolonged process to eventual CR

Huang H IJROBP 2013
FOLLOW UP AFTER RT

1. Lymph node regression

All N2-N3 Head & Neck Cancer

HPV Positive

- Complete Response: No PRND
- Incomplete Response: N3

HPV Negative

- Complete Response: No PRND
- Incomplete Response: PRND

Repeat CT/MR and/or PET every 2 months

Complete Response
- No PRND

Progression
- PRND

Stable or involuting
- PRND

Huang H IJROBP 2013
FOLLOW UP AFTER RT

2, metastasis
DM rate is similar for HPV+ and HPV- disease
But DM tend to occur later
Tend to be more disseminating, unusual sites
Prolonged survival is described after salvage for DM
FUTURE RT IN HPV+ DISEASE

- Await results ongoing trials

- Other options in combination with RT:
  - HPV vaccines
    - As adjuvant therapy after CRT
      - Example REALISTIC UK
    - Concomitant with CRT and adjuvant
      - Example EORTC studie TG4001

- Immunotherapy anti PD-/PD-L1 to improve anti-cancer immune response

- New targeted drugs: PI3K, Aurora A, EGFR and Her2Neu…
FUTURE?

Targeting the altered DNA repair capacity

[Diagram showing molecular pathways involving p16, RAD51, DSB, SSB, PARP, CDDP, olaparib, ATM, ATR, p53, Chk2, Chk1, CDK, cyclin B, apoptosis, G1, S, G2, M, STOP, Investigational, Approved]
## CONCLUSIONS

<table>
<thead>
<tr>
<th>+</th>
<th>?</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered fractionation</td>
<td>Cetuximab</td>
<td>Hypoxia modification</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Dose de-escalation</td>
<td></td>
</tr>
<tr>
<td>Protontherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA repair inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunotherapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSIONS

- Oropharyngeal carcinoma is on the rise with HPV as important causative factor

- Many interesting trials are ongoing
  - Results to be awaited, sufficient follow up

- Current recommendations: treat patients according to their stage of disease at presentation, irrespective of HPV status

- Encourage enrollment in clinical trials