Radiotherapy in oropharyngeal cancer

Sandro V Porceddu

Director, Radiation Oncology Research
Princess Alexandra Hospital, Brisbane, Australia
Professor of Medicine, University of Queensland
Considerations

Role of RT in non-distant metastatic oropharyngeal cancer depends on

- Early vs Locally advanced disease
- HPV status
- Definitive vs Post-operative RT
- Balance between curative outcomes vs treatment-related morbidity
Considerations

Role of RT in non-distant metastatic oropharyngeal cancer depends on

- Early vs Locally advanced disease
- HPV status
- Definitive vs Post-operative RT
- Balance between curative outcomes vs treatment-related morbidity
Overview

Surgery vs (Chemo)RT

- Lack of randomised data comparing modalities
- non-randomised institutional reports suggest similar disease control between modalities

Soo KC et al Br J Cancer, 2005

• Quality of Life
  - Relationship between QoL & HPV status is unclear
  - Baseline QoL lower in HPV negative patients

Broglie M et al Laryngoscope, 2013
Overview

• Standard of care when using non-surgical approach
• HPV status implication for radiotherapy
• De-escalation strategies
• Intensification strategies
• 8th Edition AJCC/UICC clinical staging
• Treatment guidelines
STANDARD OF CARE
Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial

Jens Overgaard, Hanne Sand Hansen, Lena Specht, Marie Overgaard, Cai Grau, Elo Andersen, Jens Bentzen, Lars Bastholt, Olfred Hansen, Jørgen Johansen, Lisbeth Andersen, Jan F Evensen, on behalf of the Danish Head and Neck Cancer Study Group

66-68Gy in 33-34 fractions
Altered fractionation RT superior to conventionally fractionation RT

- 15 randomised trials comparing conventional RT vs Altered fractionation RT (6515 pts)
- Significant benefit in favour of Altered Fractionation at 5 years
  - Absolute survival benefit of 3.4%
  - Absolute locoregional control benefit of 6.4%

Concurrent chemoRT superior to RT alone

<table>
<thead>
<tr>
<th>Therapy Modality</th>
<th>Absolute benefit at 5 years*</th>
<th>Risk Reduction*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N=17,493)</td>
<td>4.1 %</td>
<td>10 %</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>2.3 %</td>
<td>2 %</td>
<td>NS</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>2.2 %</td>
<td>5 %</td>
<td>NS</td>
</tr>
<tr>
<td>Concurrent</td>
<td>6.9 %</td>
<td>19 %</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Relative to Conventional Local-Regional Therapy with RT alone

Pignon & Bourhis Lancet, 2000
Chemo-RT superior to altered fractionation RT

<table>
<thead>
<tr>
<th>Study</th>
<th>Events (n)/Patients (N)</th>
<th>Observed minus expected</th>
<th>Variance</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Altered fractionation radiotherapy</td>
<td>Concomitant chemoradiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INRC-HN-94</td>
<td>58/66</td>
<td>55/70</td>
<td>5.9</td>
<td>1.24 (0.85-1.79)</td>
</tr>
<tr>
<td>ORO 930155</td>
<td>50/65</td>
<td>42/64</td>
<td>6.2</td>
<td>1.32 (0.87-1.98)</td>
</tr>
<tr>
<td>EORTC 2296245</td>
<td>7/13</td>
<td>9/15</td>
<td>0.4</td>
<td>1.11 (0.40-3.03)</td>
</tr>
<tr>
<td>GORTEC 990226</td>
<td>207/281</td>
<td>196/279</td>
<td>14.7</td>
<td>1.16 (0.95-1.41)</td>
</tr>
<tr>
<td>TMH 111437</td>
<td>34/68</td>
<td>26/65</td>
<td>6.3</td>
<td>1.54 (0.92-2.56)</td>
</tr>
<tr>
<td>Total</td>
<td>356/493</td>
<td>328/493</td>
<td>33.6</td>
<td>1.22 (1.05-1.42)</td>
</tr>
</tbody>
</table>

χ² test for heterogeneity: p=0.87, I²=0%
Treatment effect: p=0.0098

MARCH; updated meta-analysis
Lacas B et al Lancet Oncol, 2017
Treatment intensification vs heightened toxicity

Trotti A et al, Lancet Oncol, 2007
Machtay M et al, JCO, 2008
RTOG 0129

Oropharyngeal Carcinoma (N=260)

p16-positive (N=187)
≤10 pack-years (94)
N0-2a (29)
Low-risk (N=123 or 47%)
3-Y OS: 94%

>10 pack-years (93)
N2b-3 (64)
Intermediate-risk (N=73 or 28%)
3-Y OS: 67%

p16-negative (N=73)
≤10 pack-years (16)
T2-3 (9)

>10 pack-years (57)
T4 (7)
High-risk (N=64 or 25%)
3-Y OS: 42%

KK Ang et al NEJM, 2010
## RTOG 0129

### 3-Year Outcome by HPV Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>HPV-Pos (%)</th>
<th>HPV-Neg (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>82.4</td>
<td>57.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P-F survival</td>
<td>73.7</td>
<td>43.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Local-regional control</td>
<td>86.4</td>
<td>64.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>8.7</td>
<td>14.6</td>
<td>0.23</td>
</tr>
<tr>
<td>2nd primary tumour</td>
<td>5.9</td>
<td>14.6</td>
<td>0.02</td>
</tr>
</tbody>
</table>

KK Ang et al NEJM, 2010
DE-ESCALATION VS INTENSTIFICATION
Locoregional & Distant Control following (chemo) RT based on HPV status

LRC; locoregional control
DC; distant control

O’Sullivan B et al JCO, 2013
OS based on HPV status - ICON-S

Overall Survival

<table>
<thead>
<tr>
<th>strata</th>
<th>events/total</th>
<th>3 years</th>
<th>5 years</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>780 / 2603</td>
<td>79% (77-80)</td>
<td>71% (69-73)</td>
<td></td>
</tr>
<tr>
<td>HPV(-)</td>
<td>385 / 696</td>
<td>58% (55-62)</td>
<td>48% (45-52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HPV(+)</td>
<td>395 / 1907</td>
<td>86% (85-88)</td>
<td>80% (78-82)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: INST: institution
Hazard ratio: adjusted for age, smoking PY, and Chemo (Yes/No)

De-escalate
Intensify

Utility of TNM staging (7th edition) ICON-S

Overall Survival by Stage and HPV Status

## AJCC/UICC 8th Edition Staging

### Clinical N category HPV+ OPC

<table>
<thead>
<tr>
<th>N CATEGORY</th>
<th>N CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>One or more ipsilateral lymph nodes, none larger than 6 cm</td>
</tr>
<tr>
<td>N2</td>
<td>Contralateral or bilateral lymph nodes, none larger than 6 cm</td>
</tr>
<tr>
<td>N3</td>
<td>Lymph node(s) larger than 6 cm</td>
</tr>
</tbody>
</table>

*Lydiatt W et al CA Cancer J Clin, 2017*
<table>
<thead>
<tr>
<th>N CATEGORY</th>
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<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and <strong>ENE-negative</strong></td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and <strong>ENE-negative</strong>; or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and <strong>ENE-negative</strong>; or metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and <strong>ENE-negative</strong></td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and <strong>ENE-negative</strong></td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and <strong>ENE-negative</strong></td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and <strong>ENE-negative</strong></td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node larger than 6 cm in greatest dimension and <strong>ENE-negative</strong>; or metastasis in any lymph node(s) and clinically overt <strong>ENE-positive</strong></td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in a lymph node larger than 6 cm in greatest dimension and <strong>ENE-negative</strong></td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis in any node(s) and clinically overt <strong>ENE-positive</strong></td>
</tr>
</tbody>
</table>
**8th Edition Staging**
Clinical TNN category HPV pos OPC

<table>
<thead>
<tr>
<th>T CATEGORY</th>
<th>N CATEGORY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N0</td>
</tr>
<tr>
<td>T0</td>
<td>NA</td>
</tr>
<tr>
<td>T1</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td></td>
</tr>
</tbody>
</table>

*a Any M1 is stage IV.*

*Lydiatt W et al CA Cancer J Clin, 2017*
DE-ESCALATION STRATEGIES
De-escalation Strategies

- Substitute biologic agent or immunotherapy agent for cytotoxic chemotherapy
- Omit or reduce chemotherapy
- Reduce radiation dose
- Use induction chemotherapy to select responders and then reduce radiation dose
- Surgical excision and stratify further treatment based on pathologic findings
## De-escalation Phase III trials

### OPC HPV positive

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligible</th>
<th>RT</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 1016</td>
<td>All</td>
<td>AF</td>
<td>HD cis x 2</td>
<td>Cetux</td>
<td>OS</td>
</tr>
<tr>
<td>De-ESCALaTE</td>
<td>Low risk</td>
<td>CF</td>
<td>HD cis x 3</td>
<td>Cetux</td>
<td>Gr 3 -5 acute and late toxicity</td>
</tr>
<tr>
<td>TROG 12.01</td>
<td>Low risk (excludes T4&amp;/or N3)</td>
<td>CF</td>
<td>Weekly cis</td>
<td>Cetux</td>
<td>AUC MDASI-HN Symptom Severity Score</td>
</tr>
<tr>
<td>Quarterback</td>
<td>&lt; 20pack yrs TPF responders</td>
<td>CF</td>
<td>70Gy + carbo</td>
<td>56 Gy carbo + cetux</td>
<td></td>
</tr>
<tr>
<td>Adept</td>
<td>Resected N+ ECE</td>
<td>CF</td>
<td>60Gy + cis</td>
<td>60Gy RT</td>
<td></td>
</tr>
<tr>
<td>ECOG 3311</td>
<td>Resected TORS Low risk (exclude T4, N2c-3)</td>
<td>CF</td>
<td>60Gy RT (high risk postop – chemoRT)</td>
<td>50 Gy RT</td>
<td>2 yr PFS</td>
</tr>
<tr>
<td>DART-HPV</td>
<td>Resected</td>
<td>CF/AF</td>
<td>60Gy + weekly cis</td>
<td>30 – 36Gy AF + docetaxel</td>
<td>Gr3- 5 toxicities</td>
</tr>
<tr>
<td>NRG HN002</td>
<td>Low risk (excludes T4, N2c-3)</td>
<td>CF/AF</td>
<td>60 Gy+ weekly cis</td>
<td>60 Gy AF</td>
<td>2yr PFS, dysphagia</td>
</tr>
</tbody>
</table>
INTENSIFICATION
STRATEGIES
Hypoxia determinant of outcome

### Head and neck cancer - meta analysis - summary

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Events / Total</th>
<th>Odds ratio and 95% CI</th>
<th>Odds ratio</th>
<th>Risk Reduction</th>
<th>NNT**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypoxic modification</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loco-regional control</td>
<td>1203 / 2406</td>
<td>1383 / 2399</td>
<td>0.71 (0.63-0.80)*</td>
<td>8% (5-10%)*</td>
<td>13</td>
</tr>
<tr>
<td>Disease specific survival</td>
<td>1175 / 2335</td>
<td>1347 / 2329</td>
<td>0.73 (0.64-0.82)</td>
<td>7% (5-10%)</td>
<td>14</td>
</tr>
<tr>
<td>Overall survival</td>
<td>1450 / 2312</td>
<td>1519 / 2305</td>
<td>0.87 (0.77-0.98)</td>
<td>3% (0-6%)</td>
<td>31</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>159 / 1427</td>
<td>179 / 1391</td>
<td>0.87 (0.69-1.09)</td>
<td>2% (-1-4%)</td>
<td>57</td>
</tr>
<tr>
<td>Radiotherapy complications</td>
<td>307 / 1864</td>
<td>297 / 1822</td>
<td>1.00 (0.82-1.23)</td>
<td>0% (-3-2%)</td>
<td>&gt;&gt;</td>
</tr>
</tbody>
</table>

* 95% CI.

** Numbers of patients Needed to Treat to achieve benefit in one patient.
Nimorazole Study (DAHANCA 5)

DAHANCA 5-85
SUPRAGLOTTIC and PHARYNX CARCINOMA

STRATIFY:
T-size
Region
Sex
Hemoglobin*
Institution

RANDOMIZE

RT + Nimorazole (219 pts)
(NIM: 1.2 g/m² x 30)
(RT: 62-68 Gy/ 31-34 fx, 5 Fx/wk)

RT + Placebo (195 pts)
(RT: 62-68 Gy/ 31-34 fx, 5 Fx/wk)

Loco-regional control (%)

Nimorazole (219 pts) 49%
Placebo (195 pts) 33%
P=0.002

Months after treatment

Overgaard J et al Radiother Oncol, 1998
**KEYNOTE-012**

Recurrent and/or metastatic HNSCC

Single agent Pembrolizumab (anti-PD1 checkpoint inhibitor)

Total cohort = 192

- Cohort B - 132 pts 200mg Q3W

61% had received ≥2 therapies

Overall Response Rate = 17.7%

- HPV pos = 21.9%
- HPV neg = 15.9%

Median FU duration in responders 12.5 months

Grade 3-4 treatment-related AEs = 12%

*Mehra R et al JCO, 2016*
KEYNOTE-055
R/M HNSCC progressed following platinum/cetuximab
Single agent Pembrolizumab (200mg Q3W)
Total cohort = 172 patients
  ▪ First 50 patients
84% had ≥2 prior lines of therapy
Overall Response Rate 18.0%
Grade 3-4 treatment-related AEs = 12%
Identification of reliable biomarker predictor of response ongoing

Bauml J et al JCO, 2016
Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>No. of Deaths</th>
<th>1-Yr Overall Survival Rate % (95% CI)</th>
<th>Median Overall Survival mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>240</td>
<td>133</td>
<td>36.0 (28.5–43.4)</td>
<td>7.5 (5.5–9.1)</td>
</tr>
<tr>
<td>Standard Therapy</td>
<td>121</td>
<td>85</td>
<td>16.6 (8.6–26.8)</td>
<td>5.1 (4.0–6.0)</td>
</tr>
</tbody>
</table>

Hazard ratio for death, 0.70 (97.73% CI, 0.51–0.96) P=0.01

Ferris RL (Gillison M) et al NEJM, 2016
Overall survival benefit was seen with Nivolumab regardless of HPV status.

Presented By Robert Ferris at 2016 ASCO Annual Meeting
Oropharyngeal p16 pos
  T4 (N0-3) M0
  N3 (T1-4) M0
Oropharyngeal p16 neg
  any T3-4 (N0-3) M0
  any N2a-3 (T1-4) M0
Laryngeal/hypopharyngeal/oral cavity
  any T3-4 (N0-3) M0
  any N2a-3 (T1-4) M0

**KEYNOTE 412**

- **RANDOMISE**

  - Arm 1
    - pembrolizumab Q3W + CRT
  - Arm 2
    - placebo Q3W + CRT
  - Maintenance
    - pembrolizumab x14 doses
    - Placebo x14 doses

**CRT**
- cisplatin 100mg/m$^2$ Q3W
- radiotherapy
  - AFX=70Gy/6 weeks
  - SFX=70Gy/7 weeks

**Primary Endpoint**
- Event Free Survival progression (RECIST 1.1), surgery or death

**Sample size**
- 780 patients
Unilateral vs bilateral elective neck irradiation

- **Unilateral neck irradiation**
  - Tonsil/soft palate T1-2 N0-2a (lateralized >1cm lateral to the midline)

- **Bilateral neck irradiation**
  - Tonsil/soft palate T3-4
  - Base of tongue (any T-stage)

- **Retropharyngeal nodes**
  - Tonsil/soft palate T3-4
  - T1 tonsil/soft palate and ≥N2b (7th Edition)
  - T3-4 BOT
  - N3
Dose/fractionation for definitive radiotherapy

*Conventional fractionation & concurrent systemic therapy
- T3-4N0-3, anyT with N2b-c or N3 (7th Edition)

** DAHANCA Fractionation
- T1-2N0-N1 (occasionally N2a)
- contra-indication to conventional fractionation & systemic therapy for advanced disease

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Site</th>
<th>Dose (Gy)</th>
<th>Fractions</th>
<th>Weeks</th>
<th>Dose (Gy)</th>
<th>Fractions</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional*</td>
<td>Gross disease</td>
<td>70</td>
<td>35</td>
<td>7</td>
<td>70</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>60</td>
<td>30</td>
<td>6</td>
<td>63</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Elective</td>
<td>50</td>
<td>25</td>
<td>5</td>
<td>56</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>Accelerated (DAHANCA)**</td>
<td>Gross disease</td>
<td>68</td>
<td>34</td>
<td>6</td>
<td>68</td>
<td>34</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>60</td>
<td>30</td>
<td>6</td>
<td>61.2</td>
<td>34</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Elective</td>
<td>50</td>
<td>25</td>
<td>5</td>
<td>54.4</td>
<td>34</td>
<td>6</td>
</tr>
<tr>
<td>Hypofractionated (T1 larynx***)</td>
<td>Field-based</td>
<td>63</td>
<td>28</td>
<td>5.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Princess Alexandra Hospital, Radiation Oncology, Guidelines 2018
Doses of adjuvant radiotherapy

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Site</th>
<th>3D-CRT</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dose (Gy)</td>
<td>Fractions</td>
</tr>
<tr>
<td>Conventional</td>
<td>Microscopic positive margin</td>
<td>66</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Tumour bed</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Operative bed</td>
<td>54</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Elective</td>
<td>50</td>
<td>25</td>
</tr>
</tbody>
</table>

Addition of chemotherapy in the presence of positive margins and/or ECE HPV+ or HPV_
T2N1M0 Base of Tongue SCC p16+

Gross Tumour Volume
T2N1M0 Base of Tongue SCC p16+

CTV 70Gy = GTV + 0.5cm
T2N1M0 Base of Tongue SCC p16+

CTV 63Gy (intermediate)
- CTV70Gy
- remaining BOT
T2N1M0 Base of Tongue SCC p16+

CTV 63Gy (intermediate)
- CTV70Gy
- remaining BOT

CTV56Gy (elective)
- Ipsilateral (RP, Ib-V)
- Contralateral (II-IV)
Node positive HPV-associated OPC outcomes with (chemo)RT

Jan 2005-Jan 2016
N+ HPV-associated OPC
(chemo)RT & 12 week re-staging PET/CT

362 patients

343 (94.7%) complete response at primary site
19 (5.3%) residual primary disease &/or distant metastases

16/343 (4.6%) neck dissection based on PET/CT
  • 10 (62%) pathological positive

Porceddu SV et al ASCO, 2018
Node positive HPV-associated OPC outcomes with (chemo)RT

Kaplan-Meier Loco-Regional Failure Free Survival

5-year LR FFS 90.6% (95% CI: 87.3-94.0)

Porceddu SV et al ASCO, 2018
Node positive HPV-associated OPC outcomes with (chemo)RT

Kaplan-Meier Distant Metastatic failure free survival

5-year DM FFS
86.9\% (95\% CI: 83.1-90.8)

Porceddu SV et al ASCO, 2018
Concluding remarks

• Debate for (chemo)RT vs surgery (PORT) unresolved
• Emergence of HPV-associated OPC has seen a move toward de-escalation trials
• Treatment intensification for non-HPV-associated OPC and non OPC warrants further investigation
• Role of definitive immunotherapy with (chemo)RT remains undefined