UPDATE ON HEAD & NECK CANCERS

Oropharynx
The global incidence of oropharynx cancer
A steep rise in oropharynx cancer

Denmark 1977-2017
DAHANCA database

Oropharynx

Larynx

Number of patients

Year


70%

74%*

55%

33%

42%

37%

*p16-pos

Updated from Lassen Radiother Oncol 2010
TNM – UICC 8th classification

Oropharynx p16- negative tumors

Tx: primary tumor cannot be assessed
T0: no evidence of primary tumor
T1: Tumor ≤ 2 cm
T2: Tumor > 2 cm and ≤ 4 cm
T3: > 4 cm or with extension lingual surface of epiglottis*
T4a: invades: larynx, deep/extrinsic muscle of tongue, med. pterygoid, hard palate or mandible
T4b: invades: lat pterygoid m, pterygoid plate, lat nasopharynx, skull base or encases carotid artery

* Mucosal ext. to lingual surface of epiglottis from base of tongue and vallecula doesn’t constitute invasion of the larynx
TNM – UICC 8th classification

Oropharynx p16+ positive tumors

Tx: primary tumor cannot be assessed
T0: no evidence of primary tumor
T1: Tumor ≤ 2 cm
T2: Tumor > 2 cm and 4 cm
T3: > 4 cm or with extension lingual surface of epiglottis*
T4: invades: larynx, deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, styloglossus), med pterygoid, hard palate or mandible, lat pterygoid m, pterygoid plate, lat nasopharynx, skull base or encases carotid artery

* Mucosal ext. to lingual surface of epiglottis from base of tongue and vallecula doesn’t constitute invasion of the larynx
TNM – UICC 8th classification

Oropharynx p16- negative tumors

N0: no regional node metastasis
Nx: regional nodes cannot be assessed
N1: single ipsilateral node, $\leq 3$ cm
N2a: single ipsilateral node, $> 3$ cm and $\leq 6$ cm
N2b: multiple ipsilateral nodes, $\leq 6$ cm
N2c: contralateral or bilateral nodes, $\leq 6$ cm
N3a: node $> 6$ cm without ECS
N3b: single/multiple node(s) with ECS
TNM – UICC 8th classification

Oropharynx p16+ positive tumors

N0: no regional node metastasis

Nx: regional nodes cannot be assessed

N1: unilateral metastasis in node(s), ≤ 6 cm

N2: contralateral or bilateral node(s), ≤ 6 cm

N3: node(s) > 6 cm
Considerations for treatment strategy

- Patient performance
- Co-morbidity
- Personal choice
- Tumor location
- Tumor extension
- Lymph node invasion
- Efficacy, functionality and morbidity
Treatment of early oropharynx cancer

Surgery for T1-2, N0-1

- Cold / cautery knife
- CO₂ laser
- TORS

Resection of the tumor and neck dissection when organ-function sparing surgery is suitable. Avoid multiple treatment when only one modality is enough!

<table>
<thead>
<tr>
<th></th>
<th>IMRT 2-y control</th>
<th>IMRT 2-y OS</th>
<th>TORS 2-y control</th>
<th>TORS 2-y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eisbruch et al multicenter</td>
<td>91%</td>
<td>96%</td>
<td>NA</td>
<td>89%</td>
</tr>
<tr>
<td>Galloway et al Fox Chase</td>
<td>92%</td>
<td>84%</td>
<td>NA</td>
<td>94%</td>
</tr>
<tr>
<td>Garden et al MDACC</td>
<td>97%</td>
<td>93%</td>
<td>NA</td>
<td>94%</td>
</tr>
<tr>
<td>Hodge et al Wisconsin</td>
<td>96%</td>
<td>94%</td>
<td>NA</td>
<td>94%</td>
</tr>
<tr>
<td>Mendenhall et al Florida</td>
<td>93%</td>
<td>NA</td>
<td>NA</td>
<td>97%</td>
</tr>
<tr>
<td>Scher et al Dana Farber</td>
<td>97%</td>
<td>89%</td>
<td>NA</td>
<td>98%</td>
</tr>
<tr>
<td>Cohen et al Pensylvania</td>
<td>NA</td>
<td>81%</td>
<td>NA</td>
<td>97%</td>
</tr>
<tr>
<td>Almeida et al Mount Sinai</td>
<td>94%</td>
<td>94%</td>
<td>NA</td>
<td>94%</td>
</tr>
<tr>
<td>Moore et al Mayo clinic</td>
<td>94%</td>
<td>94%</td>
<td>NA</td>
<td>97%</td>
</tr>
<tr>
<td>Weinstein Pensylvania 2010</td>
<td>98%</td>
<td>82%</td>
<td>NA</td>
<td>98%</td>
</tr>
<tr>
<td>Weinstein Pensylvania 2012</td>
<td>97%</td>
<td>NA</td>
<td>NA</td>
<td>97%</td>
</tr>
</tbody>
</table>

~94% ~91% ~96% ~86%

- Difference in morbidity!

Adapted from Almeida Laryngoscope 2014
68 patients recruited

68 patients randomly assigned

34 allocated to radiotherapy group
- 32 received allocated intervention
  - 9 received radiotherapy alone
  - 23 received concurrent CRT
- 2 lost to follow-up*

34 allocated to TORS + ND group
- 34 received allocated intervention
  - 10 received TORS + ND alone
  - 16 received TORS + ND plus RT
  - 8 received TORS + ND plus CRT

34 analysed

34 analysed

MDADI Total

Time (Years)

RT Arm
TORS Arm

p < 0.0001

MDADI Total at 1-Year

RT
CRT
TORS
TORS-RT
TORS-CRT

*Nichols Lancet Oncol 2019*
Orator study

- Survival was similar
- Spectrum of Toxicity and QOL at 1 year differed between arms

<table>
<thead>
<tr>
<th>Favor RT</th>
<th>Favor Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Swallowing</td>
<td>• Less Tinnitus and Hearing Loss</td>
</tr>
<tr>
<td>• MDADI</td>
<td>• Less neutropenia</td>
</tr>
<tr>
<td>• FOIS</td>
<td>• Less constipation</td>
</tr>
<tr>
<td>• Less pain and pain medications use</td>
<td></td>
</tr>
<tr>
<td>• No bleeding</td>
<td></td>
</tr>
<tr>
<td>• Less Trismus</td>
<td></td>
</tr>
<tr>
<td>• Less shoulder impairment</td>
<td></td>
</tr>
</tbody>
</table>

Inclusion criteria:
- T1-2 (UICC 7th ed.)
- N0-2 <4 cm in any plane
- No ECE on imaging

Nichols Lancet Oncol 2019
Treatment of early oropharynx cancer

Surgery for T1-2, N0-1

**EORTC 1420**
"Best of" trial

- T1-2 N0, M0
- HPV status
- 170, 1:1 randomisation
- IMRT or TORS
- Prim. endpoint MDADI over 1 year
- Sec. QoL, LRC and survival
- Cost-effectiveness

**DAHANCA 34**
"QoLATI"

- T1-2 N0-1, M0 (UICC7th ed)
- HPV status
- 138, 2:1 randomisation
- TORS or IMRT
- Prim. endpoint MDADI at 1 year
- Sec. QoL, MBS, FEES, LRC and survival
- Cost-effectiveness

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Treatment of (early) oropharynx cancer

Unilateral radiotherapy

Lateral head and neck cancers rarely spread to contralateral neck nodes

Lateral oropharyngeal tumors include tonsil and tonsillar fossa

DAHANCA 12 - 134 pts with tonsillar cancer

<table>
<thead>
<tr>
<th></th>
<th>Ipsilateral RT</th>
<th>Bilateral RT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3+4</td>
<td>11%</td>
<td>10%</td>
<td>N.S.</td>
</tr>
<tr>
<td>N+</td>
<td>73%</td>
<td>77%</td>
<td>N.S</td>
</tr>
<tr>
<td>Stage 3 + 4</td>
<td>78%</td>
<td>79%</td>
<td>N.S</td>
</tr>
</tbody>
</table>

Jensen Radiother Oncol 2007
Unilateral radiotherapy to lateralized OPCC

Loco-regional control

- Ipsilateral
- Bilateral
- Ipsilateral despite midline involvement

- Uni RT
- Bi RT
Unilateral IMPT to lateralized OPCC

Comparison of baseline to end-of-treatment outcomes for pts w/ ipsi IMPT or IMRT

Inclusion criteria:

- Treated off-protocol, 2015-18
- Parotid, submandibular, or lateralized tonsil
- Adjuvant or definitive ipsilat RT +/-chemo
- RT dose >60 Gy
- Completed PRO questionnaires

- N=37; 23 IMRT and 14 IMPT
- Comparable in terms of dose and volume
Unilateral IMPT to lateralized OPCC

Comparison of baseline to end-of-treatment outcomes for pts w/ ipsi IMPT or IMRT

- EORTC QLQ-H&N 35: pain
  - PROTON IMRT
    - Baseline: -5
    - End of treatment: -29.8

- EORTC QLQ-H&N 35: swallowing function
  - PROTON IMRT
    - Baseline: -1.1
    - End of treatment: -23.3
    - p = 0.02

- EORTC QLQ-H&N 35: speech
  - Baseline: -18.9
  - End of treatment: -44.2

- EORTC QLQ-H&N 35: senses
  - PROTON IMRT
    - Baseline: -5
    - End of treatment: -26.7
    - p = 0.01
Unilateral IMPT to lateralized OPCC

Comparison of baseline to end-of-treatment outcomes for pts w/ ipsi IMPT or IMRT

- EORTC QLQ-H&N 35: pain

**Oral Cavity**

- **Constrictors**
  - PROTON IMRT
  - EORTC C

**Contralateral Submandibular**

**Contralateral Parotid**

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Candidates
- Squamous cell carcinoma of the pharynx or larynx (excl. st. 1/2 glottic larynx)
- Indication for radiotherapy with curative intent
- Absence of severe co-morbidity

Photon doseplan >10% risk of either dysphagia or xerostomia
- DAHANCA score >= grade 2
- Moderate-severe xerostomia (EORTC HN 35)

\[ \Delta \text{NCPT} > 8\% \]
- Treatment and follow-up according to routine guidelines

Proton doseplan Proton/photon comparison
\[ \Delta \text{NCPT} > 8\% \]
for either dysphagia or xerostomia

Randomisation
Protons vs photons 2:1
Endpoint based on selection criterion (\(\Delta \text{NTCP}\))

Dysphagia (n=242)
Assessed at 6 months

Xerostomia (n=363)
Assessed at 6 months

Secondary endpoints analysed for both groups combined
Treatment of (locally advanced) oropharynx cancer
Radiotherapy in oropharyngeal cancers

MARCH-HPV Meta-analysis (RTOG9003, DAHANCA6&7, ARTSCAN, RTOG 0129)

PFS

Survival

HPVpos (non smoker)

HPVpos (smoker)

HPVneg (non smoker)

HPVneg (smoker)

At risk

\[
\begin{array}{cccccccc}
\text{p16+ / Never} & 86 & 76 & 70 & 60 & 34 & 10 & 8 \\
\text{p16+ / Former-current} & 252 & 170 & 145 & 126 & 78 & 38 & 34 \\
\text{p16- / Never} & 21 & 10 & 9 & 9 & 3 & 3 & 1 \\
\text{p16- / Former-current} & 290 & 99 & 68 & 55 & 30 & 14 & 12 \\
\end{array}
\]
### Meta-analysis on altered fractionation HNSCC

<table>
<thead>
<tr>
<th>CF</th>
<th>HF</th>
<th>CB</th>
<th>AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>70Gy/ 2.0 Gy/ 7w</td>
<td>80.5Gy/ 2x1.15 Gy/ ti=6h/ 7w</td>
<td>70Gy/ 2.0 Gy/ 5w</td>
<td>66-68Gy/ 2.0 Gy/ 5.5w</td>
</tr>
</tbody>
</table>

**Expectations:**

- Increased tumor control
- Increased early reactions
- Unchanged or decreased late damage

*Lacas Lancet Oncol 2017*
Meta-analysis on altered fractionation HNSCC

Randomized trials 1970-2010; 33 trials included (11423 individual patients data)

- Increasing the therapeutic window:
- Increased control (and survival)
- Increased acute grade 3+4 toxicity
- NO increase in late morbidity

Lacas Lancet Oncol 2017
HPV/p16 and accelerated fractionation?

Loco-regional tumour control – DAHANCA7 trial

- There are no evidence to suggest that HPV p16+ and HPV p16- OPCC should be treated differently in terms of fractionation (Hyperfractionation can be discussed)

HR=0.77 [0.60-0.99]  
HR=0.57 [0.34-0.97]
Meta-analysis on chemotherapy in HNSCC

<table>
<thead>
<tr>
<th>Timing</th>
<th>No. Deaths / No. Entered</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LRT+CT</td>
<td>LRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant</td>
<td>3171/4824</td>
<td>3386/4791</td>
<td>-326.4</td>
<td>1587.7</td>
<td>0.81 [0.78;0.86]</td>
</tr>
<tr>
<td>Induction</td>
<td>1877/2740</td>
<td>1813/2571</td>
<td>-40.0</td>
<td>900.7</td>
<td>0.95 [0.90;1.02]</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>631/1244</td>
<td>661/1323</td>
<td>17.9</td>
<td>317.4</td>
<td>1.06 [0.95;1.18]</td>
</tr>
<tr>
<td>Total</td>
<td>5679/8808</td>
<td>5863/8685</td>
<td>-348.5</td>
<td>2605.8</td>
<td>0.88 [0.85;0.92]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2_{107} = 179.8$, $p = 0.0001$; $p = 4.1\%$ LRT+CT better | LRT better

Test for interaction: $\chi^2_2 = 26.60$, $p = 0.0001$

LRT+CT effect: $p < 0.0001$

Absolute difference at 5 years ± standard deviation:

- Concomitant chemotherapy: $6.5 \pm 1.0\%$
- Control: $33.7\%$
- LRT: $27.2\%$

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Pignon Radiother Oncol 2009
Lessons learned from the MACH-NC meta-analyses

- Small benefit of CT on survival: confirmed
- Higher benefit with concomitant CH: confirmed (8%)
- Benefit with concomitant CDDP: 11% at 5 years
- Benefit of CT observed in post-op, and with primary RT (conventional/altered fractionation)
### Meta-analysis on AF and C-RT in HNSCC

Randomized trials 1970-2010; 33 trials included (11423 individual patients data)

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>INRC-HN-94</td>
<td>58/66</td>
<td>55/70</td>
<td>5.9</td>
</tr>
<tr>
<td>ORO 9301</td>
<td>50/65</td>
<td>42/64</td>
<td>6.2</td>
</tr>
<tr>
<td>EORTC 22962</td>
<td>7/13</td>
<td>9/15</td>
<td>0.4</td>
</tr>
<tr>
<td>GORTEC 9902</td>
<td>207/281</td>
<td>196/279</td>
<td>14.7</td>
</tr>
<tr>
<td>TMH 1114</td>
<td>34/68</td>
<td>26/65</td>
<td>6.3</td>
</tr>
<tr>
<td>Total</td>
<td>356/493</td>
<td>328/493</td>
<td>33.0</td>
</tr>
</tbody>
</table>

χ² test for heterogeneity: p=0.087, I²=0%

Treatment effect: p=0.0098

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Lacas Lancet Oncol 2017

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Altered fractionation or C-RT?

GORTEC 9902

70 Gy / 7 weeks
5FU / carboplatin concomitant (3 cycles)

Accelerated concomitant boost RT
70 Gy / 6 weeks
5FU / carboplatin concomitant (2 cycles)

Very accelerated RT 64.8 Gy / 3.5 weeks

At 3 years (95% CI)
Conventional CRT 42.6% (37.0-48.5)
Accelerated RT-CT 39.4% (33.8-45.3)
Very accelerated RT 36.5% (31.1-42.3)

Bourhis Lancet Oncol 2012
RTOG 0129: Is AFX-C better than SFX-C?

Nguyen-Tan, JCO 2010

70 Gy (7w) + cis x 3 = 70 Gy (6w) + cis x 2
Keeping the entire individual in mind

Overall survival by age

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Events / No. Entered</th>
<th>Hazard ratio (Alt. fractionated RT/Control)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>=&lt;50</td>
<td>1768/1311</td>
<td></td>
<td>0.97 [0.8650.894]</td>
</tr>
<tr>
<td>51-60</td>
<td>1455/2300</td>
<td></td>
<td>0.99 [0.8830.899]</td>
</tr>
<tr>
<td>61-70</td>
<td>1521/2346</td>
<td></td>
<td>0.89 [0.7841.006]</td>
</tr>
<tr>
<td>&gt;70</td>
<td>7843/1085</td>
<td></td>
<td>0.90 [0.8691.23]</td>
</tr>
<tr>
<td>Total</td>
<td>4528/7042</td>
<td></td>
<td>0.85 [0.7860.897]</td>
</tr>
</tbody>
</table>

Test of interaction: p = 0.02
Test for trend: p = 0.002
Test for trend: p = 0.003

Alt. Frac. RT better | Control better
Alt. fractionated RT effect p = 0.02
## Cause of death in the elderly

<table>
<thead>
<tr>
<th></th>
<th>MAR CH</th>
<th>51 - 60</th>
<th>61 - 70</th>
<th>&gt;70</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer death</td>
<td>74.7 %</td>
<td>68.1 %</td>
<td>60.8 %</td>
<td>47.2 %</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non cancer death</td>
<td>18.2 %</td>
<td>23.8 %</td>
<td>29.3 %</td>
<td>41.2 %</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unknown cause of death</td>
<td>7.0 %</td>
<td>8.1 %</td>
<td>9.9 %</td>
<td>11.6 %</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MACH-NC</th>
<th>51 - 60</th>
<th>61 - 70</th>
<th>&gt;70</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer death</td>
<td>80.4 %</td>
<td>73.1 %</td>
<td>68.8 %</td>
<td>54.6 %</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non cancer death</td>
<td>14.6 %</td>
<td>21.3 %</td>
<td>26.5 %</td>
<td>38.7 %</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unknown cause of death</td>
<td>5.0 %</td>
<td>5.6 %</td>
<td>4.7 %</td>
<td>6.7 %</td>
<td></td>
</tr>
</tbody>
</table>
What is the place for EGFR-I?

Randomized phase III: n=424
RTOG 0522: C-RT +/- cetuximab

Ang, JCO 2010

[Graphs showing progression-free survival, overall survival, locoregional failure, and distant metastasis rates over time for RT +/– cetuximab.]
### Triplets better than dublets?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 0522</td>
<td>SFX+cis +/- cetuximab</td>
<td>N.S</td>
</tr>
<tr>
<td>Concert 1</td>
<td>SFX+cis +/- panitumumab</td>
<td>N.S</td>
</tr>
<tr>
<td>DAHANCA 19</td>
<td>AF+cis +/- zalutumumab</td>
<td>N.S</td>
</tr>
</tbody>
</table>

EGFR-I and cisplatin both inhibits DNA repair (although by different mechanisms)
De-escalation of treatment in HPV/p16+ OPCC

HPV, smoking and risk groups in RTOG 0129

- p16pos - smoking
- p16pos + smoking (p16neg - smoking)
- High risk

Overall Survival (%)

Years since Randomization

Ang Sem Rad Oncol 2012
# De-escalation of treatment in HPV/p16+ OPCC

## Primary RT

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Stage</th>
<th>Smoking</th>
<th>Design</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>De-Escalate</td>
<td>III-IVa</td>
<td>non-smoking smoking&lt; N2b</td>
<td>70Gy + 3-weekly cddp vs 70 Gy + weekly cetuximab</td>
<td>2018</td>
</tr>
<tr>
<td>NRG HN002</td>
<td>III-IV</td>
<td>&lt; 10 pack/y</td>
<td>60 Gy (5w) + weekly cddp vs 60 Gy (5w)</td>
<td>2018</td>
</tr>
<tr>
<td>Quaterback</td>
<td>III-IV</td>
<td>≥ 20 pack/y</td>
<td>TPFx3 + 70Gy and weekly carbo vs TPFx3 + 56Gy and weekly carbo</td>
<td>2021</td>
</tr>
<tr>
<td>RTOG-1016</td>
<td>III-IV</td>
<td>all pts</td>
<td>70 Gy + CDDP (x2) vs 70 Gy + weekly cetuximab</td>
<td>2018</td>
</tr>
<tr>
<td>TROG-12.01</td>
<td>III-IV</td>
<td>non-smoking smoking&lt; N2b</td>
<td>70Gy + weekly cddp vs 70 Gy + weekly cetuximab</td>
<td>2020</td>
</tr>
</tbody>
</table>

## PORT

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Stage</th>
<th>Smoking</th>
<th>Design</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADEPT</td>
<td>III-IV</td>
<td>all pts</td>
<td>PORT 60 Gy vs PORT 60 Gy + weekly cddp</td>
<td>2021</td>
</tr>
<tr>
<td>ECOG-331*</td>
<td>III-IV R1 ≠ECS</td>
<td>&lt; 10 packs/y &gt; 10 packs/y</td>
<td>TOS + 60 Gy vs TOS + 50 Gy</td>
<td>2016</td>
</tr>
<tr>
<td>PATHOS</td>
<td>I-IV</td>
<td>non-smoking smoking&lt; N2b</td>
<td>1) PORT 60Gy vs PORT 50Gy 2) PORT 60Gy + CH vs PORT 60Gy</td>
<td>2019?</td>
</tr>
</tbody>
</table>
De-escalation of treatment in HPV/p16+ OPCC

RTOG 1016: a randomised, multicentre, non-inferiority trial

Stratify:
- T 1-2
- T3-4
- N0-2a
- N2b-c
- Smoking
- Zubrod 1-2

HR 1.45, one-sided 95% upper CI 1.94

N=700

987 pts recruited before closure in July 2014

HR 2.05 (95% CI 1.35–3.10)

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Gillison Lancet 2018
De-escalation of treatment in HPV/p16+ OPCC

De-ESCALaTE: an open-label randomised controlled phase 3 trial

**Primary outcome**

- Overall
  - Grade 3-5: 4.81 (4.23–5.40) vs 4.82 (4.22–5.43; p = 0.98)
  - All grades: 29.15 (27.33–30.97) vs 30.05 (28.26–31.85; p = 0.49)

**Secondary outcomes**

- Acute short-term toxicities
  - Grade 3-5: 4.43 (3.88–4.97) vs 4.35 (3.84–4.86; p = 0.84)
  - All grades: 19.96 (18.81–21.12) vs 20.35 (19.18–21.52; p = 0.64)

- Severe late toxicities
  - Grade 3-5: 0.41 (0.29–0.54) vs 0.48 (0.30–0.67; p = 0.53)
  - All grades: 9.44 (8.53–10.34) vs 9.87 (9.02–10.72; p = 0.49)

**Table 2:** Mean number of acute, late, and overall toxicity events per patient, by treatment group

N=334
Conclusions

- Primary Surgery for early OPCC if multimodal treatment can be avoided
- Altered fractionation or chemo-radiotherapy for locally advanced OPCC
- Better outcome for HPV+ patients
- Not the proper time yet for treatment de-intensification or change in treatment strategy!
- Different trials for HPV+ and HPV- patients
- Routine p16 staining for oropharyngeal SCC
Thank you