HPV positive Ca Oropharynx

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Regional Cancer Centre
Trivandrum, Kerala
Contents

- Clinical presentation
- Why a new disease entity?
- New staging system
- Current status of de intensification protocols
- Future directions
<table>
<thead>
<tr>
<th>Feature</th>
<th>HPV-negative</th>
<th>HPV-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Above 60 years</td>
<td>Middle-aged</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Tobacco +/- alcohol</td>
<td>Sexual behaviour</td>
</tr>
<tr>
<td>Field cancerization</td>
<td>yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Predilection site</td>
<td>None</td>
<td>Oropharynx</td>
</tr>
<tr>
<td>T stage</td>
<td>Higher T Stage</td>
<td>Lower T Stage</td>
</tr>
<tr>
<td>Nodal status</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>TP53 mutations</td>
<td>Frequent</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Histology</td>
<td>Insitu changes</td>
<td>Basaloid/poorly diff</td>
</tr>
</tbody>
</table>

No primary or small primary
Work up for MUO
Phase II Trial  
ECOG2399  
N=96  
38/96- HPV positive

**Improved Survival of Patients With Human Papillomavirus–Positive Head and Neck Squamous Cell Carcinoma in a Prospective Clinical Trial**

Carole Fakhry, William H. Westra, Sigui Li, Anthony Cmelak, John A. Ridge, Harlan Pinto, Arlene Forastiere, Maura L. Gillison

**2 yr OS** 95% Vs 62% p=0.005

2 cycles of IC→CCRT 70Gy/35Fr.Ca Oropharynx and Ca Larynx, Median FU 39.1 months .

*J Natl Cancer Inst* 2008;100:261–269
Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer


Prognostic Implications of HPV in Oropharyngeal Cancer

Douglas R. Lowy, M.D., and Karl Munger, Ph.D.
# HPV and better H&N Cause-specific survival

<table>
<thead>
<tr>
<th>Study</th>
<th>N pts</th>
<th>Subsite</th>
<th>% Hpv</th>
<th>Rx</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fahkry, 08 ECOG 2399</td>
<td>96</td>
<td>Oroph+Lar</td>
<td>40</td>
<td>IndCT +CTRT</td>
<td>0.36</td>
</tr>
<tr>
<td>Lassen, 09 DAHANCA 05</td>
<td>135</td>
<td>H &amp;N</td>
<td>22</td>
<td>RT(100%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Rischin, 10 TROG 02.02</td>
<td>172</td>
<td>Oroph</td>
<td>57</td>
<td>CTRT</td>
<td>0.36</td>
</tr>
<tr>
<td>Posner, 11 TAX 324</td>
<td>111</td>
<td>Oroph</td>
<td>50</td>
<td>Ind +CTRT</td>
<td>0.20</td>
</tr>
<tr>
<td>Gillison, 12 RTOG 9003</td>
<td>190</td>
<td>Oroph</td>
<td>39</td>
<td>RT</td>
<td>Nrp&lt;0.001</td>
</tr>
<tr>
<td>Ang, 10 RTOG 0129</td>
<td>323</td>
<td>Oroph</td>
<td>64</td>
<td>CTRT</td>
<td>0.42</td>
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<tr>
<td>Lassen, 11 DAHANCA 6 &amp; 7</td>
<td>769</td>
<td>H&amp;N</td>
<td>-</td>
<td>RT</td>
<td>0.54</td>
</tr>
</tbody>
</table>
HPV positive

Nodal stage –N1 (Single or Multiple, Ipsilateral, if not more than 6 cm) - up to T-T2, Stage I (Lower border of cricoid is not included)

5x4cm

Stage I

Stage III

HPV -Ve

N1—stage III single, ipsilateral, 3 cm or less in greatest dimension

Minimum Stage III
Nodal Staging

HPV positive - Nodal stage – N1 (Single or Multiple, Ipsilateral, if not more than 6 cm) - Stage I

HPV negative Oropharynx, Oral vaity, Larynx or Hypopharynx - N2b
Stage IVa

HPV negative Oropharynx, Oral vaity, Larynx or Hypopharynx - N2c
Stage IVa

Ca Nasopharynx – N2 Bilateral (if not more than 6 cm) – Stage II

Nasopharynx – N3 (Any node below lower border of cricoid cartilage) – Stage IVa

HPV positive – N2. Bilateral (Single or multiple). No sub classification for N2. (if not more than 6 cm) – Stage II

Ca Nasopharynx – N2 Bilateral (if not more than 6 cm) – Stage III
HPV Positive - T2N2 - Stage II

HPV Negative, N2c, Stage IVa
## Nodal staging - HPV +ve

<table>
<thead>
<tr>
<th>N Category</th>
<th>N Criteria</th>
</tr>
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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>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>

No ENE
N3b /Stage IVb or N3 Disease/Stage III?
## Oropharynx p16 Positive tumors

<table>
<thead>
<tr>
<th>Stage</th>
<th>T Location</th>
<th>N Location</th>
<th>M Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1, T2</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 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>Stage 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>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Human Papillomavirus Testing in Head and Neck Carcinomas

Guideline From the College of American Pathologists

James S. Lewis Jr, MD; Beth Beadle, MD, PhD; Justin A. Bishop, MD; Rebecca D. Chernock, MD; Carol Colasacco, MLIS, SCT(ASCP); Christina Lacchetti, MHSc; Joel Todd Moncur, MD, PhD; James W. Rocco, MD, PhD; Mary R. Schwartz, MD; Raja R. Seethala, MD; Nicole E. Thomas, MPH, CT(ASCP)\textsuperscript{CM}; William H. Westra, MD; William C. Faquin, MD, PhD

Guideline Summary

Human Papillomavirus Testing in Head and Neck Carcinomas: ASCO Clinical Practice Guideline Endorsement Summary of the CAP Guideline

Carole Fakhry, Christina Lacchetti, and Bayardo Perez-Ordenez
Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial

Hisham Mehanna, Max Robinson, Andrew Hartley, Anthony Kong, Bernadette Foran, Tessa Fulton-Lieuw, Matthew Dalby, Pankaj Mistry, Mehmet Sen, Lorcan O’Toole, Hoda Al Booz, Karen Dyker, Rafael Moleron, Stephen Whitaker, Sinead Brennan, Audrey Cook, Matthew Griffin, Eleanor Aynsley, Martin Rolles, Emma De Winton, Andrew Chan, Devraj Srinivasan, Joanna Nixon, Joanne Grumett, C René Leemans, Jan Buter, Julia Henderson, Kevin Harrington, Christopher Conkey, Alastair Gray, Janet Dunn, on behalf of the De-ESCALaTE HPV Trial Group*

Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial

348 patients registered

14 excluded
- 4 ineligible
- 4 patient decision
- 5 did not want to delay treatment
- 1 clinician decision

334 randomly assigned

166 allocated to cisplatin and radiotherapy group
- 4 withdrawals
  - 3 patient decision
  - 1 other

162 received allocated intervention
- 6 deaths
  - 4 due to disease
  - 2 other causes
- 3 withdrawals
  - 1 relocated to site not in trial
  - 2 patient decision

162 analysed for primary outcome;
166 analysed for secondary outcomes

168 allocated to cetuximab and radiotherapy group
- 4 withdrawals
  - 1 patient decision
  - 1 ineligible
  - 1 progression of disease
  - 1 death

164 received allocated intervention
- 19 deaths
  - 15 due to disease
  - 4 other causes
  - 3 withdrawals
    - 1 progression of disease
    - 1 non-compliance
    - 1 patient decision

165 analysed for primary outcome;
168 analysed for secondary outcomes
Toxicity - Primary end point

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin plus radiotherapy (95% CI)</th>
<th>Cetuximab plus radiotherapy (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>4.81 (4.23–5.40)</td>
<td>4.82 (4.22–5.43)</td>
<td>0.98</td>
</tr>
<tr>
<td>Grade 3–5</td>
<td>4.43 (3.88–4.97)</td>
<td>4.35 (3.84–4.86)</td>
<td>0.84</td>
</tr>
<tr>
<td>All grades</td>
<td>19.96 (18.81–21.12)</td>
<td>20.35 (19.18–21.52)</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute short-term toxicities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3–5</td>
<td>0.41 (0.29–0.54)</td>
<td>0.48 (0.30–0.67)</td>
<td>0.53</td>
</tr>
<tr>
<td>All grades</td>
<td>9.44 (8.53–10.34)</td>
<td>9.87 (9.02–10.72)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

*Lancet* 2019; 393: 51–60
Results- Median follow up 22 months

2 yr OS 97.5% Vs 89.4% p=0.0012

2 yr Recurrence 16.1% Vs 6 % p=0.0007
Conclusions – De- ESCALaTE (low risk)

- HPV positive disease have good prognosis
- There was no difference toxicity between the two arms
- Better OS and less recurrence - with CDDP plus RT
- CDDP plus RT remains standard of care in low risk HPV +ve Disease
RTOG 1016
OS - Primary end point
Non inferiority margin 1.45

987 patients enrolled
138 not randomised
50 p16 negative or not evaluable
7 no tissue submitted for p16 testing
44 patient refusal
13 physician preference
3 disease progression
21 other
849 randomised

424 assigned to intensity-modulated radiotherapy plus cisplatin
18 excluded
17 did not meet eligibility criteria
1 HIV positive
406 patients eligible
394 received intensity-modulated radiotherapy plus cisplatin
3 received intensity-modulated radiotherapy only
1 received cisplatin only
8 no protocol treatment
31 lost to follow-up
26 patient withdrew consent
5 unknown reason
14 discontinued intensity-modulated radiotherapy
4 adverse events
4 patient refusal
2 deaths
1 alternative therapy
3 other
18 discontinued cisplatin
12 adverse events
1 alternative therapy
1 other
406 patients included in analysis

425 assigned to intensity-modulated radiotherapy plus cetuximab
26 excluded
23 did not meet eligibility criteria
3 HIV positive
399 patients eligible
393 received intensity-modulated radiotherapy plus cetuximab
1 received cetuximab only
5 no protocol treatment
23 lost to follow-up
22 patient withdrew consent
1 unknown reason
19 discontinued intensity-modulated radiotherapy
3 adverse events
8 patient refusal
1 disease progression
3 deaths
1 alternative therapy
1 other complicating disease
2 other
66 discontinued cetuximab
39 adverse events
11 patient refusal
1 disease progression
3 deaths
1 alternative therapy
1 other complicating disease
10 other
399 patients included in analysis

Lancet 2019; 393: 40–50
<table>
<thead>
<tr>
<th>Grade</th>
<th>Intensity-modulated radiotherapy plus cisplatin</th>
<th>Intensity-modulated radiotherapy plus cetuximab</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute period patient total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early death</td>
<td>6 (1.5%)</td>
<td>6 (1.5%)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Grade 3–4 overall</td>
<td>325 (81.7%)</td>
<td>305 (77.4%)</td>
<td>0.1586</td>
</tr>
<tr>
<td>Grade 3–4 anaemia</td>
<td>11 (2.8%)</td>
<td>0</td>
<td>0.0009*</td>
</tr>
<tr>
<td>Grade 3–4 hearing impaired</td>
<td>12 (3.0%)</td>
<td>1 (0.3%)</td>
<td>0.0032*</td>
</tr>
<tr>
<td>Grade 2–3 dry mouth</td>
<td>198 (49.7%)</td>
<td>211 (53.6%)</td>
<td>0.2872</td>
</tr>
<tr>
<td>Grade 3–4 dysphagia</td>
<td>149 (37.4%)</td>
<td>126 (32.0%)</td>
<td>0.1171</td>
</tr>
<tr>
<td>Grade 3–4 mucositis oral</td>
<td>165 (41.5%)</td>
<td>182 (46.2%)</td>
<td>0.1974</td>
</tr>
<tr>
<td>Grade 3 nausea</td>
<td>76 (19.1%)</td>
<td>32 (8.1%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Grade 3–4 vomiting</td>
<td>48 (12.1%)</td>
<td>16 (4.1%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Grade 3 fatigue</td>
<td>23 (5.8%)</td>
<td>17 (4.3%)</td>
<td>0.4178</td>
</tr>
<tr>
<td>Grade 3–4 dermatitis radiation</td>
<td>32 (8.0%)</td>
<td>49 (12.4%)</td>
<td>0.0462</td>
</tr>
<tr>
<td>Grade 3–4 lymphocyte count decreased</td>
<td>68 (17.1%)</td>
<td>69 (17.5%)</td>
<td>0.9252</td>
</tr>
<tr>
<td>Grade 3–4 neutrophil count decreased</td>
<td>61 (15.3%)</td>
<td>2 (0.5%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Grade 3 weight loss</td>
<td>31 (7.8%)</td>
<td>23 (5.8%)</td>
<td>0.3241</td>
</tr>
<tr>
<td>Grade 3–4 white blood cells decreased</td>
<td>48 (12.1%)</td>
<td>0</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Grade 3–4 anorexia</td>
<td>89 (22.4%)</td>
<td>61 (15.5%)</td>
<td>0.0144*</td>
</tr>
<tr>
<td>Grade 3–4 dehydration</td>
<td>61 (15.3%)</td>
<td>24 (6.1%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Grade 3–4 hyponatremia</td>
<td>21 (5.3%)</td>
<td>4 (1.0%)</td>
<td>0.0008*</td>
</tr>
<tr>
<td>Grade 3–4 acute kidney injury</td>
<td>13 (3.2%)</td>
<td>1 (0.3%)</td>
<td>0.0017*</td>
</tr>
<tr>
<td>Grade 3–4 pharyngeal mucositis</td>
<td>54 (13.6%)</td>
<td>40 (10.2%)</td>
<td>0.1535</td>
</tr>
<tr>
<td>Grade 3–4 rash acneiform</td>
<td>1 (0.3%)</td>
<td>37 (9.4%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Grade 3–4 pain (all terms)</td>
<td>58 (14.6%)</td>
<td>50 (12.7%)</td>
<td>0.4694</td>
</tr>
<tr>
<td>Mean raw T-score</td>
<td>3.19</td>
<td>2.35</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Late period patient total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3–4 overall</td>
<td>78 (20.4%)</td>
<td>62 (16.5%)</td>
<td>0.1904</td>
</tr>
<tr>
<td>Grade 3–4 hearing impaired</td>
<td>24 (6.3%)</td>
<td>8 (2.1%)</td>
<td>0.0060*</td>
</tr>
<tr>
<td>Grade 2–3 dry mouth</td>
<td>123 (32.1%)</td>
<td>126 (33.6%)</td>
<td>0.6991</td>
</tr>
<tr>
<td>Grade 3–4 dysphagia</td>
<td>17 (4.4%)</td>
<td>23 (6.1%)</td>
<td>0.3318</td>
</tr>
<tr>
<td>Grade 3 weight loss</td>
<td>17 (4.4%)</td>
<td>11 (2.9%)</td>
<td>0.3366</td>
</tr>
<tr>
<td>Grade 3–4 osteonecrosis of Jaw</td>
<td>8 (2.1%)</td>
<td>3 (0.8%)</td>
<td>0.2234</td>
</tr>
<tr>
<td>Grade 3–4 pain (all terms)</td>
<td>5 (1.3%)</td>
<td>8 (2.1%)</td>
<td>0.4154</td>
</tr>
<tr>
<td>Mean raw A-score</td>
<td>0.38</td>
<td>0.27</td>
<td>0.1189</td>
</tr>
</tbody>
</table>
Median follow up 4.5 yrs

5-year OS 77.9% Vs 84.6%

\[ p = 0.5056 \text{(non-inferiority)} \]

\[ P = 0.02 \text{(one sided log-rank)} \]

5-year PFS 67.3%, vs 78.4%

\[ p = 0.0002 \]
### Comparison

<table>
<thead>
<tr>
<th>RTOG 1016</th>
<th>De- ESCALaTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk and intermediate</td>
<td>Only low risk</td>
</tr>
<tr>
<td>Primary end point – OS</td>
<td>Primary end point -Toxicity</td>
</tr>
<tr>
<td>More long term follow up 4.5 yrs</td>
<td>Median follow up 22 months</td>
</tr>
<tr>
<td>Number of patients-987</td>
<td>Number of patients -348</td>
</tr>
<tr>
<td>Difference in toxicity</td>
<td>No difference in toxicities</td>
</tr>
<tr>
<td>OS better with CDDP plus RT</td>
<td>OS better with CDDP plus RT</td>
</tr>
</tbody>
</table>
Randomized Trial of Radiation Therapy With Weekly Cisplatin or Cetuximab in Low-Risk HPV-Associated Oropharyngeal Cancer (TROG 12.01) — A Trans-Tasman Radiation Oncology Group Study

Danny Rischin, MD, Madeleine King, PhD, Lizbeth Kenny, MBBS, Sandro Porceddu, MD, Christopher W writen, MBBS, Andrew Macann, MBChB, James E. Jackson, MBBS, Mathias Bressel, MSc, Alan Herschtal, PhD, Richard Fisher, PhD, Tsien Fua, MBBS, Charles Lin, MBBS, Chen Liu, MBBS, Brett G. M. Hughes, MBBS, Margaret McGrath, MBBS, Lachlan McDowell, MBBS, and June Corry, MD
Efficacy.

E1308: Phase II Trial of Induction Chemotherapy Followed by Reduced-Dose Radiation and Weekly Cetuximab in Patients With HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx—ECOG-ACRIN Cancer Research Group


<table>
<thead>
<tr>
<th>INDUCTION CT (Pacli +CDDP+C225) X 1-3 #</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>PR/SD</td>
<td></td>
</tr>
<tr>
<td>54Gy/27# 5days a week +</td>
<td>69.3Gy/33# 5days a week +</td>
<td></td>
</tr>
<tr>
<td>C225 x 6 weeks</td>
<td>C225 x 7 weeks</td>
<td></td>
</tr>
</tbody>
</table>

N=80, Primary end point – 2 yr PFS
The Quarterback Trial: A Randomized Phase III Clinical Trial Comparing Reduced and Standard Radiation Therapy Doses for Locally Advanced HPV Positive Oropharynx Cancer

- Phase III
- Stage III & IV patients
- Primary end point: PFS
- Secondary end point – LRC and OS
- 3 cycles of Induction Chemotherapy TPF
- Patients who achieve CR or PR

IMRT- 70Gy/35 fr+ Concurrent Carboplatin weekly

IMRT- 56 Gy/28 fr+ Concurrent Carboplatin weekly

PI: Marshall Posner, M.D, Mount Sinai Hospital, NY

https://clinicaltrials.gov/ct2/show/NCT01706939
T0-3 and N0-2. N=44
RT: 60 Gy IMRT + Weekly Cisplatin 30 mg/m2
Primary endpoint: Complete Response
Median FU – 14 months
CR: 98% for primary and 84% for nodal sites.

Cons
They included early stage cases
Short follow up
Planned Neck dissection
De-intensification of Radiation and Chemotherapy for Low-Risk HPV-related Oropharyngeal SCC: Follow-up Study

- Phase II
- IMRT, 60 Gy at 2 Gy/fx.
- Weekly chemotherapy regimens are Cisplatin 30 to 40 mg/m2 (first choice), Cetuximab 250mg/m2 (second choice), Carboplatin AUC 1.5 and paclitaxel 45 mg/m2.
- Chemotherapy will not be given to patients with T0-2 N0-1 disease, ≤ 10 pack years smoking history.
- Neck dissection based on PET/CT done 10-16 weeks

PI: Bhishamjit Chera, MD
University of North Carolina

https://clinicaltrials.gov/ct2/show/NCT02281955
Primary end point: 2 yr PFS
N=62
IC- Carboplatin plus nab -paclitaxel

Low risk patients
(≤ T3, ≤ N2b ≤ 10 pack-year history)

High risk patients
(≥ T4, ≥ N2c , ≥ 10 pack-year history)

Low-risk patients with 50% response received 50 (Gy)/25 RT (RT50)

Low-risk patients with 30%–50% response or high-risk patients with 50% response received 45 Gy CRT (CRT45)

Patients with lesser response received standardof-care 75 Gy CRT (CRT75)
Low risk - 95%
High Risk – 94%

Low risk- 100%
High Risk – 97%
Reduced-Dose Intensity-Modulated Radiation Therapy With or Without Cisplatin in Treating Patients With Oropharyngeal Cancer- HN002 Phase II Trial

- Phase II
- Primary end point: 2-year PFS
- T1-T2, N1-N2b or T3,N0-N2b

IMRT – 60 Gy/30 Fr over 5 in weeks

IMRT - Radiotherapy 60 Gy in 30fr in 6 weeks + Weekly CDDP 40 Mg/M2

https://clinicaltrials.gov/ct2/show/NCT02254278
IMPT Versus IMRT for the Treatment of Ca Oropharynx

- Squamous Cell Carcinoma of the oropharynx (American Joint Committee on Cancer (AJCC) v7 Stage III-IV A,B)
- Phase II/III
- Chemotherapy at the discretion of the Physician
- Rates and severity of late grade 3-5 toxicity between two arms

Randomize

IMRT – 70 Gy/33 Fr

IMPT – Radiotherapy 70Gy/33fr

https://clinicaltrials.gov/ct2/show/NCT01893307

Steven J. Frank, MD
M.D. Anderson Cancer Center
The primary endpoint - swallowing-related QOL at 1 year based on MD Anderson Dysphagia Inventory (MDADI) score
### 1 year Efficacy results

<table>
<thead>
<tr>
<th></th>
<th>RT group</th>
<th>TORS + ND group</th>
<th>Effect estimate (95% CI)</th>
<th>p value†</th>
<th>Clinically meaningful decline*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (primary endpoint)</strong></td>
<td>86.9 (11.4)</td>
<td>80.1 (13.0)</td>
<td>6.7 (0.2 to 13.2)</td>
<td>0.042</td>
<td>RT group 7/27 (26%)</td>
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<td></td>
<td>TORS + ND group 11/27 (41%)</td>
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<td></td>
<td>p value 0.25</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td>89.6 (15.1)</td>
<td>79.3 (22.6)</td>
<td>10.3 (0.2 to 20.4)</td>
<td>0.046</td>
<td>RT group 6/27 (22%)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>TORS + ND group 14/27 (52%)</td>
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<td></td>
<td>p value 0.024</td>
</tr>
<tr>
<td><strong>Emotional</strong></td>
<td>88.8 (12.0)</td>
<td>81.3 (12.5)</td>
<td>7.4 (0.9 to 14.0)</td>
<td>0.027</td>
<td>RT group 5/27 (19%)</td>
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<td></td>
<td>TORS + ND group 13/27 (48%)</td>
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<td></td>
<td>p value 0.021</td>
</tr>
<tr>
<td><strong>Functional</strong></td>
<td>89.9 (11.5)</td>
<td>86.5 (12.0)</td>
<td>3.4 (-2.9 to 9.6)</td>
<td>0.28</td>
<td>RT group 7/27 (26%)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>TORS + ND group 9/26 (35%)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>p value 0.49</td>
</tr>
<tr>
<td><strong>Physical</strong></td>
<td>83.1 (14.1)</td>
<td>75.3 (16.5)</td>
<td>7.9 (-0.3 to 16.0)</td>
<td>0.058</td>
<td>RT group 12/27 (44%)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>TORS + ND group 16/27 (59%)</td>
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<td></td>
<td></td>
<td></td>
<td>p value 0.28</td>
</tr>
<tr>
<td><strong>Composite (total score excluding global score)</strong></td>
<td>86.7 (11.4)</td>
<td>80.2 (13.1)</td>
<td>6.5 (0.0 to 13.1)</td>
<td>0.049</td>
<td>RT group 6/27 (22%)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>TORS + ND group 11/27 (41%)</td>
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<td></td>
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<td></td>
<td></td>
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<td>p value 0.14</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) unless otherwise stated. RT=radiotherapy. TORS + ND=transoral robotic surgery and neck dissection. *Defined as a decrease of at least 10 points. †p values adjusted for stratification by p16 status (post-hoc analysis): total (p=0.054), global (p=0.071), emotional (p=0.040), functional (p=0.29), physical (p=0.064), and composite (p=0.062).
# RT vs Surgery in Early OPC

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>Surgery (TORS/TLM)+/-Adjuvant Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established approach</td>
<td>Under evaluation</td>
</tr>
<tr>
<td>Functional outcomes better</td>
<td>Minimally invasive and less disfiguring</td>
</tr>
<tr>
<td></td>
<td>No external incision/scar</td>
</tr>
<tr>
<td>HPV status is prognostic</td>
<td>Outcomes independent of HPV status</td>
</tr>
<tr>
<td>Applicable in all patients</td>
<td>Requires good oral access</td>
</tr>
<tr>
<td></td>
<td>Patient selection is very important</td>
</tr>
<tr>
<td>Can be done in tumors in close proximity to critical</td>
<td>Reconstruction may be an issue</td>
</tr>
<tr>
<td>structures</td>
<td></td>
</tr>
<tr>
<td>IMRT can potential reduce toxicity and late dysphagia</td>
<td>Clearance with negative margins may be an issue</td>
</tr>
<tr>
<td>RP Nodes cannot be excised</td>
<td>Most patients need Adjuvant RT +/- chemo</td>
</tr>
<tr>
<td>No steep learning curve</td>
<td>Required</td>
</tr>
</tbody>
</table>
Surgery

- ADEPT - Phase III
- ECOG 3311 - Phase II
- PATHOS - Phase II
Post Operative Adjuvant Therapy De-intensification Trial for Human Papillomavirus-related, p16+ Oropharynx Cancer (ADEPT)

Primary endpoints
- 1. Disease-free survival (DFS)
- 2. Locoregional control

Secondary end points
- Distant metastasis rates
- Disease specific survival
- Cumulative incidence of complications/acute toxicity
- Function and quality of life (QOL)

- Transoral resection of their T1-4a oropharynx primary to a negative margin, and a neck dissection(s).
- ECS in their nodal metastasis
  N= 496

IMRT - Radiotherapy 60 Gy in 30fr

IMRT - Radiotherapy 60 Gy in 30fr + Weekly CDDP 40 Mg/M2

https://clinicaltrials.gov/ct2/show/NCT01687413
ECOG 3311 P16+ Trial – Low Risk OPSCC: Personalized Adjuvant Therapy Based on Pathologic Staging of Surgically Excised HPV+ Oropharynx Cancer

ASSess Eligibility: HPV (p16)+ SCC oropharynx
Stage III-IV: cT1-3, N1-2b (no T1N1)
Baseline Functional/QOL Assessment

LOW RISK: T1-T2N0-N1 negative margins

Observation

Radiation Therapy IMRT 50Gy/25 Fx

INTERMEDIATE: Clear margins ≤ 1 mm ECS 2–3 metastatic LN PNI LVI

Evaluate for 2-yr PFS Local-Regional Recurrence, Functional Outcomes/QOL

HIGH RISK: Positive Margins > 1 mm ECS or ≥ 4 metastatic LN

Radiation Therapy IMRT 60 Gy/30 Fx

Radiation Therapy IMRT 66 Gy/33 Fx + CDDP 40 mg/m² wkly

N=511

Courtesy of Robert Ferris

https://clinicaltrials.gov/ct2/show/NCT01898494
Results – Median follow up 35 months

3-year PFS

- 96.9% for Arm A
- 94.9% for Arm B
- 93.5% for Arm C
- 90.7% for Arm D

Primary TOS and reduced PORT retained outstanding oncologic outcome at 35 months follow up

ASCO 2021 Abstract 6010
Phase II Trial

Intermediate risk patients

Radiotherapy 50 Gy in 25fr

High risk patients

Radiotherapy 60 Gy in 30fr
Radiotherapy 60 Gy in 30fr + Weekly CDDP 40 Mg/M2

Primary end point – Swallowing dysfunction

N=242

https://clinicaltrials.gov/ct2/show/NCT02215265
Conclusions

- Replace Cisplatin with Cetuximab – 3 Negative Phase III trials
- NACT → Decreased RT doses – Positive Phase II, Phase III underway
- CTRT with decreased RT and chemo doses – 2 Positive Phase II, Phase II underway
- Omitting Chemotherapy – HN002 Phase II Trial
- Protons instead of Photons – IMRT Vs IMPRT Phase II trial underway
- Less invasive surgery (TORS) – One Phase III and 1 Phase II trials underway
Ipilimumab, Nivolumab, and Radiation Therapy in Treating Patients With HPV Positive Advanced Oropharyngeal Squamous Cell Carcinoma

- A phase II study

- T1N2, T2N1-2, and T3N0-2 HPV-related OPSCC

- Ipilimumab and anti-PD-1 (Nivolumab) in combination with RT 60Gy/30r

Programmed cell death protein -1-CD279
PDL-1- Programmed death-ligand 1-CD274
PD-1 inhibitors
PDL-1 Inhibitors

**IFN-γ-mediated upregulation of tumor PD-L1**

**PD-L1/PD-1-mediated inhibition of tumor cell killing**

**Priming and activation of T cells**

**Immune cell modulation of T cells**

**Tumor-associated fibroblast**

**Stromal PD-L1 modulation of T cells**

**PD-L2-mediated inhibition of TH2 T cells**
T-cell activation by ipilimumab (anti-CTLA-4, site of action in the periphery/lymph nodes) and nivolumab (anti-PD-1, site of action in the tumor microenvironment). MHC, major histocompatibility complex; TCR, T-cell receptor.
NCCN Guidelines Version 3.2021
Cancer of the Oropharynx (p16 [HPV]-positive)

Base of Tongue/Tonsil/Posterior Pharyngeal Wall/Soft Palate

CLINICAL STAGING

TREATMENT OF PRIMARY AND NECK

No adverse features\(^{p,q,r}\)

- Resection of primary ± ipsilateral or bilateral neck dissection\(^{i,m}\)
  - or
  - Adverse features\(^{q,r}\)
  - Positive margin

- Extranodal extension\(^{f}\) ± positive margin

ADJUVANT TREATMENT

- Systemic therapy/RT\(^{k,n,s}\) or RT\(^{k}\) (category 2B)
- Re-resection, if feasible
- Systemic therapy/RT\(^{k,n}\) or RT\(^{k}\) (category 2B)
- RT\(^{k}\) or Systemic therapy/RT\(^{k,n}\) (category 2B)

Other risk features\(^{r}\)

- Follow-up (See FOLL-A)
- Recurrent or persistent disease (See ADV-3)

See Post Systemic Therapy/RT or RT Neck Evaluation (FOLL-A, 2 of 2)

p16 (HPV)-positive T0-2,N1 (single node ≤3 cm)
- Definitive RT\(^{k}\)
- or
- Concurrent systemic therapy/RT\(^{k,n}\) (category 2B)
- or
- Clinical trials

See ORPHPV-3

p16 (HPV)-positive T1-2,N1 (single node >3 cm, or 2 or more ipsilateral nodes ≤6 cm)
NCCN Guidelines Version 3.2021
Cancer of the Oropharynx (p16 [HPV]-positive)

Base of Tongue/Tonsil/Posterior Pharyngeal Wall/Soft Palate

CLINICAL STAGING

TREATMENT OF PRIMARY AND NECK

ADJUVANT TREATMENT

- Concurrent systemic therapy/RT^{k,n} (preferred)
  - See Post Systemic Therapy/RT or RT Neck Evaluation (FOLL-A, 2 of 2)

- Resection of primary and ipsilateral or bilateral neck dissection
  - cN0–3 (unilateral)
  - cN2–3 (bilateral)
  - Resection of primary, neck dissection
  - No adverse features

- Extranodal extension and/or positive margin
  - Systemic therapy/RT^{k,n,s}
  - Follow-up (See FOLL-A)
  - RT^{k}
  - Consider systemic therapy/RT^{k,n}

- Adverse features
  - Other risk features

- Induction chemotherapy^{n,p} (category 3) followed by RT^{k} or systemic therapy/RT^{k,n}
  - See Post Systemic Therapy/RT or RT Neck Evaluation (FOLL-A, 2 of 2)

- Recurrent or persistent disease (See ADV-3)
Chapter

Human Papillomavirus Associated Oropharyngeal Carcinoma - Diagnosis and Management

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