Head and Neck Cancer Treatment

• Curative therapy with surgery or radiation
• Post operative adjuvant therapy with risk-based radiation or chemoradiation
• Organ preservation
  – Non-surgical management with chemoradiation
  – Organ-preserving surgery
• Systemic therapy
  – Historically largely with palliative intent
• Research was focused on treatment intensification
Randomized Trials Studied Increasingly Intense Therapies

- Studies conducted in predominantly HPV negative populations examined
  - Addition of 9 weeks of induction chemotherapy
  - Altered fractionation schemes
  - Higher radiation dose
  - High dose cisplatin
  - Post-operative combined modality or altered fractionation radiation

- Increased acute and chronic toxicity and increased cost
Late Effects

- Hyposalivation and xerostomia
  - dental decay
  - increased risk for osteoradionecrosis
- Nutrient deficiency
- Patient reported discomfort results in decrease in overall quality of life
- Dysphagia and pharyngeal dysfunction can precipitate aspiration, result in PEG dependency
- Even in IMRT era, high percentage of patients have persistent and severe sequelae
- Hypothyroidism
- Increased risk of non-cancer mortality

Arlene A. Forastiere et al. JCO 2013;31:845-852
Types of Head and Neck Cancer

Integrated analysis of genomic alterations

Lawrence MS et al. Nature 2015;517,576-582
HPV-Associated Cancer
Incidence Rates for HPV(+) and HPV(-) Oropharyngeal Cancers 1988 to 2004

Chaturvedi AK et al. JCO 2011;29:4294-4301
Decreasing Tobacco Exposure Among Smokers
HPV-Associated Oropharynx Cancer

R0129 analysis demonstrated high cure rates with cisplatin and radiation.

8-yr outcomes for p16+ good risk (T1-2N1-2b or T3N0-2b and ≤ 10 pk-yr)

OS 81.4%
PFS 78.3%
LRF 13.5%
DM 8.3%

R0129 Risk-of-Death Categories and Overall Survival

A

266 Patients with oropharyngeal cancer, known tumor HPV status, and known number of pack-years of smoking

178 Had HPV-positive tumors

88 Had HPV-negative tumors

88 Had ≤10 pack-years

90 Had >10 pack-years

23 Had ≤10 pack-years

65 Had >10 pack-years

26 Had N0–N2a cancer

64 Had N2b–N3 cancer

15 Had T2–T3 tumors

8 Had T4 tumors

114 of 266 (42.9%) were at low risk

79 of 266 (29.7%) were at intermediate risk

73 of 266 (27.4%) were at high risk

B

Overall Survival (%) vs Years since Randomization

No. at Risk

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>114</td>
<td>111</td>
<td>106</td>
<td>102</td>
<td>95</td>
<td>46</td>
</tr>
<tr>
<td>Intermediate</td>
<td>79</td>
<td>70</td>
<td>64</td>
<td>54</td>
<td>44</td>
<td>24</td>
</tr>
<tr>
<td>High Risk</td>
<td>73</td>
<td>52</td>
<td>43</td>
<td>33</td>
<td>28</td>
<td>8</td>
</tr>
</tbody>
</table>
TRAF3/CYLD mutations identify a distinct subset of HPV-associated HNC
HPV+ Has More Favorable Overall Survival after Disease Progression in R0129 or 0522

Fakhry C et al. JCO 2014;32:3365-3373
Prognostic significance of human papillomavirus in recurrent or metastatic head and neck cancer: an analysis of Eastern Cooperative Oncology Group trials

A. Argiris\textsuperscript{1*}, S. Li\textsuperscript{2}, M. Ghebremichael\textsuperscript{3}, A. M. Egloff\textsuperscript{4}, L. Wang\textsuperscript{5}, A. A. Forastiere\textsuperscript{6}, B. Burt\textsuperscript{7} & R. Mehra\textsuperscript{7}

\textsuperscript{1}Division of Hematology/Oncology Cancer Therapy and Research Center, Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio; \\
\textsuperscript{2}Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston; \\
\textsuperscript{3}Ragon Institute of Harvard, MIT and MGH and Harvard Medical School, Boston; Departments of \textsuperscript{4}Otolaryngology; \textsuperscript{5}Pathology, University of Pittsburgh, Pittsburgh; \textsuperscript{6}Department of Medical Oncology, Johns Hopkins University, Baltimore; \\
\textsuperscript{7}Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, USA

A

B

C

D

Log-rank $P = 0.056$

Log-rank $P = 0.014$

Log-rank $P = 0.006$

Log-rank $P = 0.027$
Refining American Joint Committee on Cancer/Union for International Cancer Control TNM Stage and Prognostic Groups for Human Papillomavirus–Related Oropharyngeal Carcinomas

Shao Hui Huang, Wei Xu, John Waldron, Lillian Siu, Xiaowei Shen, Li Tong, Jolie Ringash, Andrew Bayley, John Kim, Andrew Hope, John Cho, Meredith Giuliani, Aaron Hansen, Jonathan Irish, Ralph Gilbert, Patrick Guille, Bayarda Perez-Ordonez, Ian Weinreb, Fei-Fei Liu, and Brian O'Sullivan
### AJCC 8th Edition

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>N1</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>N2</td>
<td>II</td>
<td>II</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>N3</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
</tbody>
</table>

**Figure 4: Proposed ICON-S stage tabulation grid for 8th edition TNM**

Note that distant metastatic disease (M1) is considered stage IV.

O’Sullivan Lancet Oncology 2016
Validation of AJCC 8th Edition in the National Cancer Data Base

Husain et al. JAMA Oncol 2016
**NCCN Guidelines Version 1.2018**

**Cancer of the Oropharynx (p16 [HPV]-positive)**

### Base of tongue/tonsil/posterior pharyngeal wall/soft palate

**CLINICAL STAGING**

- Concurrent systemic therapy/RT\(^i\,k\) or induction chemotherapy\(^k\,m\) (category 3) followed by RT\(^i\)
- or systemic therapy/RT\(^i\,k\)
- or Transoral or open resection\(^j\) Primary and neck
- or Clinical trials

<table>
<thead>
<tr>
<th>p16 (HPV)-positive</th>
<th>Any T, cN1 (single node &gt;3 cm, or 2 or more ipsilateral nodes ≤6 cm), cN2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>cN1-cN3 (unilateral)</td>
<td>Resection of primary, neck dissection(^l)</td>
</tr>
<tr>
<td>cN2-3 (bilateral)</td>
<td>Resection of primary and bilateral neck dissection(^l)</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>Adverse features(^n,o,p)</td>
</tr>
<tr>
<td></td>
<td>Systemic therapy/RT(^i,k)</td>
</tr>
<tr>
<td></td>
<td>Follow-up (See FOLL-A)</td>
</tr>
<tr>
<td></td>
<td>Recurrent or persistent disease (See ADV-3)</td>
</tr>
</tbody>
</table>

**TREATMENT OF PRIMARY AND NECK**

- See Follow-Up Recommendations Post Chemoradiation or RT (FOLL-A, 2 of 2)
- No adverse features\(^n\,o\,p\)
- Extramodal extension and/or positive margin
- Adverse features\(^n\,o\,p\)
- Other risk features\(^n\,p\)
- Systemic therapy/RT\(^i\,k\)
- RT\(^i\) or Consider systemic therapy/RT\(^i\,k\)
- Follow-up (See FOLL-A)
- Recurrent or persistent disease (See ADV-3)

**ADJUVANT TREATMENT**

- Recurrent or persistent disease (See ADV-3)

---

\(^i\)See Principles of Radiation Therapy (ORPH-A).

\(^j\)See Principles of Surgery (SURG-A).

\(^k\)See Principles of Systemic Therapy (CHEM-A).

\(^m\)See Discussion on induction chemotherapy.

\(^n\)Adverse features: extranodal extension, positive margins, nodal disease in levels IV or V, perineural invasion, vascular embolism, lymphatic invasion (See Discussion). The definition of an adverse feature in the context of HPV+ disease is an area of active research. This includes the presence and extent of ENE, and the number of involved nodes.

\(^o\)The recommendations for patients at high risk with extranodal extension + positive margins are based on randomized studies involving patients for whom the HPV status of their tumors was not specified.

\(^p\)In the event of pathologic upstaging, continue to appropriate algorithm.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

---

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Goals for HPV-Associated Oropharynx Cancer

• Identify patients with near certainty of cure
  – Clinical vs. molecular criteria

• Maintain high cure rates while reducing morbidity
  – Acute toxicity grade and duration
  – Late toxicity
    • Speech and swallowing
    • Non-cancer mortality
    • Psychological effects
  – Resource utilization

• Explore novel agents for intermediate risk patients
E2399: HPV+ Responsive to Induction

Induction chemotherapy (IC)
Paclitaxel 175 mg/m² IV
Carboplatin AUC 6 IV Q21d X 2 cycles

Response Assessment

Concurrent chemoradiation
70 Gy / 35 fx / 7 weeks
Concurrent with Paclitaxel 30 mg/ m²/wk

RESPONSE: CR/PR
HPV + vs. HPV-
81.6 % vs 55.2%
p=0.01

2 yr PFS: 86% vs 53%
P=0.02

Strategies for Deintensification

• Reduce acute toxicity by
  – Lessening chemotherapy exposure
  – Shortening radiation duration
  – Avoiding multimodality care

• Reduce late morbidity by
  – Reducing radiation dose and/or field
  – Avoiding concurrent cisplatin
Lessening Chemotherapy Exposure;
The role of EGFR inhibition
What is the Role of Cetuximab in HPV-Associated Oropharynx Cancer?

- Is it active in the curative setting?
- Is it active in HPV-associated cancer?
- Are there known markers of resistance, and how do they correlate with HPV-positivity?
- Are novel strategies to overcome resistance to EGFR inhibition active in HPV-associated oropharynx cancer?
Radiation with or without Cetuximab:
Overall survival median follow-up 60 months

p16 Status in Oropharynx Cancer Patients

HR = 0.27
95% CI [0.15 - 0.51]

No. of patients at risk (n=182)

<table>
<thead>
<tr>
<th></th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P16 –Negative</td>
<td>107 76 49 37 31 19 0</td>
</tr>
<tr>
<td>P16- Positive</td>
<td>75 67 61 57 52 27 0</td>
</tr>
</tbody>
</table>
LRC in OPC subpopulation according to p16 status and treatment effect of RT + cetuximab vs RT alone

LRC interaction test p=NS

No. at risk OPC p16 evaluable (n=182)

<table>
<thead>
<tr>
<th></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>RT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p16 negative</td>
<td>64</td>
<td>34</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>p16 positive</td>
<td>31</td>
<td>24</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td>LRC (months)</td>
<td>31</td>
<td>24</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>20</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>12</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>6</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HR=0.31 [0.11–0.88] for RT+ct; p16+

HR=0.78 [0.49–1.25] for RT+ct; p16–
Overall Survival by p16 Status: Radiation with or without Cetuximab

OS interaction test $p=NS$

<table>
<thead>
<tr>
<th>OS (months)</th>
<th>RT; p16+</th>
<th>RT; p16–</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12</td>
<td>88%</td>
<td>33%</td>
</tr>
<tr>
<td>12–24</td>
<td>72%</td>
<td></td>
</tr>
<tr>
<td>24–36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36–48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48–60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–72</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR=0.38 [0.15–0.94]

HR=0.85 [0.61–1.19]

No. at risk OPC p16 evaluable (n=182)

<table>
<thead>
<tr>
<th></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>0–12</td>
<td>64</td>
<td>34</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>12–24</td>
<td>47</td>
<td>28</td>
<td>29</td>
<td>39</td>
</tr>
<tr>
<td>24–36</td>
<td>27</td>
<td>25</td>
<td>22</td>
<td>36</td>
</tr>
<tr>
<td>36–48</td>
<td>19</td>
<td>22</td>
<td>18</td>
<td>35</td>
</tr>
<tr>
<td>48–60</td>
<td>16</td>
<td>21</td>
<td>15</td>
<td>31</td>
</tr>
<tr>
<td>60–72</td>
<td>13</td>
<td>10</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>72</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
NCIC Trial: RT/cis vs. A-RT/Pmab

**Arm A:** CIS 100 mg/m² IV days 1, 22, 43
   - Standard Fractionation RT (70 Gy/35 over 7 wks)
   - n = 160

**Arm B:** PMab 9 mg/kg given 1 week prior to RT and days 15 and 36
   - Accelerated Radiation (70 Gy/35 over 6 wks)
   - n = 160

- **Total sample size:** 320
- **Trial activated:** December 2008
- **Last pt randomized:** November 2011
- **Clinical cut-off:** October 31, 2014
- **Median follow-up:** 46 months (93 PFS events)

Stratify by RT Delivery Modality, T category, N status, Anatomic Location
NCIC Trial: RT/cis vs. A-RT/Pmab

Primary Endpoint: PFS

- **Study arm**
  - Panitumumab: 76.0%, 68 – 92%
  - Cisplatin: 73.0%, 65 – 79%

**HR 0.95 (95% CI = 0.60 – 1.50)**
**Stratified log rank**
**p-value = 0.83**

Upper bound > 1.15
Non inferiority not proven

Time (Months)

Siu L. ASCO 2015
RTOG 1016: Cetuximab-RT vs. ChemoRT

Eligibility

Oropharynx p16 pos

- T1-2, N2a-3
- T3-4 any N

N=1000
4 yrs to enroll
8 yr to analysis

T-stage
T 1,2
T 3,4

N-stage
N0-2A
N2B-C

Smoking
<10 PY
>10 PY

Zubrod
1 2

Randomize

AFX 70 Gy for 6 wks + cisplatin x 2

AFX 70 Gy for 6 wks + cetuximab for 8 wks
Lessening Radiation Exposure
ECOG 1308: Can Induction Serve as a Dynamic Biomarker of Radiation Sensitivity?

Eligibility
- OPSCC
- resectable
- HPV ISH + and / or p16+
- Stage III, IVA

Induction Chemotherapy
- Cisplatin 75mg/m² d1
- Paclitaxel 90mg/m²d1,8,15
- Cetuximab 250mg/m² d1,8,15
- Q 21 days for 3 cycles

Concurrent Chemoradiation
- CLINICAL CR
  Low dose IMRT 54Gy/27fx* + Cetuximab qWeek
- CLINICAL PR/SD
  Full dose IMRT 69.3Gy/33fx* + Cetuximab qWeek

IMRT margins for primary: 1.0 to 1.5cm around gross dz
Nodal margin: 1cm margin minimum
Statistics

• Anticipating 69% CCR (n=52) to IC, accrual n=75

• A 2 year PFS of 85% or better in low-dose (54Gy) patients would be considered worthy of pursuing this study further

• Because of novel design and perceived accrual barriers, small non-randomized study
Results

Study activated: March 2010
Accrual: July 2010 to October 2011
Eligible: 80/90

INDUCTION CHEMOTHERAPY
3 cycles: 77/80 (96%)
1 cycle: 3/80 (3.8%)
Withdrawn: 3

LOW DOSE RT/Cetuximab
- 4000 cGy: 2
- 5200 cGy: 1
- 5400 cGy: 59

STD DOSE RT/Cetuximab
- 6930 cGy: 14
- 6510 cGy: 1
### Results: Smoking History

<table>
<thead>
<tr>
<th>SMOKING HISTORY</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>37</td>
<td>46%</td>
</tr>
<tr>
<td>Pipe or Cigar only</td>
<td>4</td>
<td>5%</td>
</tr>
<tr>
<td>No</td>
<td>67</td>
<td>83%</td>
</tr>
<tr>
<td>Yes</td>
<td>14</td>
<td>17%</td>
</tr>
<tr>
<td>Cigarette smoker, &gt;10-20 pk-yr</td>
<td>8</td>
<td>10%</td>
</tr>
<tr>
<td>Cigarette smoker, &gt;20-40 pk-yr</td>
<td>12</td>
<td>15%</td>
</tr>
<tr>
<td>Cigarette smoker, ≥40 pk-yr</td>
<td>11</td>
<td>14%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CURRENT SMOKER</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>67</td>
<td>83%</td>
</tr>
<tr>
<td>Yes</td>
<td>14</td>
<td>17%</td>
</tr>
</tbody>
</table>
## Low Dose Arm Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash Acneiform</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Concurrent CRT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash Acneiform</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Radiation dermatitis</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>13</td>
<td>1</td>
</tr>
</tbody>
</table>
### Response: Induction

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>Primary Site</th>
<th>Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>75 (71%)*</td>
<td>48 (61%)</td>
</tr>
<tr>
<td>PR</td>
<td>7 (9%)</td>
<td>19 (24%)</td>
</tr>
<tr>
<td>SD</td>
<td>11 (14%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Unevaluable</td>
<td>5 (6%)</td>
<td>5 (6%)</td>
</tr>
</tbody>
</table>

* 6 patients had biopsies performed on primary after baseline scans

<table>
<thead>
<tr>
<th>Radiographic Response</th>
<th>Primary Site</th>
<th>Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>38 (48%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>PR</td>
<td>24 (30%)</td>
<td>55 (70%)</td>
</tr>
<tr>
<td>SD</td>
<td>9 (11%)</td>
<td>17 (22%)</td>
</tr>
<tr>
<td>Unevaluable</td>
<td>9 (11%)</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>
## Endpoint: 2yr PFS and OS

<table>
<thead>
<tr>
<th>Cohort (n)</th>
<th>2 year PFS (90% CI)</th>
<th>2 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All low dose pts (62)</td>
<td>0.80 (0.70, 0.88)</td>
<td>0.93 (0.85, 0.97)</td>
</tr>
<tr>
<td>T4a (7)</td>
<td>0.54 (0.19, 0.79)</td>
<td>0.86 (0.45, 0.97)</td>
</tr>
<tr>
<td>Non-T4a (55)</td>
<td>0.84 (0.73, 0.91)</td>
<td>0.94 (0.86, 0.98)</td>
</tr>
<tr>
<td>N2c (19)</td>
<td>0.77 (0.56, 0.89)</td>
<td>0.95 (0.76, 0.99)</td>
</tr>
<tr>
<td>Non-N2c (43)</td>
<td>0.82 (0.69, 0.90)</td>
<td>0.93 (0.82, 0.97)</td>
</tr>
<tr>
<td>Smoker &gt; 10pk-yrs (22)</td>
<td>0.57 (0.35, 0.73)</td>
<td>0.86 (0.67, 0.94)</td>
</tr>
<tr>
<td>Smoker ≤ 10pk-yrs (40)</td>
<td>0.92 (0.81, 0.97)</td>
<td>0.97 (0.87, 0.995)</td>
</tr>
<tr>
<td>Smoker ≤ 10pk-yrs, &lt;T4, &lt;N2c (27)</td>
<td>0.96 (0.82, 0.99)</td>
<td>0.96 (0.82, 0.99)</td>
</tr>
<tr>
<td>All high-dose pts (15)*</td>
<td>0.65 (0.41, 0.82)</td>
<td>0.87 (0.63, 0.96)</td>
</tr>
</tbody>
</table>

* 3 high-dose pts did not go on to receive RT
PFS and Survival:  Dose

Progression free survival by RT dose

- Low dose
- Std dose
- All

Overall survival by RT dose

- Low dose
- Std dose
- All

2-yr = 80%
2-yr = 65%
2-yr = 87%
2-yr = 93%
Best Outcome: <T4, T1-N2b, <10 pk-yr

Progression free survival - the most favorable cohort vs. all other
2-yr = 96%
2-yr = 64%

Overall survival - the most favorable cohort vs. All other
p=0.012
p=0.36
**Symptom Reduction From IMRT Dose Deintensification: Results from ECOG 1308 Using the Vanderbilt Head and Neck Symptom Survey Version 2**


<table>
<thead>
<tr>
<th>Symptom</th>
<th>High Dose (n=9)</th>
<th>Low Dose (n=35)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Mouth Pain</td>
<td>1</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>General Pain</td>
<td>2</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td>Swallowing solids</td>
<td>5</td>
<td>100</td>
<td>11</td>
</tr>
<tr>
<td>Swallowing Liquids</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>3</td>
<td>60</td>
<td>19</td>
</tr>
</tbody>
</table>
Conclusions

• Low dose radiation resulted in a 2 year PFS of 80%
  • (95% CI .70 - .88)

• Patients with best risk disease (non-T4, non-N2c/N3, < 10 pack years tobacco exposure) did exceptionally well with 96% 2 year PFS and OS

• Apparently allows significant reduction in toxicity while maintaining high PFS and OS
UCLA Study

55 patients assessed for eligibility

10 patients excluded
  3 did not meet inclusion criteria
  4 declined to participate
  3 other reasons

45 patients enrolled and assigned to treatment

1 patient withdrew consent and did not receive treatment

44 patients received induction chemotherapy

24 patients achieved complete or partial response and were assigned 54 Gy radiation

20 patients achieved minor response or stable disease and were assigned 60 Gy radiation

44 patients included in analysis

p16 positive
16% T4, 25% >10 pack years
24/44 PR or CR -> 54Gy
20/44 SD -> 60Gy
No neck dissections for residual disease
UCLA Outcome

Median follow-up 30 m (IQR 26–37)
One (2%) pt developed distant metastasis
Three (7%) patients had locoregional disease recurrence
2-year PFS 92% (95% CI 77–97)
2-year LRC 95% (80–99)
Distant metastasis occurred at 12 mo in T2N2a BOT, 60 Gy after <PR; CR to systemic therapy
LRR occurred at 23 m in never smoker with T1N2b of tonsil, 60 Gy after < PR
LRR occurred at 16 m in pt with 20 pk-yr smoking hx and T4N2b of BOT, 54 Gy after PR
LRR occurred at 15 min never smoker with T2N2b of tonsil, 60 Gy after < PR
All without evidence of disease after surgical salvage.
De-intensified Chemoradiotherapy

- Intensity Modulated Radiotherapy
- 60 Gy at 2 Gy/fx, 30 fx, 6 weeks
- Weekly Cisplatin 30 mg/m² X 6 doses

4 to 8 weeks

Clinical Response
- Contrasted Neck CT
- Fiberoptic Laryngoscopy

2 to 6 weeks

Pathological Response
- Biopsy of Primary Site
- Selective neck dissection of pre-treatment positive nodes

Primary Endpoint

Routine Follow-up
N=43 Complete Pathological Response

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>40/41 (98%)</td>
<td></td>
</tr>
<tr>
<td>(2 were T0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck</td>
<td>33/39 (84%)</td>
<td></td>
</tr>
<tr>
<td>(4 were N0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>37/43 (86%)</strong></td>
<td></td>
</tr>
</tbody>
</table>

- 6 non-pCR cases were limited to microscopic foci of residual cancer: 1 primary site, 5 nodal.
- **Surgery** (mean: 9 weeks, range: 6.5-21 weeks)
  - Median number of levels dissected was 2 (range, 1-6)
  - Median # of nodes dissected was 11 (range, 1-46)
- **All patients alive with no evidence of disease**
  (median f/u 20 months, 4-37 months)
NRG HN 002: Favorable Risk

Patient Population:
Oropharyngeal squamous cell carcinoma

REGISTER

Positive for p16

STRATIFY: RT planning: unilateral vs. bilateral

RANDOMIZE

ARM 1: 60 Gy in 6 weeks + Cisplatin weekly for 6 weeks

ARM 2: 60 Gy in 5 weeks using 6 fractions per week
Transoral Robotic Surgery (TORS)

Images courtesy of Marshall Posner, MD.
**ECOG 3311 p16⁺ Trial**

### Assess Eligibility:
- HPV (p16)⁺
- SCC oropharynx

### Stage III-IV:
- cT1-2, N1-2b

### Baseline Functional/QOL Assessment

#### LOW RISK:
- T1-T2N0-N1
- negative margins

- **Randomize**

#### HIGH RISK:
- Positive Margins
- > 1mm ECS or 
- ≥5 metastatic LN

- **Randomize**

#### INTERMEDIATE:
- N2a Clear/close margins
- < 1mm ECS
- 2-4 metastatic LN
- PNI
- LVI

- **Randomize**

#### Radiation Therapy
- IMRT 50Gy/25 Fx
- IMRT 66 Gy/33 Fx + CDDP 40 mg/m² weekly

- **Randomize**

#### Observation

**Evaluate 2-year PFS**
- Local-Regional Recurrence,
- Functional Outcomes/QOL

**Accrual goal = 377**
Resected Disease

- Joint analysis of RTOG and EORTC trials led to acceptance of positive margin and ECE as indications for adding cisplatin to RT
- EORTC trial would also suggest perineural invasion is an indication
- High node number (≥5) also accepted by some
- These clinical parameters are not well described in original papers, and no molecular studies are available
R0501 ECE+ and/or Margin +

![Graph showing data for R0501 ECE+ and/or Margin +](image-url)
The prognostic value of extranodal extension in human papillomavirus-associated oropharyngeal squamous cell carcinoma
The prognostic value of extranodal extension in human papillomavirus-associated oropharyngeal squamous cell carcinoma

Median follow-up 28.4 m, ENE associated with worse 3-year OS 89.3% vs 93.6%; P = .01
Novel Agents to Spare Chemotherapy or Radiation Dose

- PD1 blockade, RR 22 – 32% for HPV+
  - Few hyperprogressors among HPV+

- Progress with synthetic lethal approaches for p53 mutated HPV negative cancers may also be active in HPV-associated cancers where E6 fosters p53 degradation
Future Directions

• Can the radiation dose to elective nodal volumes be reduced?
• What is the best composite measure of function and QOL?
• Phase III comparison of E1308 approach to standard chemoradiation
• How to integrate novel immunotherapies
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