HPV+ Oropharynx Cancer: Are We Ready to De-Intensify Treatment?

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What is Oropharyngeal cancer

- Anatomically distinct from oral cavity cancers
- Classically treated with radiation-based approaches
- Classically associated with smoking/alcohol risk factors
- 5-year survival rates 43-58%

Paradigm shift: De-intensification

- Intergroup: 70Gy vs 70Gy+cisplatin vs splitcourse-chemoRT
- RTOG 0129: 70Gy+cisplatin vs Accel70Gy+cisplatin
- RTOG 0522: Accel70 Gy+cisplatin vs Accel70Gy+cisplatin+cetuximab
- RTOG 1016: Accel70 Gy+cisplatin vs Accel70Gy+cetuximab – closing 2014
- NRG HN002: In development, based on principles of de-intensification
What is P16

- Cyclin-dependent kinase (CDK) inhibitor
- Inactivates CDKs that phosphorylate retinoblastoma (Rb)
- HPV oncprotein E7 binds and inactivates Rb, causing upregulation of p16

- Immunohistochemical stain
- Cheap and readily optimized for clinical labs
- Has become the surrogate marker for HPV – and a selection criterion in RTOG clinical trials
Acute Toxicity Burden of current chemoradiation approach

- Swallowing dysfunction
- Pharyngeal strictures
- Xerostomia and dental effects
- Chronic pain
- Osteoradionecrosis/chondroradionecrosis

- Particularly germane because HPV+ OPC patients are 15 years younger than other HN cancer patients
What Can We DO?

1) Decrease chemotherapy
   a) Less toxic chemotherapy
   b) Radiation Alone
   c) Surgery alone and Surgery + prn XRT/chemo

2) Decrease the XRT
   − Induction Chemo and Chemo Selection-E1308

3) New Trials
   − TORS
   − HN01

RTOG 1016

**Less Toxic Chemotherapy**

Phase III Trial of Radiotherapy Plus Cetuximab versus Chemoradiotherapy in HPV-Associated Oropharynx Cancer

**SCHEMA (9/25/13)**

<table>
<thead>
<tr>
<th>T Stage</th>
<th>R</th>
<th>S</th>
<th>E</th>
<th>M Mandatory p16</th>
<th>N Stage</th>
<th>D</th>
<th>Arm 1 (Control):</th>
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<tbody>
<tr>
<td>1. T1-2</td>
<td>R</td>
<td>2. T2-4</td>
<td>E</td>
<td>Arm 2: Accelerated IMRT, 70 Gy for 6 weeks</td>
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<td></td>
<td>T</td>
<td>N</td>
<td>G</td>
<td>Arm 2: Accelerated IMRT, 70 Gy for 6 weeks</td>
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<td>I</td>
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<td>Arm 2: Loading dose pre-IMRT, then</td>
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<td></td>
<td>F</td>
<td>Status</td>
<td>I</td>
<td>Cetuximab (400 mg/m²)</td>
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<tr>
<td></td>
<td>R</td>
<td>Y</td>
<td>Z</td>
<td>Loading dose pre-IMRT, then</td>
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<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>250 mg/m² weekly during IMRT</td>
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<td></td>
<td></td>
<td>and for 1 week after IMRT for a total</td>
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<td>1. ± 10 pack-years</td>
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<td></td>
<td></td>
<td></td>
<td>of 8 doses of cetuximab</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>2. ± 10 pack-years</td>
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</tbody>
</table>

Patients must be positive for p16, determined by the Innovation Center CLIA lab at The Ohio State University (OSU) prior to Step 2 registration (randomization); see 10.2 for
RTOG 1016

a) Less Toxic Chemotherapy

- Primary Objective - 5 Year Survival
- Opened June 2011
  - After a hiatus the study was enlarged to 1,000 patients to allow for 834 eligible patients
- Waiting for 45 events....
  - The study is doing well...

b) Radiation Alone
**PMH XRT Alone**

b) Radiation Alone

![Graphs showing overall survival and local control for PMH XRT Alone]

**Natural History of HPV Disease**

![Graphs showing distant control rates for HPV and non-HPV cases]

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**Fig 5.** Distant control (DC) profile by STREE analysis. (A) Distant metastasis ICI risk stratification based on STREE analysis of human papillomavirus (HPV)-positive and HPV-negative cohorts separately. 18, 11 CT of the risk groups segregated by receive partitioning analysis (RPA). RPA was performed on HPV-positive CT and HPV-negative CT cohorts separately. Two Patients and Methods. The clinicopathologic parameters included in the RPA were smoking status, age, and sex. Smoking (pack years) was not identified as significant in the RPA model for CT. The HPV-positive cohort continued to decline until 5 years, in contrast to the rising distant metastasis in the HPV-negative cohort observed beyond 3 years. The 5-year DC rates with chemotherapy RT alone and chemoradiation (CRT) were 75% and 92%, respectively, in the HPV-positive low-risk, ND subgroup (P = 0.03). UNC, Incidental control; OPC, oesophageal carcinoma.
b) Radiation Alone

- The Distant Control rates for +HPV low risk patients (T1-T3, N0-N2a, or less than 10 pack year N2b) was... similar between RT and CRT alone
- MD Anderson-Similar
- Would keep T3 out of LR group

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c) Surgery alone

Transoral Robotic Surgery Alone for Oropharyngeal Cancer

An Analysis of Local Control

Gregory S. Weinstein, MD; Harry Quam, MD; H. Jason Newman, MD; J. Ara Chalian, MD; Kelly Matlasy, MD; Alexander Lin, MD; Arati Desai, MD; Virginia A. Livohsi, MD; Kathleen T. Montone, MD; K. Roger Cohen, MD; Bert W. O'Malley Jr, MD

Under the treatment regimen of primary TORS and staged neck dissection without postoperative radiation, this cohort achieved local, regional, and distant disease control in 29 of 30 (97%), 27 of 30 (90%), and 30 of 30 (100%) cases, respectively, at a minimum follow-up of 18 months. Overall survival for this cohort at the time of last follow-up was 30 of 30 (100%), also at a minimum follow-up of 18 months.
Surgery + prn XRT/Chemo

Transoral Robotic Surgery for Advanced Oropharyngeal Carcinoma

Gregory S. Weinstein, MD; Bert W. O'Malley Jr, MD; Marc A. Cohan, MD; Harry Quon, MD

Table 2. TNM Staging of the 47 Study Patients

<table>
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<tr>
<th>T Stage</th>
<th>0</th>
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<th>2a</th>
<th>2b</th>
<th>2c</th>
<th>Total</th>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>8</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>5</td>
<td>1</td>
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<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>9</td>
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<tr>
<td>4</td>
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<td>1</td>
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<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>24</td>
<td>1</td>
<td>18</td>
<td>2</td>
<td>47</td>
</tr>
</tbody>
</table>

38% avoided chemotherapy and 11% avoided XRT

Lots of Enthusiasm(2012)


Conclusions: Enrollment has just completed with no data analysis available.
Data on PFS are premature.

A 2 year PFS of 85% or better will be considered worthy of further study.
2014

E1308: Reduced-dose IMRT in human papilloma virus (HPV)-associated resectable oropharyngeal squamous carcinomas (OPSCC) after clinical complete response (cCR) to induction chemotherapy (IC).


Median follow up was 23.4 months. This is from time of registration and includes three 21-day cycles of induction chemo and 2-3 weeks for assessment of response. Possible lead time bias? 3 Months

At 23 months, ECOG 1308 just MISSED it’s target

Conclusions: IC + reduced-dose Cetux-MRT produced high tumor control rates. Late toxicities were minimal. Pts with low dose pts achieved 84% PFS at 23mo and 95% 2-yr survival. Pts with <10 yrs smoking, T1-3 and NO-2o disease achieved 96% PFS. Further studies of reduced-dose MRT in chemoresponsive HPV+ pts are warranted. Clinical trial information: NCT01064083.

A 2 year PFS of 85% or better will be considered worthy of further study.
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:
- Positive Margins > 1 mm ECS or ≥ 4 metastatic LN

HIGH RISK:
- Positive Margins ≤ 1 mm ECS or ≤ 3 metastatic LN

Randomize:
- Radiation Therapy IMRT 50Gy/25 Fx
- Radiation Therapy IMRT 66 Gy/33 Fx + CDDP 40 mg/m² wkly

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

LOW RISK:
- T1-T2N0-N1 negative margins

23mo PFS (96% CI) 24mo OS (90% CI)

<table>
<thead>
<tr>
<th>Variable (n)</th>
<th>23mo PFS (96% CI)</th>
<th>24mo OS (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All reduced-dose pts (92)</td>
<td>0.64 (0.74, 0.90)</td>
<td>0.87 (0.74, 0.93)</td>
</tr>
<tr>
<td>T4A (7)</td>
<td>0.69 (0.29, 0.89)</td>
<td>0.86 (0.45, 0.97)</td>
</tr>
<tr>
<td>T1-T3(55)</td>
<td>0.85 (0.75, 0.92)</td>
<td>0.86 (0.83, 0.99)</td>
</tr>
<tr>
<td>II2C (19)</td>
<td>0.77 (0.56, 0.89)</td>
<td>0.95 (0.76, 0.99)</td>
</tr>
<tr>
<td>II0-II2b(43)</td>
<td>0.87 (0.75, 0.94)</td>
<td>0.95 (0.85, 0.95)</td>
</tr>
<tr>
<td>Smoker &gt; 10 pkyr (21)</td>
<td>0.71 (0.48, 0.85)</td>
<td>0.96 (0.71, 0.97)</td>
</tr>
<tr>
<td>Smoker ≤ 10 pkyr (40)</td>
<td>0.92 (0.81, 0.97)</td>
<td>0.97 (0.87, 0.995)</td>
</tr>
<tr>
<td>Smoker &lt; 10 pkyr, &lt; T1, N2c (n=27)</td>
<td>0.66 (0.32, 0.90)</td>
<td>0.96 (0.82, 0.99)</td>
</tr>
<tr>
<td>All standard-dose pts (15)</td>
<td>0.64 (0.39, 0.81)</td>
<td>0.87 (0.63, 0.99)</td>
</tr>
</tbody>
</table>
NRG HN002: A Randomized Phase II Trial for Patients with P16 Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer

Eligibility

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

44% of RTOG 1016 population eligible

Randomize

Central review p16+ IHC
- Declare Intent
- Unilateral vs Bilateral Neck XRT

STRATIFY

REGISTER

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

Waiting Until Hurricane Arthur Had Passed

Sometimes time clears the air....