Clinical Trial Update in HPV Associated Oropharynx Cancer

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Disclosures

- UNC School of Medicine
  – Employment

- ASTRO/AAPM Radiation Oncology Health Advisory Committee
  – Consultant

- Naveris
  – Scientific advisory board with equity
Learning Objectives

- Discuss de-intensified treatment for patients with HPV-Associated Oropharynx Cancer
- Define the utility of circulating HPV DNA
- Describe newer de-intensification treatment strategies

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**Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States**

↑28% in **all OPSCC**
2.6→3.6 cases/100k

↑225% in **HPV+ OPSCC**
0.8→2.6 cases/100k

↓50% in **HPV- OPSSC**
2.0→1.0 cases/100k

Chatruvedi et al, J Clin Oncol, 29(32), 2011
RTOG 0129

Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 year OS</td>
<td>93%</td>
<td>71%</td>
</tr>
</tbody>
</table>

Proposed Staging System for Patients With HPV-Related Oropharyngeal Cancer Based on Nasopharyngeal Cancer N Categories

Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study

Lancet Oncol 2015; 16:440-51
Standard Chemoradiotherapy for Oropharyngeal Cancer

**Primary RT (Stage 1-2):**
- 70 Gy @ 2 Gy (T1: 66 Gy)

**Chemo (Stage 3-4):**
- Concurrent Cisplatin (100 mg/m² q 3 wks)
- Induction ➔ T4, N3

**Neck dissection:**
- Only PET positive ~12 wks

*Many are cured but most live with QoL problems*

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**HPV**

RT: 70 Gy
Chemo: cisplatin (high dose)

ECOG 1308
Induction chemo
RT: 54 Gy
Chemo: cetuximab

Quarterback
Induction chemo
RT: 56 vs. 70 Gy
Chemo: carboplatin

RTOG 1016
RT: 70 Gy
Chemo: cisplatin vs cetuximab

Low Risk: Observation

ECOG 3311
Surgery
Intermediate Risk: 50 vs 60 Gy
High Risk: 66 Gy + cisplatin

UNC/UF
RT: 60 Gy
Chemo: cisplatin (low dose)
Rationale for Neoadjuvant Chemotherapy

• HPV associated OPX responds better to chemotherapy

• Omission/Reduction of Radiotherapy
  – 9 weeks of chemo for 1 week of RT
  – Minimally decreasing RT and Maximally increasing Chemo

• Improve Distant Control
  – HPV positive patients have more distant mets?
  – HPV positive patients distant mets are more aggressive?

Phase II study of N=80 patients
• Stage III/IV HPV-associated OPSCC
• Regardless of smoking status
Neoadjuvant chemotherapy (3 cycles, every 21 days)
• Cisplatin 75mg/m2
• Paclitaxel 90 mg/m2
• Cetuximab 400 mg/m2 (cycle 1 day 1), then 250mg/m2 weekly

Response to Induction chemotherapy
• Primary site = manual and endoscopic
• Nodal sites = palpation

cCR 54 Gy in 27 fx
cPR 69.3 Gy in 33 fx

70% had cCR at primary site
58% had cCR at nodal sites

Protocol deviations in 13 of 80 patients
5 with cCR primary site received 69.3 Gy
8 with cPR primary site received 54 Gy
All recurrences occurred in patients with > 10 pack years

Median f/u = 35 months

70 Gy + Cetuximab vs. Cisplatin

RTOG 1016

De-ESCALaTE:

<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>Grade 3: S 4.81 (4.74-4.87)</td>
<td>Grade 4: S 4.82 (4.80-4.83)</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>All grades 29.15 (29.09-29.18)</td>
<td>All grades 20.05 (20.03-20.07)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute short-term toxicities</td>
<td>Grade 3: S 4.43 (4.33-4.57)</td>
<td>Grade 4: S 4.35 (4.33-4.38)</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>All grades 19.96 (19.91-20.01)</td>
<td>All grades 20.35 (20.31-20.39)</td>
<td>0.64</td>
</tr>
<tr>
<td>Severe late toxicities</td>
<td>Grade 3: S 4.41 (4.39-4.43)</td>
<td>Grade 4: S 4.39 (4.37-4.41)</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>All grades 9.44 (9.43-9.45)</td>
<td>All grades 9.87 (9.85-9.89)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

I test used to compare treatment groups. No adjustments have been made for multiple testing. Toxicity assessed with Common Toxicity Criteria for Adverse Events, version 4.0.
Rational for Transoral Surgery

- **Omission/reduction of RT**
  - Single modality therapy ➔ significant reduction in toxicity
  - Pathological risk based assessment
  - 4 to 10 Gy reduction (70 Gy ➔ 66 to 60 Gy)

- **Omission of Chemotherapy**
  - Traditional indications ➔ positive margins and ECE
  - Used less often than indicated after TOS

Morbidity of Neck Dissection

Prior to TORS, we thought it was important to avoid neck dissection

TOS studies add neck dissection(s) but publications do not focus on endpoints reported in the 20 yrs of studies showing a high rate of moderate morbidity- especially with postop RT
**Primary endpoint: Dysphagia @ 1 year**

<table>
<thead>
<tr>
<th>1 year</th>
<th>Clinically meaningful decline*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT group</td>
</tr>
<tr>
<td>Total (primary endpoint)</td>
<td>86 (91%)</td>
</tr>
<tr>
<td>Global</td>
<td>89 (155.1)</td>
</tr>
<tr>
<td>Emotional</td>
<td>88 (122.6)</td>
</tr>
<tr>
<td>Functional</td>
<td>89 (115.1)</td>
</tr>
<tr>
<td>Physical</td>
<td>83 (144.1)</td>
</tr>
<tr>
<td>Composite (total score excluding global score)</td>
<td>86 (115.1)</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=0.042), global (p=0.037), emotional (p=0.042), functional (p=0.029), physical (p=0.064), and composite (p=0.062).

Table 2: Quality-of-life scores at 1 year for the MD Anderson Dysphagia Inventory
UNC Cancer Network Presented on October 22, 2019

For Educational Use Only

Phase II Evaluation of Aggressive Dose De-Escalation for Adjuvant Chemoradiotherapy in Human Papillomavirus–Associated Oropharynx Squamous Cell Carcinoma

UNC/UF Paradigm (1st generation, LCCC 1120)

Phase 2 Trial of De-intensified Chemoradiation Therapy for Favorable-Risk Human Papillomavirus–Associated Oropharyngeal Squamous Cell Carcinoma

- De-intensified Chemoradiotherapy
  - 60 Gy at 2 Gy/fx, daily, 6 weeks (IMRT)
  - Cisplatin 30mg/m², 6 weekly doses

Primary endpoint (IJROBP 2015):
- pCR rate = 86%

Secondary endpoints (Cancer 2018):
- 3 year PFS = 100%
- 3 year OS = 95%
- Global QoL returned to baseline
- Swallowing returned to baseline
- Dry mouth continues to improve > 1 year

All patients had biopsy of primary site and supraselective neck dissection
2nd Generation UNC Phase II De-Intensification Study (LCCC 1413)

• Eligibility
  – T0-3, N0 to N2c, M0 (AJCC 7th edition)
  – Oropharyngeal or Unknown primary
  – Squamous cell carcinoma, HPV and/or p16 +
  – Minimal smoking history

• De-intensified Chemoradiotherapy
  – 60 Gy at 2 Gy/fx, daily, 6 weeks (IMRT)
  – Cisplatin 30mg/m², 6 weekly doses

1) 12 week post-CRT PET/CT used to guide surgical evaluation
2) Omission of chemotherapy in T1-T2 N0-1
3) ≤ 30 pack years and ≥ 5 years abstinence were eligible
4) Other weekly chemotherapy regimens were allowed (weekly cisplatin is preferred, first choice)
5) Primary endpoint = 2 year Progression Free Survival
Enrolled Patients (N = 113)
1. T0 - 3 N0 – N2c M0
2. Squamous Cell Carcinoma
3. HPV positive and/or p16 positive
4. Minimal/moderate smoking history
5. Oropharyngeal Primary

Chemoradiotherapy (6 weeks)
60 Gy at 2 Gy/fx
Weekly Chemotherapy

Post-Treatment Response
(PET/CT & Fiberoptic Laryngoscopy)

Follow-up every 2-3 months X 2 years
Primary Endpoint: 2 year PFS

ClinicalTrials.gov, NCT02281955

Phase II Trial of De-Intensified Chemoradiotherapy for Human Papillomavirus–Associated Oropharyngeal Squamous Cell Carcinoma

Bhishamjit S. Chera, MD1,2; Robert J. Amdur, MD; Rebecca Green, MSW; Colette Shen, MD, PhD1,2; Gaorav Gupta, MD, PhD1,2; Xianning Tan, PhD2; Mary Knowles, ANP1; David Fried, PhD2; Neil Hayes, MPH, MD2; Jared Weiss, MD1,2; Juneko Grilley-Olsen, MD1,2; Shetal Patel, MD, PhD1,2; Adam Zanation, MD; Trevor Hackman, MD; Jose Zevallos, MPH, MD; Jeffrey Blumberg, MD; Samip Patel, MD; Mohit Kasibhatla, MD; Nathan Sheets, MD; Mark Weissler, MD; Wendell Yarbrough, MMHC, MD1,2; and William Mendenhall, MD3

Journal of Clinical Oncology®
### Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>N=114</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>62 (37-87)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>96</td>
<td>84%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>104</td>
<td>91%</td>
</tr>
<tr>
<td>Married</td>
<td>90</td>
<td>79%</td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>54</td>
<td>47%</td>
</tr>
<tr>
<td>&lt;= 10 pack years</td>
<td>38</td>
<td>33%</td>
</tr>
<tr>
<td>&gt;10 pack years</td>
<td>22</td>
<td>19%</td>
</tr>
<tr>
<td>T1-T2 Stage</td>
<td>96</td>
<td>84%</td>
</tr>
<tr>
<td>N0-1 Stage</td>
<td>96</td>
<td>84%</td>
</tr>
<tr>
<td>HPV/p16 status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV+/p16+</td>
<td>46</td>
<td>40%</td>
</tr>
<tr>
<td>HPV-/p16+</td>
<td>12</td>
<td>11%</td>
</tr>
<tr>
<td>HPV unk/p16+</td>
<td>56</td>
<td>49%</td>
</tr>
</tbody>
</table>

- 100% received 60 Gy
- Chemotherapy:
  - 89/114 (78%) received chemo
  - 57/89 (64%) received 6 doses cisplatin
  - 10/89 (11%) received cetuximab
- 11 patients had neck dissection (4 pathologically positive)

### 2 Year Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Control</td>
<td>96%</td>
</tr>
<tr>
<td>Regional Control</td>
<td>99%</td>
</tr>
<tr>
<td>Distant Metastasis Free Survival</td>
<td>91%</td>
</tr>
<tr>
<td>Progression Free Survival</td>
<td>86%</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>95%</td>
</tr>
</tbody>
</table>

### Overall Survival

- **Duration of follow-up**
  - Median = 31.8 months (1.1 to 51.4)
  - 92/114 (81%) had minimum of 2 years
EORTC QLQ C30 and H&N35

Global Quality of Life

Dry Mouth

Sticky Saliva

Difficulty Swallowing

Timepoint

Pre-treatment (n=108) 3 mo post tx (n=101) 6 mo post tx (n=66) 12 mo post tx (n=94) 24 mo post tx (n=63)

EORTC QLQ Score

Dry Mouth

Sticky Saliva

Difficulty Swallowing

PRO-CTCAE

4 = Very Severe
3 = Severe
2 = Moderate
1 = Mild
0 = None

Timepoint

Pre-treatment (n=108) 3 mo post tx (n=101) 6 mo post tx (n=66) 12 mo post tx (n=94) 24 mo post tx (n=63)
NRG-HN002: A Randomized Phase II Trial for Patients with p16-Positive, Non-Smoking-Associated, Locoregionally Advanced Oropharyngeal Cancer

Sue S Yom1, Pedro Torres-Saavedra2, Jimmy J Caudell3, John N Waldron4, Maura L Gillison5, Minh T Truong6, Richard Jordan1, Rathan M Subramaniam7, Min Yao8, Christine H Chung9, Jessica L Geiger10, Jason W Chen11, Brian O’Sullivan12, Dukagjin M Blakaj13, Loren K Mell14, Wade L Thorstad15, Christopher U Jones16, Robyn N Banerjee17, Christopher Lominska17, Quynh-Thu Le18

1University of California – San Francisco, 2NRG Oncology, 3Moffitt Cancer Center, 4Princess Margaret Hospital, 5M D Anderson Cancer Center, 6Boston Medical Center, 7University of Texas – Southwestern, 8Case Comprehensive Cancer Center, 9Cleveland Clinic, 10The Ohio State University, 11University of California - San Diego, 12Washington University School of Medicine, 13Sutter Cancer Research Consortium, 14Tom Baker Cancer Centre, 15University of Kansas, 16Stanford University

Annual Meeting of American Society for Radiation Oncology
Plenary Session - September 16, 2019

Schema

N = 308 randomized

AJCC 7th ed

Eligibility

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

Central review

p16+ IHC

Stratify

Declare Intent

Unilat vs Bilat Neck XRT

Randomize

Arm 1: 60 Gy XRT (2 Gy/fx) in 6 weeks + cisplatin 40 mg/m2 weekly x 6 cycles

Arm 2: 60 Gy XRT (2 Gy/fx) at 6 fractions/week for 5 weeks
Results: Primary PFS Endpoint

- Median follow-up is 2.6 years.
- 2-year PFS estimate for IMRT + C arm is 90.5% (95% CI 84.5-94.7%) with p=0.0350 rejecting the null hypothesis.
- 2-year PFS estimate for IMRT arm is 87.6% (95% CI 81.1-92.5%) with p=0.2284 failing to rejecting the null hypothesis.

The next NRG Oncology phase II study with two new experimental arms:
NRG-HN005: A Randomized Phase II/III Trial of De-intensified Radiation Therapy for Patients with Early Stage, p16-Positive, Non-Smoking-Associated Oropharyngeal Cancer

Eligibility
- Oropharynx SCCA
- p16+
- ≤10 pack-yr
- T1-2N1 or T3 N0-1

Randomized Phase

- 70 Gy in 6 weeks + cisplatin 100 mg/m2 q21 days x 2 cycles
- 60 Gy in 6 weeks + cisplatin 100 mg/m2 q21 days x 2 cycles
- 60 Gy in 5 weeks + nivolumab 240 mg q14 days x 6 cycles

Phase III Continuation
N = 104 additional pts PER ARM
Nested co-primary endpoints: PFS and MDADI

PROs: MDADI, HHIA-S, EORTC QLQ-C30, EQ-5D-5L Toxicity: CTCAE, PRO-CTCAE
3rd Generation
UNC Phase II De-Intensification Study
(LCCC 1612, ongoing)

Eligible Patient Population (N = 80)
1. T0 - 3 M - N0 - M0
2. Squamous Cell Carcinoma
3. HPV positive and/or p53 positive
4. Oropharyngeal Primary

Tumor genetics if > 10 pack year history

Chemosradiation (5 weeks)
45 Gy at 2 Gy/week
Weekly Chemotherapy

>10 pack years
p53 mutated

Circulating free HPV-DNA

Post-Treatment Response
PET/CT & Fiberoptic Laryngoscopy

Follow up every 2-3 months X 2 years
Primary Endpoint: 2 year PFS

TruSight Tumor Panel

- AKT1 exon 2
- ALK exon 23
- APC exon 15
- BRAF exon 11
- BRF exon 15
- CDH1 exon 8
- CDH1 exon 9
- CDH1 exon 12
- CTNNB1 exon 2
- EGFR exons 18-21
- ERBB2 exon 20
- FBXW7 exons 7 - 11
- FGFR2 exon 6
- FOX2L exon 1
- GNAQ exons 4-6
- GNAS exon 6
- GNAS exon 8
- KIT exon 9
- KIT exon 11
- KIT exon 13
- KIT exon 17
- KIT exon 18
- KRAS exons 1-4
- MAP2k exon 2
- MET exon 1
- MET exon 4
- MET exon 13
- MET exon 15
- MET exon 16
- MET exon 17
- MET exon 18
- MET exon 20
- MSH6 exon 5
- NRAS exons 1-4
- PDGFRA exon 11
- PDGFRA exon 13
- PDGFRA exon 17
- PIK3CA exon 1
- PIK3CA exon 2
- PIK3CA exon 7
- PIK3CA exon 9
- PIK3CA exon 20
- PTEN exons 1-7
- PTEN exon 9
- SMAD4 exon 8
- SMAD4 exon 11
- SRC exon 10
- STK11 exon 1
- STK11 exon 4
- STK11 exon 6
- STK11 exon 8
- TP53 exons 2-11
Multi-analyte digital PCR (dPCR) assay for ctHPVDNA

- Standardized multi-step analytical protocol to optimize specificity and sensitivity
- Distinguishes fragmented ctDNA from native viral genomes
- **Linear**: absolute quantification over 5 orders of magnitude (5-50,000 copies)
- **Precise**: Exceptional reproducibility
- **Sensitive**: Detects as few as 6 copies of HPV16 with ~80% sensitivity
- Detects ctHPV-16, -18, -31, -33, and -35 (more high-risk strains coming)

Cohort of 115 control subjects (healthy and non-HPV cancer patients) and 103 non-metastatic HPV-OPSCC patients (p16 IHC positive)

98% Specificity
89% Sensitivity

It is plausible that some of the 11 ctHPVDNA-negative patients were false positives of the p16 IHC assay, and may in fact be HPV negative OPSCC.
Variable kinetics of ctHPV16DNA clearance during CRT

Favorable ctHPV16DNA clearance profile correlates with disease control
LCCC 1912:
Not activated
R01 proposal

Figure 6: Clinical Trial Schema. All patients will receive definitive CRT of varying intensities depending upon 1) ctHPV16DNA risk and 2) smoking history. There will be 3 radiation dose levels in this study: 54 Gy, 60 Gy, and 70 Gy. The number of weekly chemotherapy doses patients received will be depend upon the intensity of radiation received (e.g. 54 Gy, will receive 5 weekly doses). ctHPVDNA will be assessed pre-treatment, weekly during CRT, and post-treatment. Additionally, we will perform tumor genomic profiling and assess association with disease control. Patient reported outcomes will be prospectively collected.

Plasma Circulating Tumor HPV DNA for Early Detection of Cancer Recurrence in HPV-associated Oropharyngeal Cancer
**HPV-associated Oropharyngeal Cancer**

- Rising prevalence
- Lower rate of recurrence
- More sensitive to therapy (RT, chemo)
- Ongoing efforts to de-intensify therapy

**~15% will recur**

- Unusual sites/timing of recurrence
- Recurrence is potentially salvageable
- Better survival after relapse (~55% @ 2 years)

---

**Plasma ctHPVDNA is a circulating biomarker for HPV-associated oropharyngeal cancer**

- ~90% sensitivity and >98% specificity for detection of localized disease
- ctHPVDNA can be used to monitor response to therapy
  - Localized disease
  - Recurrent/metastatic disease

**Unanswered Question:** Can ctHPVDNA be used to monitor for disease recurrence in patients who have been treated with curative intent therapy?

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*Cited References*

- Chera BS et al. Clin Cancer Res. 2019
- Damerla RR et al. JCO Precision Oncol. 2019
### Prospective Biomarker Study Design

**Setting:**
Academic medical centers – UNC-CH, UNC-Rex, and Univ of Florida

**Patients:**
115 patients with p16+ stage I-III oropharyngeal cancer treated with chemoradiation

**Followup:**
Clinical exams every 2 - 4 months for years 1 - 2, every 6 months for years 3 – 5;  
Chest imaging every 6 months. Median follow-up 23 months

**ctHPVDNA Testing:**
Blood specimens collected every 6-9 months during followup;  
Analyzed for ctHPVDNA using an optimized, multi-analyte dPCR assay

**Study Endpoints:**
Measurement of **Negative Predictive Value (NPV)** and **Positive Predictive Value (PPV)** for ctHPVDNA-based detection of recurrent/metastatic disease

**Disease Events:**
12/115 patients developed biopsy-proven recurrent/metastatic disease  
(1 local and distant; 2 regional only; 1 regional and distant; 8 distant only)

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### Case Example

<table>
<thead>
<tr>
<th>T1N1 L BOT SCC (p16+)</th>
<th>PET → CR</th>
<th>Neck/Chest CT → NED</th>
<th>PET → biopsy bone metastasis</th>
</tr>
</thead>
<tbody>
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</tr>
</tbody>
</table>

![Graph showing ctHPVDNA (copies/mL) over days post-CRT](image)
ctHPVDNA relapse predicts clinical recurrence

**Undetectable ctHPVDNA during surveillance**
- N = 87
- 0/87 with recurrence
- NPV = 100%

**Detectable ctHPVDNA during surveillance**
- N = 28
- 15/28 with recurrence
- PPV = 54% single +ve test
- PPV = 94% two consecutively +ve tests

ctHPVDNA relapse predicts clinical recurrence

- cHPVDNA positive, 2x (n = 16)
- cHPVDNA negative (n = 99)

****, P<0.0001
Early detection of recurrence by ctHPVDNA

Median Lead Time = 100 days

ctHPVDNA-based monitoring to facilitate oligorecurrence clinical trials
Conclusions

- Plasma ctDNA tests can have high NPV and PPV for early detection of cancer recurrence
- Some patients may develop a transient spike in ctDNA without clinical recurrence (possible immune clearance?) → opportunity for early intervention?
- ctDNA monitoring can lead to earlier detection of recurrent/metastatic disease
  - Greater incidence of oligorecurrence?
  - Greater efficacy of salvage therapy?
  - Opportunity to conduct oligorecurrence clinical trials
- Cost-efficient assays for ctDNA monitoring can reduce the overall cost of post-treatment surveillance by eliminating radiographic scans in patients who remain ctDNA negative

PIK3CA mutation is an adverse prognostic factor in HPV-associated oropharynx cancer

Beaty BT¹, DH Moon¹, CJ Shen¹, RJ Amdur², J Weiss³,⁴, J Grilley-Olson³,⁴, S Patel³,⁴, A Zanation⁵, T Hackman⁶, B Thorp⁶, J Blumberg⁶, SN Patel⁶, M Weissler⁶, WG Yarbrough⁶, NC Sheets¹, J Parker⁴, DN Hayes⁷, WM Mendenhall², R Dagan², X Tan³, GP Gupta¹,³, BS Chera¹

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³UNC Lineberger Comprehensive Cancer Center, University of North Carolina Hospitals, Chapel Hill, NC
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⁵Department of Otolaryngology, University of North Carolina, Chapel Hill, NC
⁶Department of Genetics, University of North Carolina, Chapel Hill, NC
⁷Department of Medical Oncology, University of Tennessee, Memphis, TN
**PIK3CA mutations**

- PI-3K is an important oncogene, and mutations in its p110α subunit (PIK3CA) have been associated with adverse outcomes in cervical SCC
- HPV+ HNSCC patients have lower overall mutational burden, but significantly increased incidence of PIK3CA mutations (Stransky, 2011)
- Unclear if PIK3CA mutations affect outcomes in OPSCC

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**PIK3CA mutations in p16+ OPSCC**

**LCCC 1413/1612 phase II trials**

Inclusion criteria:
- Age >18 years old
- ECOG 0-1
- T0-3, N0-2c OPSCC (N0-2; 8th ed)
- p16+ (IHC) or HPV+ (ISH)

**Sequencing**
- LCCC 1413: UNCseq
- LCCC 1612 (> 10 py): UNCseq, Illumina solid tumor mutation panel

**De-intensified chemoRT**
- 60Gy IMRT → 70Gy if TP53 mutation[+]
- Cisplatin (weekly 30mg/m² - 1st choice)
- T0-2N0-1, < 10py smoking – RT alone

77 patients with sequencing data (34/77 with mutations)
**PIK3CA mutations in p16+ OPSCC**

![PIK3CA Mutations](image)

Tumor sequencing mutational profile. Each box represents one patient, grey indicates no mutations.

- 16 **PIK3CA**, 4 **PTEN**, 3 **KRAS**, 3 **FBXW7**, 3 **FGFR3**, 2 **TP53**

---

**Sites of PIK3CA mutations in p16+ OPSCC**

![Sites of PIK3CA Mutations](image)

Common sites of PIK3CA mutation (16 patients total)
- E545K – 8
- E542K – 2

Modified from Berg, 2013
### PIK3CA mutations in p16+ OPSCC

#### Clinical characteristic

<table>
<thead>
<tr>
<th></th>
<th>N=77 (%)</th>
<th>WT-PIK3CA (n=61)</th>
<th>PIK3CA mutated (n=16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>60</td>
<td>53</td>
<td>60</td>
<td>0.53</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>66 (86%)</td>
<td>53 (85%)</td>
<td>13 (81%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Female</td>
<td>11 (14%)</td>
<td>9 (15%)</td>
<td>2 (12%)</td>
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</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>23 (30%)</td>
<td>17 (28%)</td>
<td>6 (38%)</td>
<td>0.68</td>
</tr>
<tr>
<td>&lt; 10 years</td>
<td>21 (27%)</td>
<td>16 (26%)</td>
<td>5 (31%)</td>
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<tr>
<td>&gt; 10 years</td>
<td>23 (30%)</td>
<td>17 (28%)</td>
<td>6 (38%)</td>
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<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>T0</td>
<td>5 (7%)</td>
<td>4 (7%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>18 (23%)</td>
<td>14 (23%)</td>
<td>4 (25%)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>50 (65%)</td>
<td>39 (64%)</td>
<td>11 (69%)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>4 (5%)</td>
<td>4 (7%)</td>
<td>0</td>
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<tr>
<td>Nodal stage (7th edition)</td>
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<td></td>
</tr>
<tr>
<td>N0</td>
<td>7 (9%)</td>
<td>5 (8%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>10 (13%)</td>
<td>10 (16%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>N2a</td>
<td>3 (5%)</td>
<td>2 (3%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>N2b</td>
<td>47 (61%)</td>
<td>37 (61%)</td>
<td>10 (63%)</td>
<td></td>
</tr>
<tr>
<td>N2c</td>
<td>11 (14%)</td>
<td>7 (11%)</td>
<td>3 (19%)</td>
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</tr>
<tr>
<td>N3</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Radiation dose</td>
<td></td>
<td></td>
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<td>0.47</td>
</tr>
<tr>
<td>60 Gy</td>
<td>55 (97%)</td>
<td>55 (97%)</td>
<td>16 (100%)</td>
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</tr>
<tr>
<td>70 Gy</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
<td>0</td>
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<tr>
<td>Concurrent chemotherapy / systemic therapy</td>
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<td>0.82</td>
</tr>
<tr>
<td>Yes</td>
<td>66 (86%)</td>
<td>55 (90%)</td>
<td>11 (69%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11 (14%)</td>
<td>6 (10%)</td>
<td>2 (13%)</td>
<td></td>
</tr>
</tbody>
</table>

#### Median f/u – 2 years
- 9 patients had disease recurrence, no deaths
  - 2 regional only, 4 distant only, 3 regional and distant
  - 5/9 patients w/ recurrence had PIK3CA mutations, no patients with other cancer-associated mutations had recurrence
- 5 patients with PIK3CA mutations and recurrence - 2 E542K, 2 E545K, 1 E726K
• On MVA, PIK3CA mutation was the only variable associated with disease recurrence

Discussion

• Pittsburgh retrospective series – 75 HPV+ OPSCC patients treated with surgery → adjuvant (chemo)RT (64/75), similar to our cohort, but 13% T4 or N3

• Recurrences / DFS not reported
• Could PIK3CA mutated patients may have worse outcomes after de-escalated CRT, but similar DSS to WT-PIK3CA patients after surg/RT?

Chiosea, BMC Cancer 2013
Harbison, JCI Insight 2018
Conclusions

• PIK3CA mutations present in ~20% of HPV-associated OPSCC
• PIK3CA mutations were associated with worse outcomes in HPV+ OPSCC patients treated with de-intensified CRT, independent of T/N stage or smoking history
  – 3 year DFS – 92% (WT) vs. 64% (mutated)
• Limitations: small sample size, limited availability of NGS
• In the future, PIK3CA mutational status may be used to better select OPSCC patients for de-intensified chemoradiation

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