Clinical Trial Update in HPV Associated Oropharynx Cancer

Bhisham Chera, MD
Associate Professor
Associate Chair Clinical Operations and Improvement
Director Patient Safety and Quality
Department of Radiation Oncology
UNC Lineberger Comprehensive Cancer Center
UNC School of Medicine
University of North Carolina at Chapel Hill

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
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- OPSCC
  - 2.0-1.0 cases/100k

RTOG 0129

- Low Risk: 3 year OS 93%
- Intermediate Risk: 3 year OS 71%
- High Risk: 3 year OS 40%
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/m^2 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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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 site = palpation

10% had cCR at primary site
6% 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

Median f/u = 35 months

All recurrences occurred in patients with > 10 pack years

70 Gy + Cetuximab vs. Cisplatin
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 ➔ 60 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.
UNC Cancer Network

Presented on October 22, 2019

71% postop RT
24% postop chemo

Primary endpoint: Dysphagia @ 1 year

Mayo Clinic
2 year LRC = 96%

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

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

All patients had biopsy of primary site and supraselective neck dissection

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

~9 weeks
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

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2nd Generation Phase II
(Major Differences)

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

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Schema LCCC 1413 (De-intensification #2)

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

Patient reported assessments of Symptoms and Quality of Life
Clinician assessments of Toxicity
X Modified Barium Swallow (pre-CRT & 6 months post-CRT)

ClinicalTrials.gov, NCT02281955

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

Mehrotra S, Choo, MD†, Bobak J, Arndt, MD, MPH, Bhavna Grewal, MD, MPH, G. Scott Hess, MD, PhD,†, T. Anna Goyal, MD, PhD,†, Darrin C. Paylor, MD, Michael R. Heelan, MD, MPH,†, Robert Capeci, MD, MPH,†, Michael Asbeck, MD,†, J. Scott Albritton, MD, PhD,†, Evan M. Fishbein, MD,†, William H. Byhardt, MD,†, and William E. Fazio, MD,†

Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=114</th>
<th>%</th>
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</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>≤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>
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<tr>
<td>Chemotherapy:</td>
<td></td>
<td></td>
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<tr>
<td>60 Gy</td>
<td>100%</td>
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<tr>
<td>89/114 (78%) received chemo</td>
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<tr>
<td>57/89 (64%) received 6 doses cisplatin</td>
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<td></td>
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<tr>
<td>18/89 (11%) received cetuximab</td>
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<tr>
<td>Neck dissection (4 pathologically positive)</td>
<td>11 patients</td>
<td></td>
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Overall Survival

<table>
<thead>
<tr>
<th>Outcome</th>
<th>2 Year Outcomes</th>
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<tbody>
<tr>
<td>Local Control</td>
<td>96%</td>
</tr>
<tr>
<td>Regional Control</td>
<td>96%</td>
</tr>
<tr>
<td>Distant Metastasis-Free Survival</td>
<td>93%</td>
</tr>
<tr>
<td>Progression-Free Survival</td>
<td>88%</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>96%</td>
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</tbody>
</table>

2 Year Outcomes

Overall Survival

- Median follow-up: 31.8 months (1.1 to 51.4)
- 92/114 (81%) had minimum of 2 years

Duration of follow-up

- Median = 31.8 months (1.1 to 51.4)
**Schema**

N = 308 randomized

- AJCC 7th ed
- Eligibility
  - OP 6CC
  - ≤10 pack-year
  - T1-T2 N1-N2b
  - T3 N0-N2b

**Randomize**

- Intention
- Uni or Bilat
- Neck XRT

**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

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**Results: Primary PFS Endpoint**

- Median follow-up is 2.6 years.
- 2-year PFS estimate for IMRT + C arm is 86.5% (95% CI 81.5-91.7%) with p=0.0150 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 reject the null hypothesis.

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**The next NRG Oncology phase II study with two new experimental arms:**

NRG-HN005: A Randomized Phase II Trial of De-intensified Radiation Therapy for Patients with Early Stage, p16-Positive, Non-Smoking-Associated Oropharyngeal Cancer

- Eligibility
  - Oropharynx
  - SCCA
  - ≥18 yrs

**Randomized Phase**

- N = 399

**Phase III Continuation**

- N = 104 additional pts PER ARM

**Nested co-primary endpoints:**

- PFS and MDADI
  - N = 399

**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**

**70 Gy in 6 weeks + cisplatin 100 mg/m² q21 days x 2 cycles**

**1 or 2 experimental arms**
3rd Generation
UNC Phase II De-Intensification Study
(LCCC 1612, ongoing)

TruSight Tumor Panel

- AKT1 exon 2
- ALK exon 23
- APC exon 15
- BRCA1 exon 5
- BRCA2 exon 15
- CEB1 exon 15
- CDK4R exon 15
- CTNNB1 exon 2
- DCC exon 10-13
- DKK2 exon 18
- DNM2 exon 1-13
- FGFR1 exon 6
- FGFR4 exon 12-14
- GNAS exon 1-6
- GNAS exon 8
- GNAS exon 9
- HG1 exon 5
- KIT exon 9
- KIT exon 11
- KIT exon 13
- KIT exon 17
- KIT exon 18
- KRAS exons 1-4
- MAP2K1 exon 2
- MET exon 1
- MET exon 5
- MET exon 11
- 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 exons 1-20
- PIK3CA exon 7
- PIK3CA exon 9
- PIK3CA exon 20
- PTEN exons 1 -7
- PTEN exons 9
- PTEN exon 11
- PTEN exon 12
- PTEN exon 13
- PTEN exon 14
- PTEN exon 15
- PTEN exon 16
- PTEN exon 17
- PTEN exon 18
- PTEN exon 20
- TP53 exons 2-11
- TP53 exon 5
- TP53 exon 12
- TP53 exon 13
- TP53 exon 14
- TP53 exon 15
- TP53 exon 16
- TP53 exon 17
- TP53 exon 18
- TP53 exon 20

- 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)

Chera B, …, Gupta G ASTRO 2017
Gupta G, …, Chera B ASTRO/ASCO 2018
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 ctHPV DNA-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

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?

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)

Case Example

<table>
<thead>
<tr>
<th>Days post-CRT</th>
<th>ctHPVDNA (copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>100</td>
<td>101</td>
</tr>
<tr>
<td>200</td>
<td>102</td>
</tr>
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<td>300</td>
<td>103</td>
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<tr>
<td>400</td>
<td>104</td>
</tr>
<tr>
<td>500</td>
<td>105</td>
</tr>
</tbody>
</table>

Chera BS et al Clin Cancer Res. 2019
Damerla RR et al JCO Precision Oncol. 2019
Hanna GJ et al Ann Oncol. 2018
ctHPVDNA relapse predicts clinical recurrence

Undetectable ctHPVDNA during surveillance

N = 87
DET with recurrence NPV = 100%

Detectable ctHPVDNA during surveillance

N = 28
SGS with recurrence PPV = 54%

ctHPVDNA relapse predicts clinical recurrence

ChemoRT Surveillance

N = 87
0/87 with recurrence
NPV = 100%

ChemoRT Surveillance

N = 28
15/28 with recurrence
PPV = 54%

Early detection of recurrence by ctHPVDNA

Median Lead Time = 100 days
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.
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

PIK3CA mutations in p16+ OPSCC

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 1413/1612 phase II trials
  - UNCseq, Illumina solid tumor mutation panel
  - 77 patients with sequencing data (34/77 with mutations)

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

Tumor sequencing mutational profile. Each box represents one patient, grey indicates no mutations.
- 16 PIK3CA, 4 PTEN, 3 KRAS, 3 FGFR3, 2 TP53
Sites of PIK3CA mutations in p16+ OPSCC

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

* Modified from Berg, 2013

PIK3CA mutations in p16+ OPSCC

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 - E542K, E545K, E726K
PIK3CA mutations in p16+ OPSCC

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?

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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Our Patients
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