Clinical Trial Update in HPV Associated Oropharynx Cancer

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1

Disclosures

- UNC School of Medicine
  - Employment
- ASTRO/AAPM Radiation Oncology Health Advisory Committee
  - Consultant
- Naveris
  - Scientific advisory board with equity

2

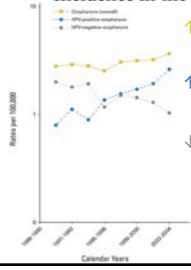
Learning Objectives

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

3

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States



↑28% in all OPSCC
2.6→3.6 cases/100k

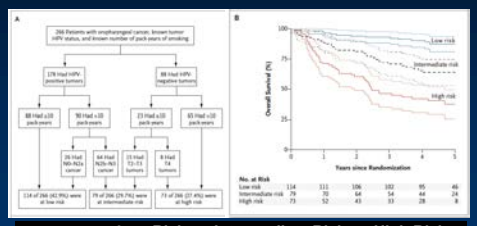
↑225% in HPV+ OPSCC
0.8→2.6 cases/100k

↓50% in HPV- OPSSC
2.0→1.0 cases/100k

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

4

RTOG 0129 Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer



	Low Risk	Intermediate Risk	High Risk
3 year OS	93%	71%	46%

5

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

J Clin Oncol 34. © 2016

Kristina R. Dahlstrom, Adam S. Garden, William N. William Jr, Ming Yann Lim, and Erich M. Sturgis

	T1	T2	T3	T4
N0	IA	IB	II	III
N1	IA	IB	II	III
N2	IA	IB	II	III
N3	II	II	II	III

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 2016; 17: 440-51

6

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

7

Standard		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
ECOG 3311	Surgery	Low Risk: Observation Intermediate Risk: 50 vs 60 Gy High Risk: 66 Gy + cisplatin
UNC/UF		RT: 60 Gy Chemo: cisplatin (low dose)

8

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?

9

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

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

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

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

→ Protocol deviations in 13 of 80 patients
5 with cCR primary site received 69.3 Gy
8 with cPR primary site received 54 Gy

J Clin Oncol 34. © 2016

10

All recurrences occurred in patients with > 10 pack years

Table 3. Two-Year PFS and OS in Subsets Treated in the E1308 Trial

Cohort	2-Year PFS (95% CI)	2-Year OS (95% CI)
All patients (N = 80)	0.78 (0.67 to 0.86)	0.91 (0.82 to 0.96)
cCR to IC, RND 54 Gy (n = 51)	0.80 (0.65 to 0.89)	0.94 (0.84 to 0.98)
All cCR/PR/SD to IC, RRD ≤ 54 Gy (n = 62)	0.81 (0.69 to 0.89)	0.93 (0.83 to 0.97)
SPD[a]	0.67 (0.39 to 0.85)	0.67 (0.56 to 0.96)
Subsets cCR to IC, treated on RRD (n = 51)		
Cohort	0.80 (0.71 to 0.87)	0.97 (0.79 to 0.999)
Smoker > 10 pk-yr[b]	0.65 (0.41 to 0.82)	0.90 (0.66 to 0.97)
Smoker ≤ 10 pk-yr, and < T4N2c[b]	0.85 (0.71 to 0.93)	0.95 (0.71 to 0.99)
Smoker > 10 pk-yr or T4 or N2c[b]	0.69 (0.49 to 0.83)	0.93 (0.75 to 0.98)
Non-T4a (n = 45)	0.84 (0.69 to 0.92)	0.95 (0.83 to 0.99)
T4a[a]	0.50 (0.11 to 0.80)	0.83 (0.27 to 0.97)
N2c[a]	0.73 (0.44 to 0.89)	0.93 (0.61 to 0.99)
Non-N2c (n = 36)	0.82 (0.65 to 0.92)	0.94 (0.79 to 0.98)

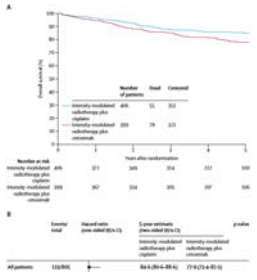
Abbreviations: cCR, complete clinical response; IC, induction chemotherapy; pk-yr, pack-year; OS, overall survival; PFS, progression-free survival; PR, partial response; RRD, reduced radiation dose; SD, stable disease; SRD, standard radiation dose.

Median f/u = 35 months

11

70 Gy + Cetuximab vs. Cisplatin

RTOG 1016



De-ESCALaTE:

	Cisplatin plus radiotherapy (95% CI)	Cetuximab plus radiotherapy (95% CI)	p value
Primary outcome			
Overall			
Grade 3–5	4·81 (4·23–5·40)	4·82 (4·22–5·43)	0·98
All grades	29·15 (27·33–30·97)	30·05 (28·26–31·85)	0·49
Secondary outcomes			
Acute short-term toxicities			
Grade 3–5	4·43 (3·88–4·97)	4·35 (3·84–4·86)	0·84
All grades	19·96 (18·81–21·12)	20·35 (19·18–21·52)	0·64
Severe late toxicities			
Grade 3–5	0·41 (0·29–0·54)	0·48 (0·30–0·67)	0·53
All grades	9·44 (8·53–10·34)	9·87 (9·03–10·72)	0·49

t 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.

Table 2: **Mean number of acute, late, and overall toxicity events per patient, by treatment group**

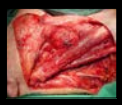
12

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

13

Morbidity of Neck Dissection

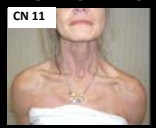


Prior to TORS, we thought it was important to avoid neck dissection

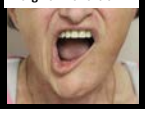
TOS studies add neck dissection(s) but publications do not focus on endpoints reported in the 20 yrs of studies showing a high rate of moderate morbidity- especially with postop RT

Fibrosis and cosmesis

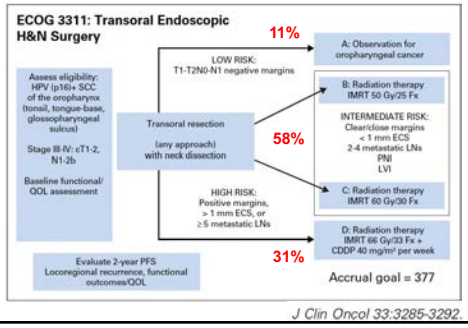
CN 11



Marginal Mandiblar N



14



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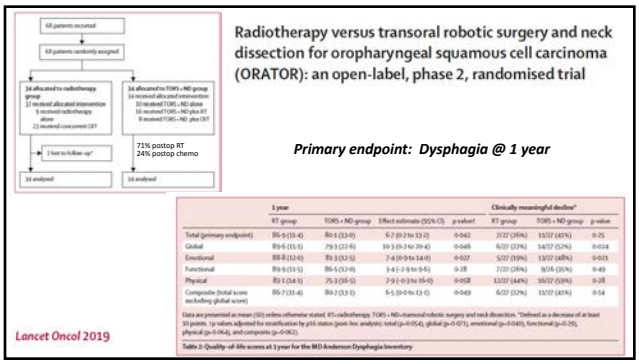
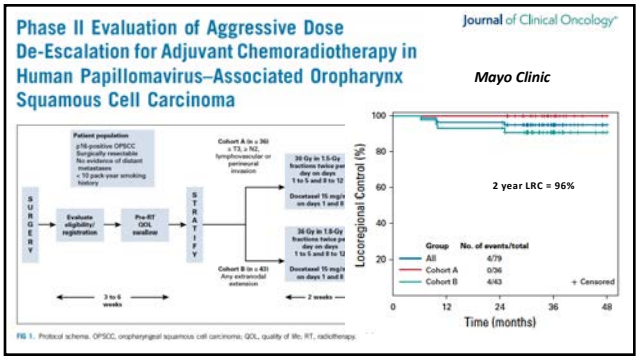
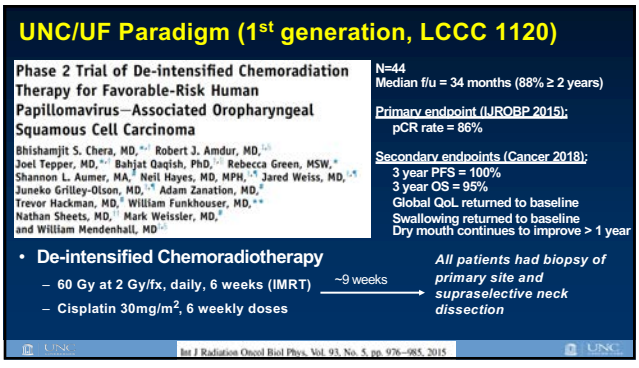

Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial
Primary endpoint: Dysphagia @ 1 year
71% postop RT
24% postop chemo
Lancet Oncol 2019

16


Phase II Evaluation of Aggressive Dose De-Escalation for Adjuvant Chemoradiotherapy in Human Papillomavirus–Associated Oropharynx Squamous Cell Carcinoma
Journal of Clinical Oncology
Mayo Clinic
2 year LRC = 96%
Locoregional Control (%)
Time (months)
Censored

17


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
N=44
Median f/u = 34 months (88% ≥ 2 years)
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
De-intensified Chemoradiotherapy
60 Gy at 2 Gy/fx, daily, 6 weeks (IMRT)
Cisplatin 30mg/m2, 6 weekly doses
~9 weeks
All patients had biopsy of primary site and supraselective neck dissection
Int J Radiation Oncol Biol Phys, Vol. 93, No. 5, pp. 976–985, 2015

18

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/m^2, 6 weekly doses

RT → 10 Gy reduction
Chemo → 40% reduction

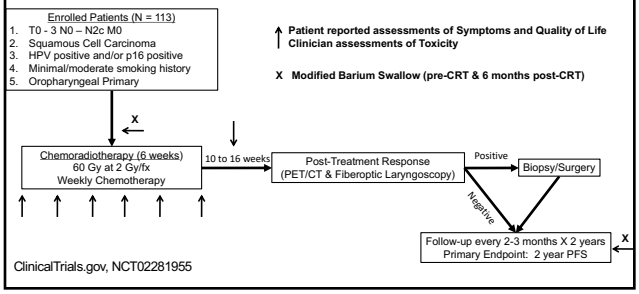
19

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

20

Schema LCCC 1413 (De-intensification #2)



21

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

Bhishamjit S. Chera, MD[1,2]; Robert J. Amdur, MD[1]; Rebecca Green, MSW[1]; Colette Shen, MD, PhD[1,2]; Gaorav Gupta, MD, PhD[1,2]; Xianming Tan, PhD[2]; Mary Knowles, ANP[1]; David Fried, PhD[1]; Neil Hayes, MPH, MD[4]; Jared Weiss, MD[1,2]; Juneko Grilley-Olson, MD[1,2]; Shetal Patel, MD, PhD[1,2]; Adam Zanation, MD[2]; Trevor Hackman, MD[2]; Jose Zevallos, MPH, MD[5]; Jeffrey Blumberg, MD[1]; Samip Patel, MD[1]; Mohit Kasibhatla, MD[6]; Nathan Sheets, MD[7]; Mark Weissler, MD[1]; Wendell Yarbrough, MMHC, MD[1,2]; and William Mendenhall, MD[3]

Journal of Clinical Oncology

22

Patient Characteristics

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

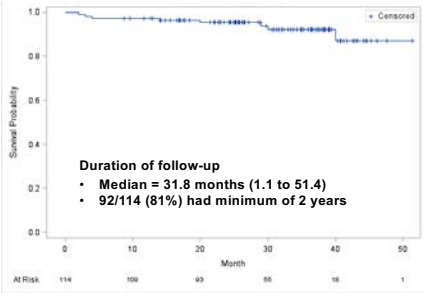
- 100% received 60 Gy
- Chemotherapy:
  - 89/114 (78%) received chemo
  - 57/89 (64%) received 6 doses cisplatin
  - 10/89 (11%) received cetuximab
- 11 patients had neck dissection (4 pathologically positive)

23

2 Year Outcomes

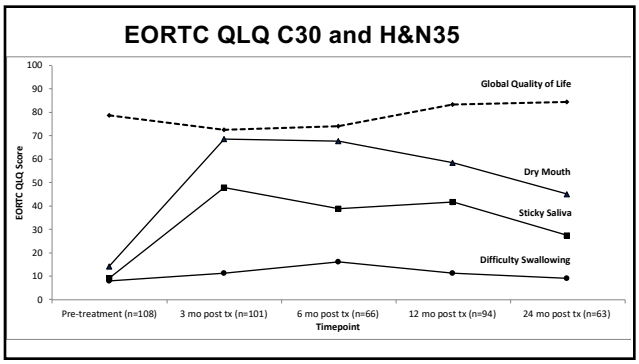
Local Control	96%
Regional Control	99%
Distant Metastasis Free Survival	91%
Progression Free Survival	**86%**
Overall Survival	95%

Overall Survival

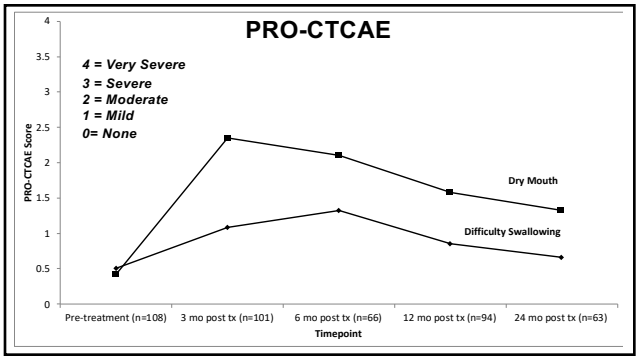


Duration of follow-up
- Median = 31.8 months (1.1 to 51.4)
- 92/114 (81%) had minimum of 2 years

24


EORTC QLQ C30 and H&N35
EORTC QLQ Score
Global Quality of Life
Dry Mouth
Sticky Saliva
Difficulty Swallowing
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)
Timepoint

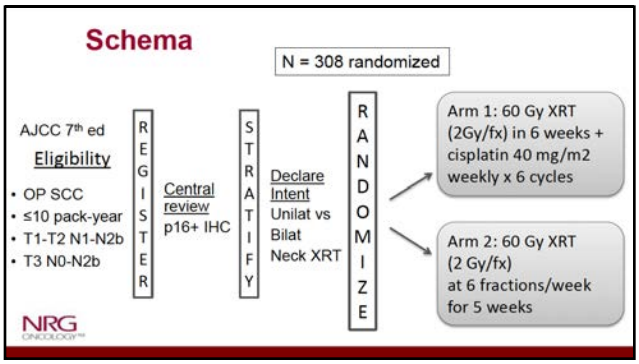
25


PRO-CTCAE
4 = Very Severe
3 = Severe
2 = Moderate
1 = Mild
0= None
PRO-CTCAE Score
Dry Mouth
Difficulty Swallowing
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)
Timepoint

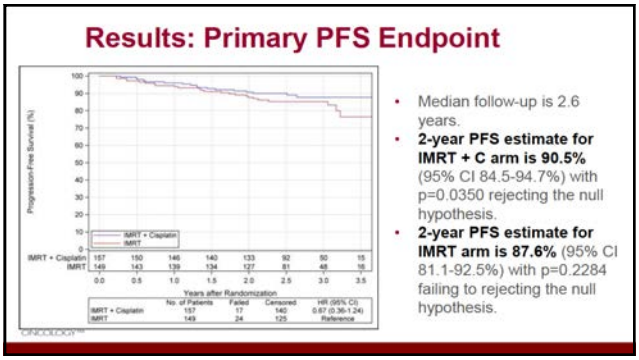
26


NRG ONCOLOGY
Advancing Research. Improving Lives.™
NRG-HN002: A Randomized Phase II Trial for Patients with p16-Positive, Non-Smoking-Associated, Locoregionally Advanced Oropharyngeal Cancer
Sue S Yom[1], Pedro Torres-Saavedra[2], Jimmy J Caudell[3], John N Waldron[4], Maura L Gillison[5], Minh T Truong[6], Richard Jordan[1], Rathan M Subramaniam[7], Min Yao[8], Christine H Chung[9], Jessica L Geiger[9], Jason W Chan[1], Brian O'Sullivan[4], Dukagjin M Blakaj[10], Loren K Mell[11], Wade L Thorstad[12], Christopher U Jones[13], Robyn N Banerjee[14], Christopher Lominska[15], Quynh-Thu Le[16]
[1]University of California – San Francisco, [2]NRG Oncology, [3]Moffitt Cancer Center, [4]Princess Margaret Hospital, [5]M D Anderson Cancer Center, [6]Boston Medical Center, [7]University of Texas – Southwestern, [8]Case Comprehensive Cancer Center, [9]Cleveland Clinic, [10]The Ohio State University, [11]University of California - San Diego, [12]Washington University School of Medicine, [13]Sutter Cancer Research Consortium, [14]Tom Baker Cancer Centre, [15]University of Kansas, [16]Stanford University
Annual Meeting of American Society for Radiation Oncology
Plenary Session - September 16, 2019

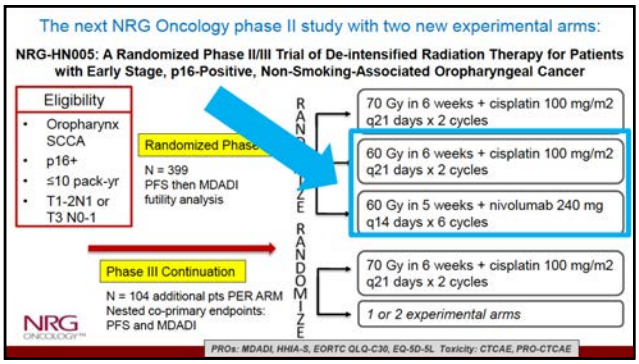
27


Schema
N = 308 randomized
AJCC 7th ed
Eligibility
• OP SCC
• ≤10 pack-year
• T1-T2 N1-N2b
• T3 N0-N2b
REGISTER
Central review p16+ IHC
STRATIFY
Declare Intent
Unilat vs Bilat Neck XRT
RANDOMIZE
Arm 1: 60 Gy XRT (2Gy/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
NRG

28

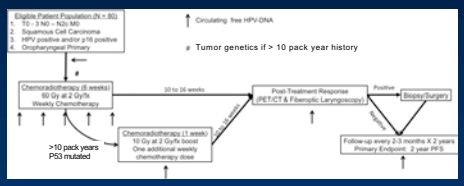

Results: Primary PFS Endpoint
Progression-Free Survival (%)
IMRT + Cisplatin
IMRT
Years after Randomization
• Median follow-up is 2.6 years.
• 2-year PFS estimate for IMRT + C arm is 90.5% (95% CI 84.5-94.7%) with p=0.0350 rejecting the null hypothesis.
• 2-year PFS estimate for IMRT arm is 87.6% (95% CI 81.1-92.5%) with p=0.2284 failing to rejecting the null hypothesis.

29


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
N = 399
PFS then MDADI
futility analysis
RANDOMIZE
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
RANDOMIZE
70 Gy in 6 weeks + cisplatin 100 mg/m2 q21 days x 2 cycles
1 or 2 experimental arms
PROs: MDADI, HNIA-S, EORTC QLQ-C30, EQ-5D-5L Toxicity: CTCAE, PRO-CTCAE
NRG

30

3rd Generation UNC Phase II De-Intensification Study (LCCC 1612, ongoing)



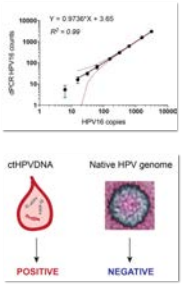
31

TruSight Tumor Panel

- AKT1 exon 2
- ALK exon 23
- APC exon 15
- BRAF exon 11
- BRAF 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 exon17
- 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

32

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)*

Chera B, …, Gupta G *ASTRO* 2017
Gupta G, …, Chera B *ASTRO/ASCO* 2018

33

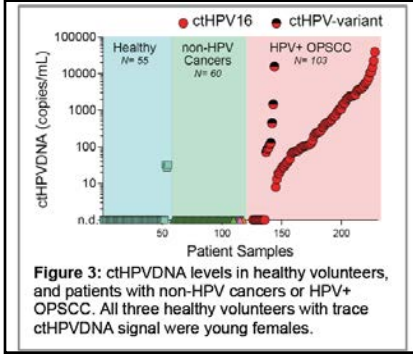


Figure 3: ctHPVDNA levels in healthy volunteers, and patients with non-HPV cancers or HPV+ OPSCC. All three healthy volunteers with trace ctHPVDNA signal were young females.

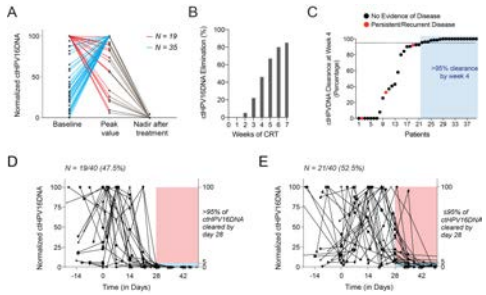
Cohort of 115 control subjects (healthy and non-HPV cancer patients) and 103 non-metastatic HPV-OPSCC patients (p16 IHC positive)

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.

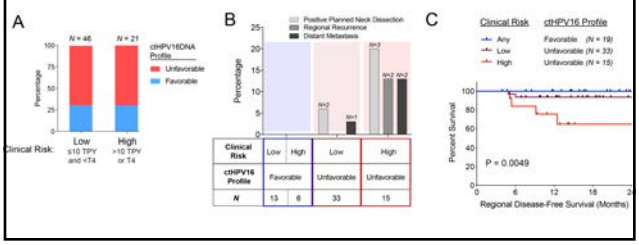
34

Variable kinetics of ctHPV16DNA clearance during CRT



35

Favorable ctHPV16DNA clearance profile correlates with disease control



36

LCCC 1912:
Not activated
R01 proposal

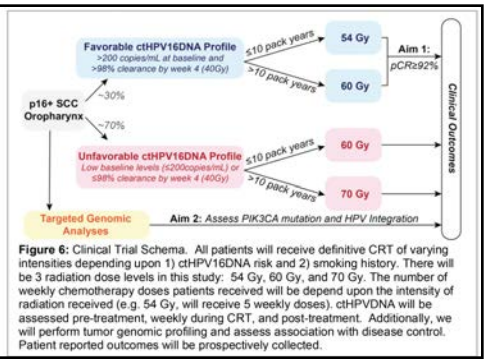


Figure 6: Clinical Trial Schema. All patients will receive definitive CRT of varying intensities depending upon 1) ctHPV16DNA risk and 2) smoking history. There will be 3 radiation dose levels in this study: 54 Gy, 60 Gy, and 70 Gy. The number of weekly chemotherapy doses patients received will be depend 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.

37

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

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38

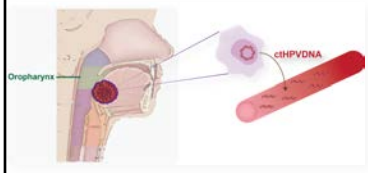
HPV-associated Oropharyngeal Cancer

- 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)

39

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?

Chera BS et al Clin Cancer Res. 2019
Damerla RR et al JCO Precision Oncol. 2019
Hanna GJ et al Ann Oncol. 2018

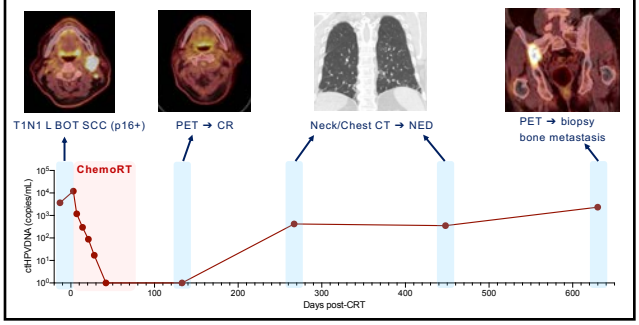
40

Prospective Biomarker Study Design

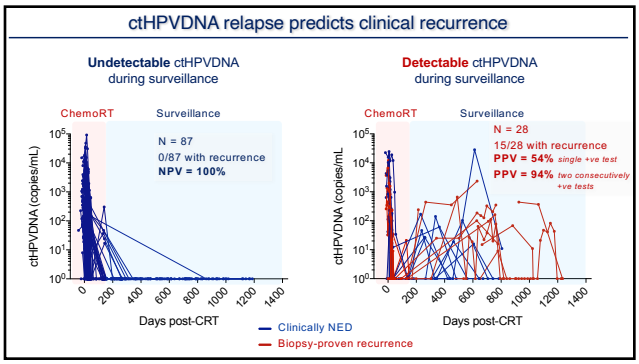
Setting:	Academic medical centers – UNC-CH, UNC-Rex, and Univ of Florida
Patients:	**115 patients with p16+ stage I-III oropharyngeal cancer** treated with chemoradiation
Followup:	Clinical exams every 2 - 4 months for years 1 - 2, every 6 months for years 3 – 5; **Chest imaging every 6 months. Median 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)

41

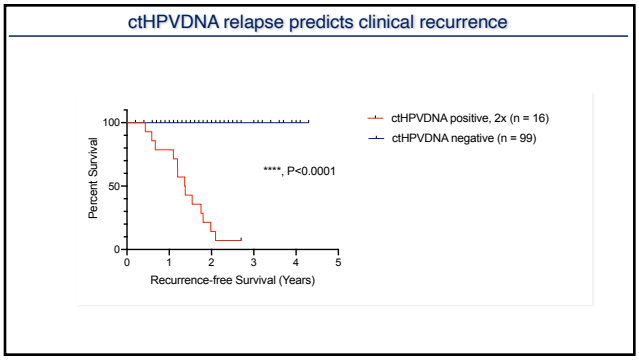
Case Example



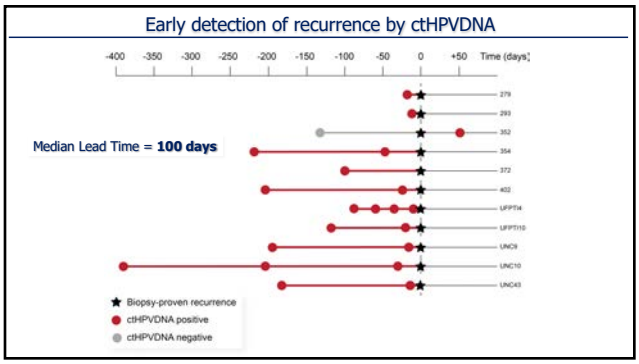
42


ctHPVDNA relapse predicts clinical recurrence
Undetectable ctHPVDNA during surveillance
Detectable ctHPVDNA during surveillance
ChemoRT
Surveillance
N = 87
0/87 with recurrence
NPV = 100%
N = 28
15/28 with recurrence
PPV = 54% single +ve test
PPV = 94% two consecutively +ve tests
ctHPVDNA (copies/mL)
Days post-CRT
Clinically NED
Biopsy-proven recurrence

43

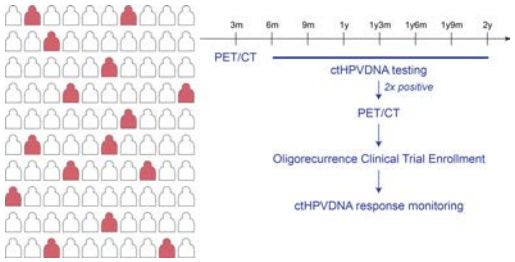

ctHPVDNA relapse predicts clinical recurrence
ctHPVDNA positive, 2x (n = 16)
ctHPVDNA negative (n = 99)
****, P<0.0001
Percent Survival
Recurrence-free Survival (Years)

44


Early detection of recurrence by ctHPVDNA
Time (days)
Median Lead Time = 100 days
Biopsy-proven recurrence
ctHPVDNA positive
ctHPVDNA negative

45

ctHPVDNA-based monitoring to facilitate oligorecurrence clinical trials



46

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

47

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

Beaty BT[1], DH Moon[1], CJ Shen[1], RJ Amdur[2], J Weiss[3,4], J Grilley-Olson[3,4], S Patel[3,4], A Zanation[5], T Hackman[5], B Thorp[5], J Blumberg[5], SN Patel[5], M Weissler[5], WG Yarbrough[5], NC Sheets[1], J Parker[6], DN Hayes[7], WM Mendenhall[2], R Dagan[2], X Tan[3], GP Gupta[1,3], BS Chera[1]

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[7]Department of Medical Oncology, University of Tennessee, Memphis, TN

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48

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

49

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

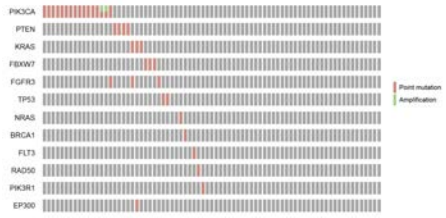
↓

77 patients with sequencing data
(34/77 with mutations)

	N=77 (%)
Mean age (years)	60
Sex	
Male	66 (86%)
Female	11 (14%)
Smoking history	
Never	33 (43%)
< 10 years	21 (27%)
> 10 years	23 (30%)
Tumor stage	
T0	5 (7%)
T1	18 (23%)
T2	50 (65%)
T3	4 (5%)
T4	0
Nodal stage - 7th edition (8th edition)	
N0	7 (9%)
N1	10 (13%)
N2a (N1)	3 (4%)
N2b (N1)	47 (61%)
N2c (N2)	11 (14%)
N3	0
Radiation dose	
60 Gy	75 (97%)
70 Gy	2 (3%)
Concurrent chemotherapy / systemic therapy	
Yes	66 (86%)
No	11 (14%)

50

PIK3CA mutations in p16+ OPSCC

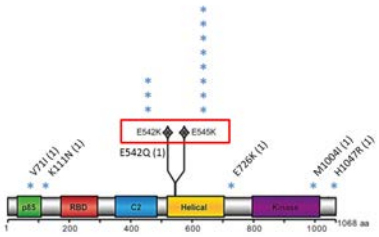


Tumor sequencing mutational profile. Each box represents one patient, grey indicates no mutations.

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

51

Sites of *PIK3CA* mutations in p16+ OPSCC



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

Modified from Berg, 2013

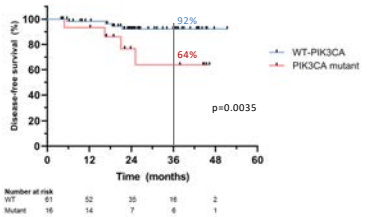
52

PIK3CA mutations in p16+ OPSCC

Clinical characteristic	*N=77 (%)*	*WT-PIK3CA (n=61)*	*PIK3CA mutated (n=16)*	*p value*
Mean age (years)	60	58	60	0.53
Sex				
Male	66 (86%)	52 (85%)	14 (88%)	0.82
Female	11 (14%)	9 (15%)	2 (12%)	
Smoking history				0.31
Never	33 (43%)	28 (46%)	5 (31%)	
< 10 years	21 (27%)	16 (26%)	5 (31%)	
> 10 years	23 (30%)	17 (28%)	6 (38%)	
Tumor stage				0.68
T0	5 (7%)	4 (7%)	1 (6%)	
T1	18 (23%)	14 (23%)	4 (25%)	
T2	50 (65%)	39 (48%)	11 (69%)	
T3	4 (5%)	4 (7%)	0	
T4	0			
Nodal stage (7th edition)				0.32
N0	7 (9%)	5 (8%)	1 (6%)	
N1	10 (13%)	10 (16%)	1 (6%)	
N2a	3 (4%)	2 (3%)	1 (6%)	
N2b	47 (61%)	37 (61%)	10 (63%)	
N2c	11 (14%)	7 (11%)	3 (19%)	
N3	0	0	0	
Radiation dose				0.47
60 Gy	75 (97%)	59 (97%)	16 (100%)	
70 Gy	2 (3%)	2 (3%)	0	
Concurrent chemotherapy / systemic therapy				0.82
Yes	66 (86%)	55 (90%)	14 (87%)	
No	11 (14%)	6 (10%)	2 (13%)	

53

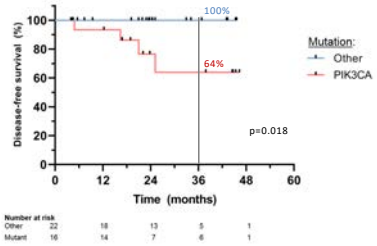
PIK3CA mutations in p16+ OPSCC



- 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 - 2 E542K, 2 E545K, 1 E726K

54

PIK3CA mutations in p16+ OPSCC



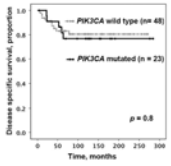
- On MVA, *PIK3CA* mutation was the only variable associated with disease recurrence

55

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?*

Chiosea, BMC Cancer 2013
Harbison, JCI Insight 2018

56

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

57

Acknowledgements

Our Patients

Gaorav Gupta, MD, PhD
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58