Head and Neck Cancer Management in North Carolina: Updates for 2020

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Disclosures

None.

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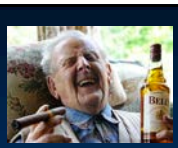
Historically



2020

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Case

Ramses T. Heel is a 55 year old white male who presents for follow up. You initially met him three weeks ago after he discovered a painless neck mass while shaving. He has noted "on and off" sore throat for the last 2 months but thought it was allergies. He denies any other symptoms including pain with swallowing, shortness of breath or weight loss.

His past medical history (PMH) is significant for asthma and well controlled hypertension on lisinopril. He has a 5 pack year smoking history during college (1980s) and drinks alcohol socially. His family history is significant for breast cancer (mother and older sister). He travels to China yearly for business for the last 10 years.

You ordered a CT neck, which showed a 3cm mass and subsequently referred him to ENT. Endoscopic evaluation reveals a 1 cm right tonsillar mass. An ultrasound guided FNA was performed in office. Pathology returned positive for squamous cell carcinoma. Additional diagnostic testing is pending.

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Learning Objectives

- Understand key risk factors and critical anatomy associated with head and neck cancers
- Distinguish differences in biology, prognosis, and treatment between HPV associated head and neck cancer and non-HPV associated head and neck cancer
- Recognize and familiarize findings from seminal head and neck cancer clinical trials in the last 2 years

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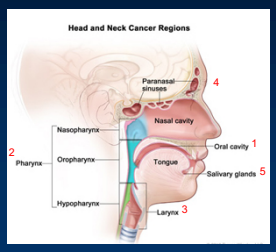
Head and Neck Cancer Anatomy

- Pathology: SCC
- 5 main anatomical locations
- Location is influenced by risk factor



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Statistics and Epidemiology

ACS Facts and Figures, 2018; Advanced Science News, 2017

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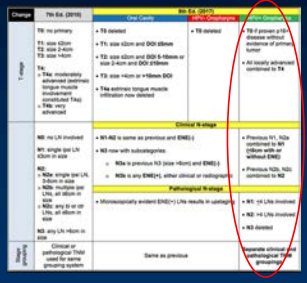
HNSCC TNM Staging is Complex



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Rate of metastatic disease at initial presentation for common cancers

Site	Metastatic Rate (%)	Source
Breast Cancer	6-10%	MBCN.org 2016
Colorectal Cancer	25%	Engstrand. BMC Cancer. 2018
Cervical Cancer	13%	Li. J Gynecol Oncol. 2016
NSCLC	25-40%	ACS 2017
Pancreatic Cancer	30-50%	ACS 2018
Prostate Cancer	5%	ACS 2018

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HNSCC rarely presents as metastatic disease

Site	Total in SEER	Number Metastatic at Presentation	Percentage	95% CI
Lip	5,975	20	0.33%	0.20-0.52%
Oral Cavity	16,385	320	1.95%	1.75-2.18%
Oropharynx	17,783	729	4.10%	3.81-4.40%
Hypopharynx	1,866	128	6.86%	5.75-8.10%
Supraglottis	8,114	270	3.33%	2.95-3.74%
Glottis	13,085	87	0.66%	0.53-0.82%
Subglottis	356	12	3.37%	1.75-5.81%
Sinus	1,068	69	6.46%	5.06-8.11%
Nasopharynx	2,610	177	6.78%	5.85-7.81%

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Non-metastatic HNSCC

- Stage at diagnosis: early stage (40%) and locally advanced (LA), 50%)
- Prognosis for LA-HNSCC remains poor
- Treatment options:
  1. Primary surgery followed by post-operative RT ± chemotherapy
  2. Concurrent chemoradiation therapy (cCRT)

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HPV-ASSOCIATED HNSCC

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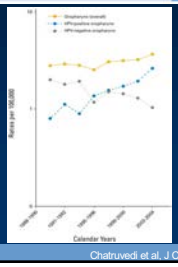
HPV and the rise of oropharynx cancer in the US

VOLUME 29 · NUMBER 32 · NOVEMBER 10 2011
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT



↑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

Chaturvedi et al, J Clin Oncol, 29(32), 2011

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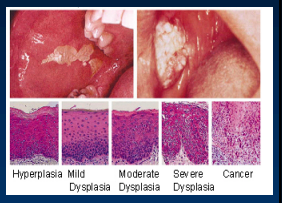
What is HPV?

- >100 types of HPV have been classified to date
  - HPV 16 is most commonly associated with OPSCC
  - Sometimes HPV 18, 31 or 33
  - Rarely other "high risk" types
- Also causes gynecological, anal, penile cancers
- HPV DNA is detected in 65% of OPSCC (tonsil & base of tongue)



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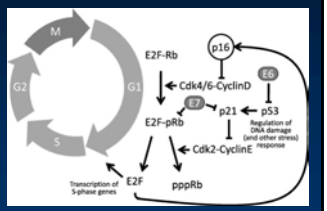
Viral oncogenes and p16 expression

- E6/E7 viral oncoproteins
  - E6 inactivates p53
  - E7 inactivates Rb
- Over expression of E2F leading to p16 expression
- >80% malignant cells positive by p16 IHC correlates with HPV+



Chan PK et al, *Crit Rev Clin Lab Sci* 49:117, 2012;
Darragh TM *et al, Arch Pathol Lab Med* 136:1266, 2012

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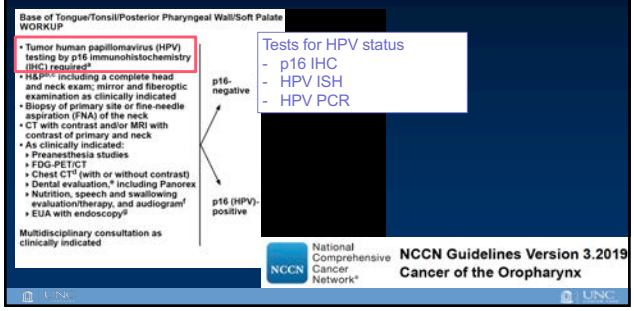
How to test for HPV?



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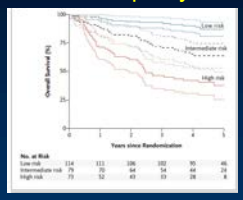
RTOG 0129: Risk Stratification in Oropharynx Cancer



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

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HPV and HNSCC prognosis

- 87% are HPV positive HNSCC are non-smokers and light drinkers
- Higher sensitivity to chemoradiation
- Independent predictor for overall survival
- Superior survival regardless of stage at diagnosis

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Treatment of HPV-associated HNSCC

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Standard		RT: 70 Gy (7 weeks) Chemo: cisplatin (weekly or bolus)	DE-INTENSIFY TREATMENT???
ECOG 1308	Induction chemo	RT: 54 Gy Chemo: cetuximab	Chemo ↑ XRT ↓
Quarterback	Induction chemo	RT: 56 vs. 70 Gy Chemo: carboplatin	
RTOG 1016		RT: 70 Gy Chemo: cisplatin vs cetuximab	Chemo ↓ XRT =
ECOG 3311	Surgery	Low Risk: Observation Intermediate Risk: 50 vs 60 Gy High Risk: 66 Gy + cisplatin	Surgery + Chemo ↓ XRT ↓
UNC/UF		RT: 60 Gy Chemo: cisplatin (low dose)	Chemo ↓ XRT ↓

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Are All HPV-Associated OPSCC the same?

Phase II study of N=80 patients
- **Stage III/IV HPV-associated OPSCC**
- **Regardless of smoking status**

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

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 (56 patients)*

↓

51 pts with cCR received cetuximab + 54 Gy
8 pts with <cCR received cetuximab + 54 Gy
9 pts w/o IC response received cetuximab + 70 Gy (SOC)

→ OUTCOMES?

J Clin Oncol 34. © 2016

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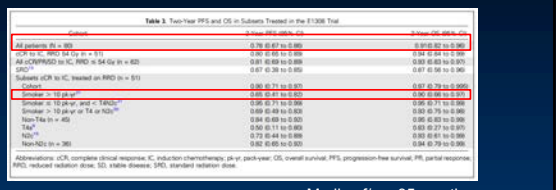

Median f/u = 35 months

Key Study Findings:

1. Outcomes were good with IC strategy and de-intensification of CRT
2. All HPV+ patients with recurrences occurred in those with >10 pack years smoking history

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Key Takeaways:

1. Risk factors matter for prognosis
2. Patients with HPV associated OPSCC who smoke <10 pack years are lowest risk.

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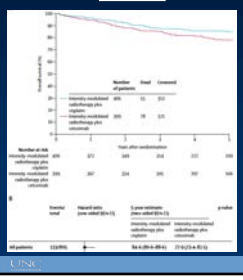
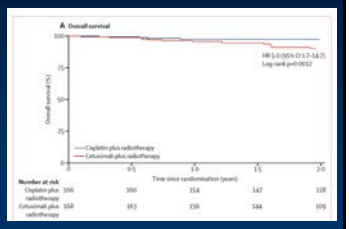
Does the type of systemic therapy matter?

70 Gy + Cetuximab vs. Cisplatin, HPV-associated OPSCC

RTOG 1016



De-ESCALaTE:



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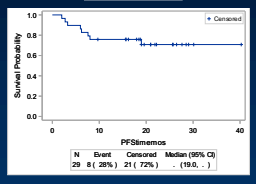
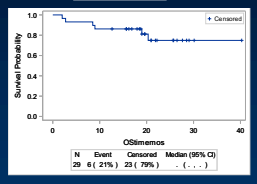
What about Radiation + Immunotherapy?

1 Year PFS = 76%



N	Event	Censored	Median (95% CI)
29	8 (28%)	21 (72%)	. (19.0, .)

1 Year OS = 86%



N	Event	Censored	Median (95% CI)
29	6 (21%)	23 (79%)	. (. , .)

Weiss J, Sheth S, et al. Concurrent definitive immunoradiotherapy for patients with Stage III-IV Head and Neck Cancer with cisplatin contraindication. Clinical Cancer Research. 2020. In Press.

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Key Takeaway:

In patients with HPV+ LA-OPSCC receiving curative therapy, cisplatin + radiation therapy remains the standard of care

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What about treatment options involving surgery?

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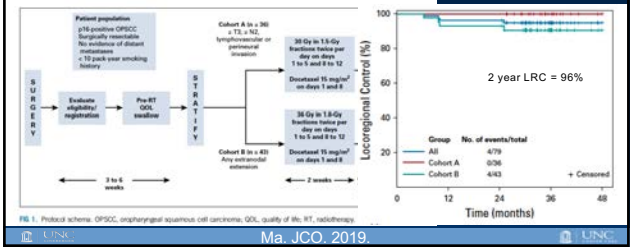
Phase II Evaluation of Aggressive Dose De-Escalation for Adjuvant Chemoradiotherapy in Human Papillomavirus–Associated Oropharynx Squamous Cell Carcinoma

Surgery followed by reduced RT dose



Ma. JCO. 2019.

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Is surgery an option?

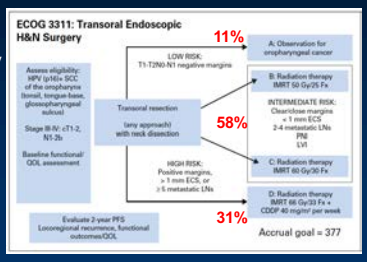
Yes.

TORS = Trans-oral robotic surgery

- Minimally invasive
- Less risks

ECOG 3311:

- Study open since 2013
- Enrolled 511 pts as of 8/1/2018
- Key results this month!?



J Clin Oncol 33:3285-3292.

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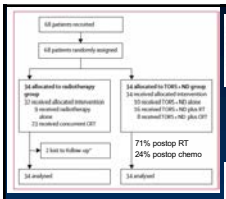
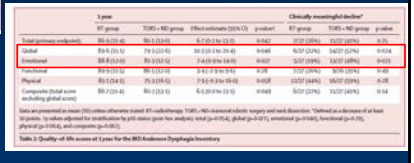
Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial



Primary endpoint: Dysphagia @ 1 year



Lancet Oncol 2019

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Key Takeaway:
Surgery (TORS) and radiation therapy are both good options for LA-OPSCC.

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How do we treat
HPV associated HNSCC at UNC?

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Can we dose reduce both chemo and RT?

Version 1: De-intensified Chemoradiotherapy

1. **60 Gy RT for 6 weeks (*instead of 70 Gy for 7 weeks*)**
2. **Cisplatin 30mg/m² for 6 weeks (*instead* of 40mg/m² for 7 weeks)**

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

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

Int J Radiation Oncol Biol Phys, Vol. 93, No. 5, pp. 976–985, 2015

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Version 2: 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)

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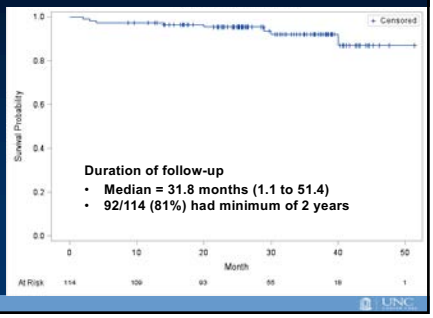
2 Year Outcomes

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

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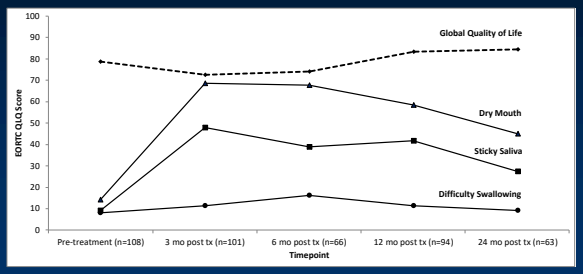
Quality of Life Scores



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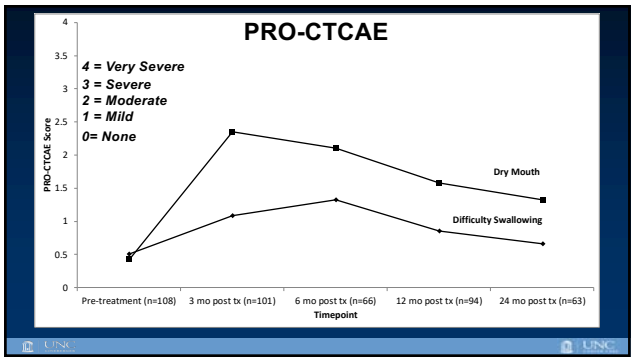
PRO-CTCAE
4 = Very Severe
3 = Severe
2 = Moderate
1 = Mild
0= None
PRO-CTCAE Score
Dry Mouth
Difficulty Swallowing
Pre-treatment (n=108)
3 mo post tx (n=101)
6 mo post tx (n=66)
12 mo post tx (n=94)
24 mo post tx (n=63)
Timepoint

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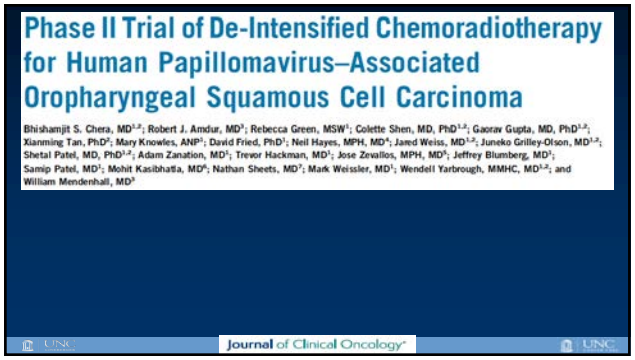
Phase II Trial of De-Intensified Chemoradiotherapy for Human Papillomavirus–Associated Oropharyngeal Squamous Cell Carcinoma
Bhishamjit S. Chera, MD; Robert J. Amdur, MD; Rebecca Green, MSW; Colette Shen, MD, PhD; Gaorav Gupta, MD, PhD; Xianming Tan, PhD; Mary Knowles, ANP; David Fried, PhD; Neil Hayes, MPH, MD; Jared Weiss, MD; Juneko Grilley-Olson, MD; Shetal Patel, MD, PhD; 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, MD; and William Mendenhall, MD
Journal of Clinical Oncology

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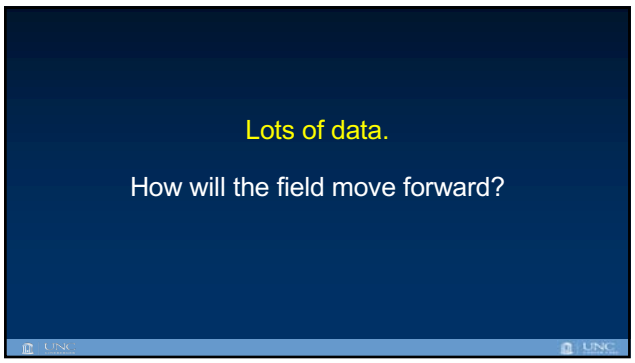
Lots of data.
How will the field move forward?

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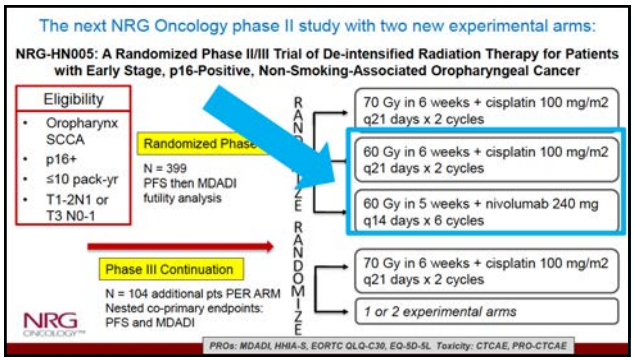
The next NRG Oncology phase II study with two new experimental arms:
NRG-HN005: A Randomized Phase II/III Trial of De-intensified Radiation Therapy for Patients with Early Stage, p16-Positive, Non-Smoking-Associated Oropharyngeal Cancer
Eligibility
Oropharynx SCCA
p16+
≤10 pack-yr
T1-2N1 or T3 N0-1
Randomized 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
NRG ONCOLOGY
PROs: MDADI, HNIA-S, EORTC QLQ-C30, EQ-5D-5L Toxicity: CTCAE, PRO-CTCAE

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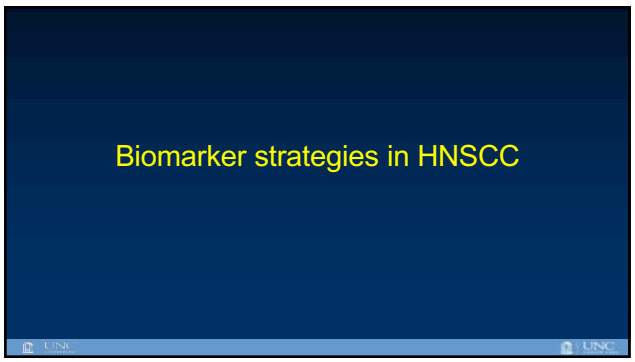
Biomarker strategies in HNSCC

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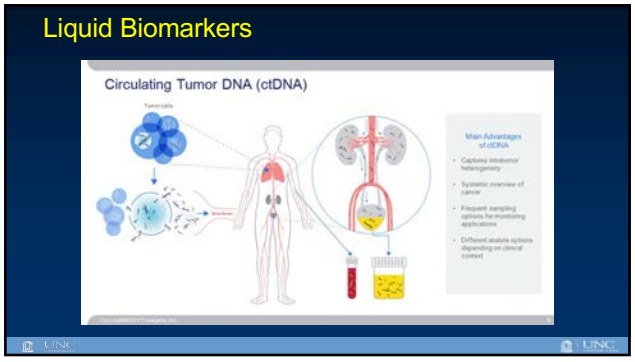
Liquid Biomarkers
Circulating Tumor DNA (ctDNA)

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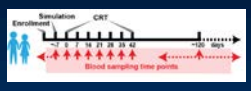
ctDNA as a circulating biomarker of treatment response for HPV-related HNSCC

Since 2016, our UNC group has prospectively analyzed ctHPVDNA
- 3 clinical trials (LCCC 1121,1413,1612)
- ~160 patients, >1500 blood samples to date



Ultimate goal of ctDNA:
1. Guide therapeutic intensity
2. Earlier detection of disease recurrence

Chera. JCO. 2020

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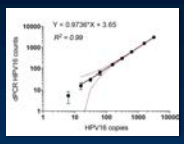
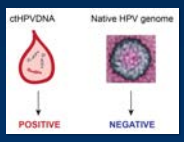
Multi-analyte digital PCR (dPCR) assay for ctHPVDNA





- Standardized multi-step analytical protocol to optimize specificity and sensitivity
- Distinguishes fragmented ctDNA from native viral genomes
- Detects ctHPV16, 18 ,31, 33, and 35 *(more high-risk strains coming)*
- **Linear:** absolute quantification over 5 orders of magnitude (5-50,000 copies)
- **Precise:** High reproducibility
- **Sensitive:** Detects as few as 6 copies of HPV16 with ~80% sensitivity

Chera. JCO. 2020

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Is ctHPVDNA detectable?

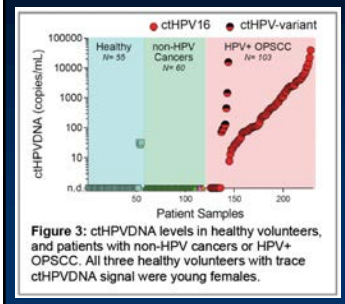

Figure 3: ctHPVDNA levels in healthy volunteers, and patients with non-HPV cancers or HPV+ OPSCC. All three healthy volunteers with trace ctHPVDNA signal were young females.

Cohort of 218 pts
- 55 healthy (no cancer)
- 60 non-HPV cancer patients
- 103 non-metastatic HPV-OPSCC patients (p16 IHC+)

98% Specificity
89% Sensitivity

Hypothesize:
- 11 ctHPVDNA-negative pts were false positives of the p16 IHC assay
- May be HPV negative OPSCC

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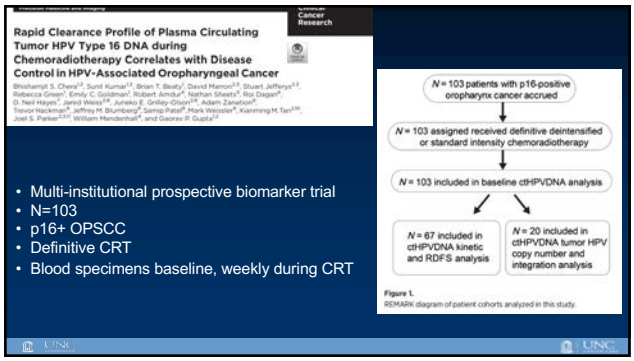
Rapid Clearance Profile of Plasma Circulating Tumor HPV Type 16 DNA during Chemoradiotherapy Correlates with Disease Control in HPV-Associated Oropharyngeal Cancer
Clinical Cancer Research
• Multi-institutional prospective biomarker trial
• N=103
• p16+ OPSCC
• Definitive CRT
• Blood specimens baseline, weekly during CRT
N = 103 patients with p16-positive oropharynx cancer accrued
N = 103 assigned received definitive deintensified or standard intensity chemoradiotherapy
N = 103 included in baseline ctHPVDNA analysis
N = 67 included in ctHPVDNA kinetic and RDFS analysis
N = 20 included in ctHPVDNA tumor HPV copy number and integration analysis
Figure 1.
REMARK diagram of patient cohorts analyzed in this study.

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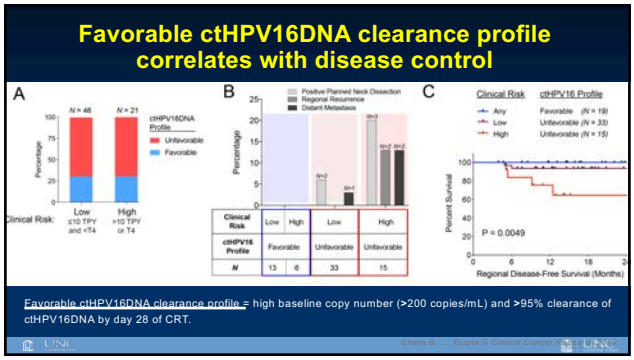
Favorable ctHPV16DNA clearance profile correlates with disease control
A
B
C
ctHPV16DNA Profile
Unfavorable
Favorable
Clinical Risk:
Low ≤10 TPY and <T4
High >10 TPY or T4
Positive Planned Neck Dissection
Regional Recurrence
Distant Metastasis
Percentage
Clinical Risk
ctHPV16 Profile
Low
High
Favorable
Unfavorable
Clinical Risk
ctHPV16 Profile
Any
Low
High
Favorable (N = 19)
Unfavorable (N = 33)
Unfavorable (N = 15)
Percent Survival
P = 0.0049
Regional Disease-Free Survival (Months)
Favorable ctHPV16DNA clearance profile = high baseline copy number (>200 copies/mL) and >95% clearance of ctHPV16DNA by day 28 of CRT.

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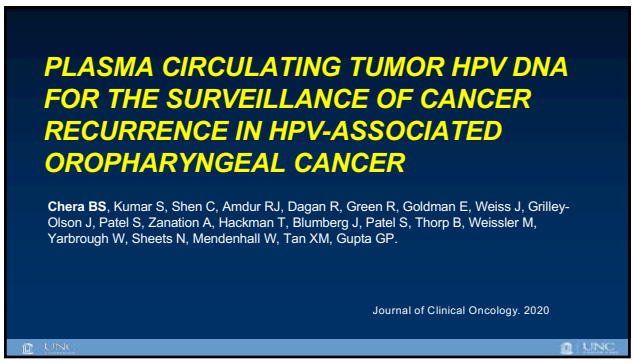
PLASMA CIRCULATING TUMOR HPV DNA FOR THE SURVEILLANCE OF CANCER RECURRENCE IN HPV-ASSOCIATED OROPHARYNGEAL CANCER
Chera BS, Kumar S, Shen C, Amdur RJ, Dagan R, Green R, Goldman E, Weiss J, Grilley-Olson J, Patel S, Zanation A, Hackman T, Blumberg J, Patel S, Thorp B, Weissler M, Yarbrough W, Sheets N, Mendenhall W, Tan XM, Gupta GP.
Journal of Clinical Oncology. 2020

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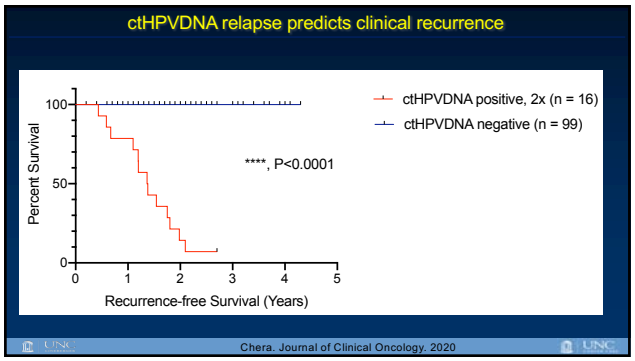
ctHPVDNA relapse predicts clinical recurrence
ctHPVDNA positive, 2x (n = 16)
ctHPVDNA negative (n = 99)
****, P<0.0001
Percent Survival
100
50
0
0
1
2
3
4
5
Recurrence-free Survival (Years)
Chera. Journal of Clinical Oncology. 2020

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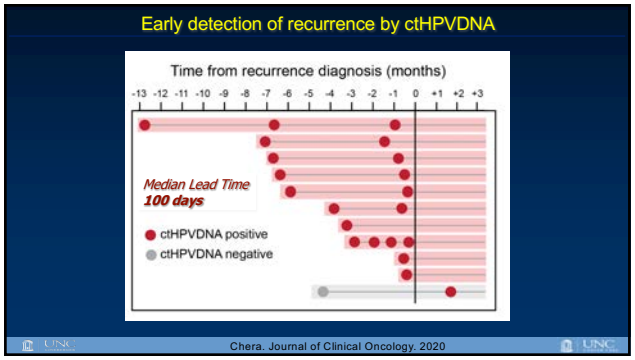
Early detection of recurrence by ctHPVDNA
Time from recurrence diagnosis (months)
-13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 +1 +2 +3
Median Lead Time
100 days
ctHPVDNA positive
ctHPVDNA negative
Chera. Journal of Clinical Oncology. 2020

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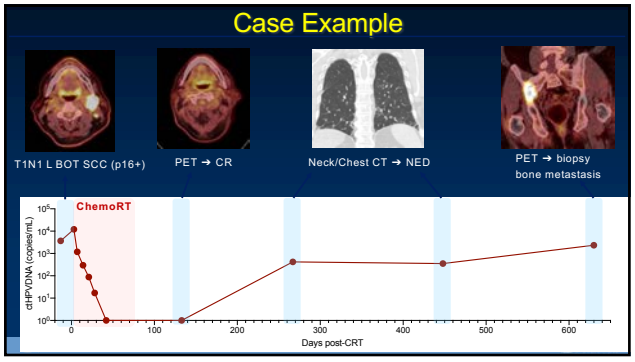
Case Example
T1N1 L BOT SCC (p16+)
PET → CR
Neck/Chest CT → NED
PET → biopsy
bone metastasis
ChemoRT
ctHPVDNA (copies/mL)
Days post-CRT

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Clinical trial to evaluate early detection of recurrence

Pan-HPV approach

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Key Takeaways for ctHPVDNA

- Plasma ctHPVDNA surveillance testing has high NPV and PPV for early detection of cancer recurrence
- ctHPVDNA based surveillance may reduce the overall cost of post-treatment surveillance in patients who remain ctDNA negative
  - Less radiographic scans
- Prospective evaluation in a clinical trial is needed. Efforts are underway

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What about ctDNA in HPV negative patients?

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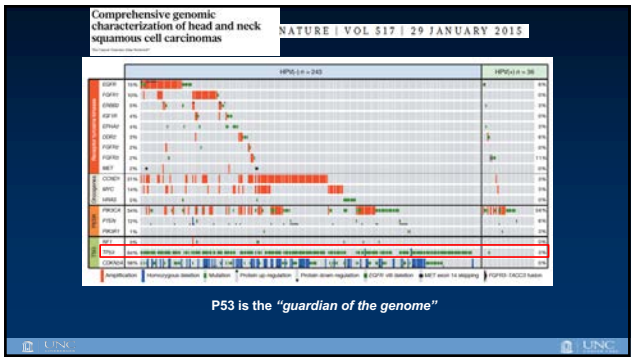
Comprehensive genomic characterization of head and neck squamous cell carcinomas
NATURE | VOL 517 | 29 JANUARY 2015
P53 is the "guardian of the genome"

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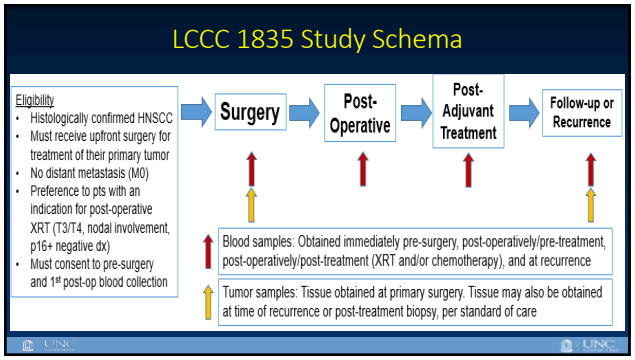
LCCC 1835 Study Schema
Eligibility
• Histologically confirmed HNSCC
• Must receive upfront surgery for treatment of their primary tumor
• No distant metastasis (M0)
• Preference to pts with an indication for post-operative XRT (T3/T4, nodal involvement, p16+ negative dx)
• Must consent to pre-surgery and 1st post-op blood collection
Surgery
Post-Operative
Post-Adjuvant Treatment
Follow-up or Recurrence
Blood samples: Obtained immediately pre-surgery, post-operatively/pre-treatment, post-operatively/post-treatment (XRT and/or chemotherapy), and at recurrence
Tumor samples: Tissue obtained at primary surgery. Tissue may also be obtained at time of recurrence or post-treatment biopsy, per standard of care

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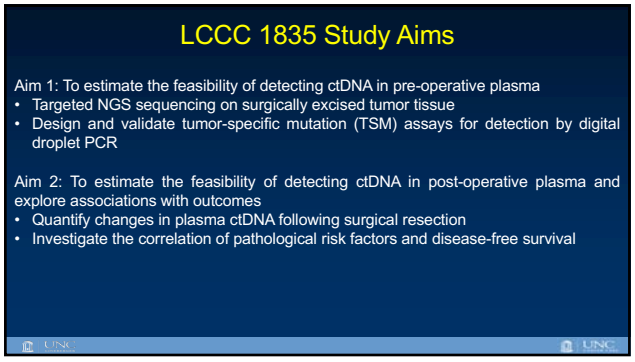
LCCC 1835 Study Aims
Aim 1: To estimate the feasibility of detecting ctDNA in pre-operative plasma
• Targeted NGS sequencing on surgically excised tumor tissue
• Design and validate tumor-specific mutation (TSM) assays for detection by digital droplet PCR
Aim 2: To estimate the feasibility of detecting ctDNA in post-operative plasma and explore associations with outcomes
• Quantify changes in plasma ctDNA following surgical resection
• Investigate the correlation of pathological risk factors and disease-free survival

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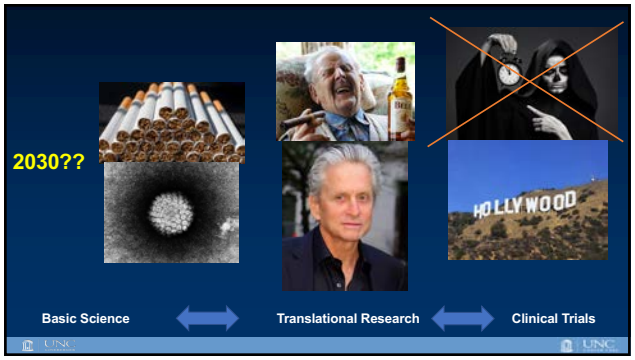

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Case Revisited

Ramses Heel is a 55 year old presents who presented with a painless neck mass. PMH of hypertension and asthma. Family history of breast cancer (mother and older sister). Admits to a 5 pack year smoking history during college and social alcohol use currently. He travels to China yearly for business for the last 10 years. Your order an neck ultrasound and CT scan which shows a 3cm neck mass. FNA positive for squamous cell carcinoma.

Your patient asks what caused his cancer?

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Conclusions

1. Head and neck cancers are common
   - Location of cancer may suggest associated risk factor
   - The incidence of oropharynx due to HPV is rising
2. HPV associated cancers are lower risk compared to smoking related HNSCC
   - Treatment deintensification will be come standard of care (when *not* if)
   - How to "best" de-intensify is still an active area of investigation
3. Biomarkers are important for cancer diagnosis, treatment, and surveillance
   - Testing for ctHPVDNA may soon become part of standard practice. How to use this assay to guide treatment decisions is being studied
   - ctDNA based on gene mutational status is also being studied for non-HPV associated HNSCC

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Our Patients

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Thank you!

Questions?

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