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Advances in Head and Neck Cancer Management in North Carolina: Updates for 2021

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Otolaryngology/Head and Neck Surgery
University of North Carolina School of Medicine

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Family/Background

- 1981-2003: UNC
  - Undergrad
  - Medical school
  - Fellowship Surg Onc
  - Otolaryngology faculty
- 2003-2012: Vanderbilt
  - Chair Baker Lab
  - MMHC: School of Mngmnt
- 2012-2018: Yale
  - Chief Otolaryngology
  - Director HN Disease Ctr
  - Co-leader VOIC
- 2018-present: UNC
  - Dark Professor and chair OHNS

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Objectives

- **Discuss** multi-disciplinary treatment of Head and Neck Cancer with emphasis on newer techniques and treatment standards.
- **Explain** reconstruction techniques of Head and Neck Cancer.
- **Identify** HPV-Associated Head and Neck Cancer, prognostic markers and emerging therapeutic vulnerabilities.

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Head and Neck Cancer - Overview

- Many in US not aware of HN cancer
- > 60,000 cases per year in U.S.
- Vast majority SCC (squamous cell carcinoma)
- HNC classified by subsites –decreases recognition of problem

Larynx	Nasopharynx – HPV and EBV associated
Oropharynx	Sinonasal – HPV associated
Oral Cavity	Thyroid – WDTC and anaplastic
Hypopharynx	Salivary – many histologies

- 2 main molecular subtypes ofHNSCC based on causative agent
  - Tobacco-associated
  - HPV-associated

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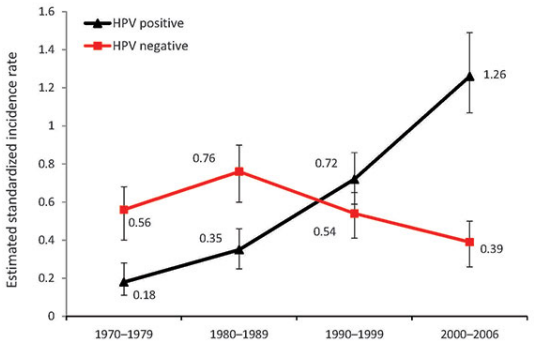
Tobacco HNSCC is decreasing HPV+ HNSCC is increasing

- Overall incidence HNSCC decreasing (1973-2004)
  - Associated with trend of decreased tobacco
- Oropharyngeal SCC (OPSCC) increasing
  - Younger patients
  - Decreased or absent traditional risk factors – Tobacco/EtOH
  - Annual change (1973-2004) - 0.8%



Chaturvedi et al. *J Clin Oncol*. 26:612-619, 2008
Sturgis et al. *Cancer.* 110:1429, 2007
Torbjörn Ramqvist & Tina Dalianis

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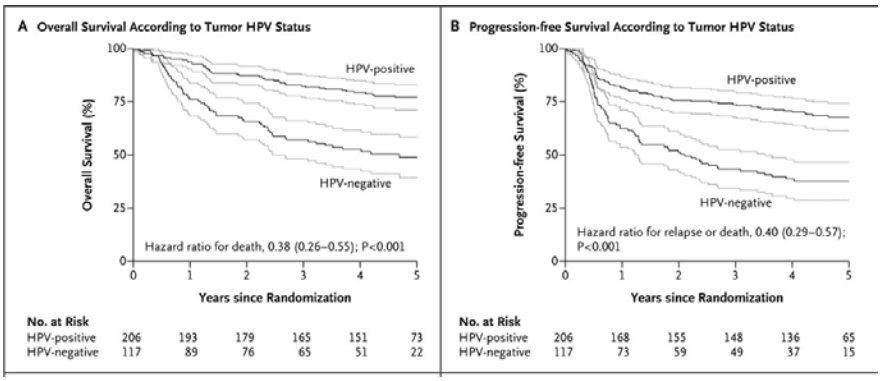
Survival HPV+ vs. HPV(-) HNSCC



Ang KK et al. N Engl J Med 2010;363:24-35

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HPV- and tobacco-associated HNSCC are distinct diseases

HPV(+) HNSCC

- Younger patients
- Risk factor
  - Sexual transmission of HPV
- More responsive to therapy
- ~75-85% cure rate
- Conserved gene alterations
  - TRAF3, CYLD
    E2F1, FGFR3
- Distinct gene expression profile
- More methylated genome

HPV(-) HNSCC

- Older patients
- Risk factor
  - Tobacco, alcohol
- Less responsive to therapy
- <50% cure rate (advanced stage)
- Conserved gene alterations
  - P53, p16, EGFR, FGFR1, cyclin D1, myc
- Distinct gene expression profile
- Less methylated genome

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Head and Neck Cancer - Overview

Tobacco-associated HNSCC

Occurs at all subsites – OC, larynx most common

Incidence in U.S. is decreasing

- Because smoking decreasing

Advanced tumors poor prognosis

- <50% cure

Treatment modalities

- Surgery
- Radiation +/- concurrent chemotherapy

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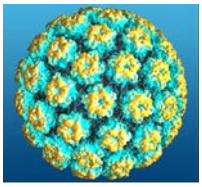
Head and Neck Cancer - Overview

HPV-associated HNSCC

- Occurs at oropharynx (almost exclusively)
- Incidence in U.S. is increasing
  - Now more than 25% of HNSCC
- Better prognosis than tobacco associated
  - 70-80% cure
- Treatment modalities
  - Surgery
  - Radiation +/- concurrent chemotherapy



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Burden of HPV(+) OPSCC - 2012

Cancer site	Average number of cancers per year in sites where HPV is often found (HPV-associated cancers)	Percentage probably caused by any HPV type[a]	Number probably caused by any HPV type[a]
Cervix	11,771	91%	10,700
Vagina	802	75%	600
Vulva	3,554	69%	2,400
Penis	1,168	63%	700
Anus	5,010	91%	4,600
Female	3,260	93%	3,000
Male	1,750	89%	1,600
Rectum	750	91%	700
Female	513	93%	500
Male	237	89%	200
Oropharynx	15,738	70%	11,000
Female	3,100	63%	2,000
Male	12,638	72%	9,100
TOTAL	**38,793**		**30,700**

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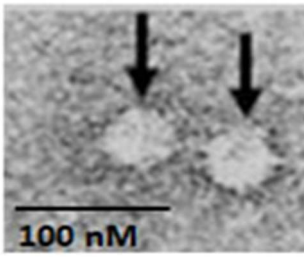
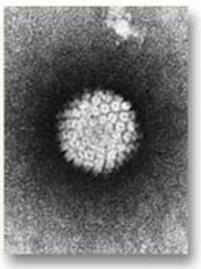
HPV Vaccine

- Prevents CIN of uterine cervix and urogenital condylomas
- Very effective and long lasting
- Currently recommended (9-valent, Guardasil-9) vaccine
  - 7 oncogenic + 2 benign types
  - HPV16
- Decreases oral HPV infection to prevent HNSCC





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Multi-Disciplinary Care HNSCC

- Includes many groups for patient care
  - OHNS (ENT), Med Onc, Rad Onc, Radiology, Pathology, Oral Medicine, SLP, Nursing (OR, Hospital, Clinic), Nutrition, APPs, Social Work, Navigators, Smoking Cessation, Addiction Services, Pain Management, Schedulers, Respiratory Therapist, Fellows, Residents, etc.
- Associated with improved survival
- Associated with better functional outcomes

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Division of Head and Neck Oncology


Samip Patel, MD, FACS
Division Chief


Trevor Hackman, MD, FACS


Catherine Lumley, MD


Jeffrey Blumberg, MD, FACS


Mark Weissler, MD, FACS


Wendell Yarbrough MD, MMHC, FACS


Travis Schrank, MD, PhD


Catie Voegler , MSPAS, PA-C

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Head and Neck Medical Oncology

Shetal Patel, MD, PhD

Siddharth Sheth, MD

Jared Weiss, MD

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Head and Neck Radiation Oncology

Bhisham Chera, MD

Colette Shen, MD, PhD

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Department of Pathology

Susan Maygarden, MD

Fredrick Askin, MD

Danielle Samulski, MD

Bart Singer, MD

Scott Smith, MD

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Division of Radiology

Valerie Jewells, DO, FACR, FAOCR

Benjamin Huang, MD

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UNC Adams School of Dentistry

Ali Shazib, DMD

Wesley Sherrell, DMD

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Speech & Language Pathology

Brian Kanapkey, MA, CCC-SLP

Celicia Benitex, MA, CCC-SLP

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Speech & Language Pathology

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Active Therapeutic HNSCC Trials

	ACTIVE TRIALS				
	Induction	**Definitive**	**Adjuvant**	**1L R/M**	**≥2L R/M**
Squamous Cell Carcinoma	LCCC1621: (M. Flores / J. Weiss) Carbo+Abraxane+ Durva for induction tx of surgically resectable LA-SCCHN **LCCC 2047** (Sheth/Chera) A Phase II trial of the addition of pembrolizumab and olaparib to definitive chemoradiation in locally advanced head and neck squamous cell carcinoma (HNSCC) Yale SPORE (Yarbrough) Window Trial of 5-AZA or Nivo or Nivo+5-AZA in Resectable HPV+ HNSCC	**LCCC1612:** (B. Green/B. Chera) P53 status and circulating free HPV DNA for management of HPV+ OPSCC	LCCC1725: (J. Barnes /S. Sheth) Phase I Study of Durva (MEDI 4736) with Radiotherapy for the adjuvant treatment of Intermediate Risk HNSCC RTOG1216: (J. Barnes/S. Sheth) Ph II/III Trial of Adjuvant XRT with Cisplatin vs. Docetaxel-Cetuximab vs. Cisplatin-Atezolizumab in high risk HNSCC	MK7902-010 (J. Barnes/S. Sheth) Rando, Ph II/III Trial of RT+Durva vs RT+Cetux in Pts with Locoregionally VERSATILE-002 (Weiss) Phase II study of HPV-16 E6/E7 and Pembro in 1L R/M high risk HPV16 HNSCC	NBTXR3-1100: (M. Flores/C. Shen) Ph 1/2 Study of NBTXR3 Activated SABR Patients w/ Adv HNSCC or NSCLC C-145-03: (M. Flores / J. Grilley-Olson) Phase 2 Study Evaluate Efficacy & Safety of Lymphocytes (LN-145) SGNTV-001 (J. Garbarino/J. Grilley-Olson) Tisotumab vedotin for SCCHN and NSCLC SIRPα -Fc-CD40L (M. O'Brien/S. Patel) Phase I Study of intratumorally administered SL-172154 for CSCC and SCCHN

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OHNS RESIDENTS 2020-2021

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Clinical Fellowships

Facial Plastics
Director: Dr. Madison Clark
Current Fellow: Deanna Menapace, MD

Neurotology (2 year)
Director: Dr. Kevin Brown
Current Fellow: A. Morgan Selleck, MD

Rhinology/Skull Base
Director: Dr. Charles Ebert
Current Fellows: Craig Miller, MD
Justin Morse, MD

Head & Neck/Microvascular Reconstruction
AHNS-accredited
Director: Dr. Trevor Hackman
Current Fellow: Andrew Coniglio, MD

Pediatric Otolaryngology
Director: Dr. Lauren Kilpatrick

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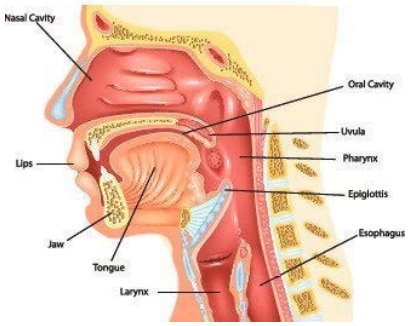
Goals of Head & Neck Cancer Reconstruction

Head and Neck Area is Complex

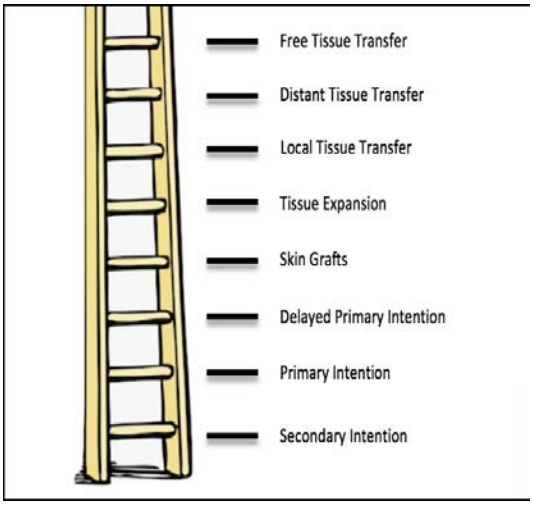
- Functionally important
  - Along with healing, restoration of function is the **first goal**
  - Eating, Breathing, Vision, Facial expression, Talking
- High-value real estate
  - Airway
  - Brain
  - Eyes
  - Tongue
  - Palate
  - Lips/nose/eyelids/etc.
- Cosmetically important area
  - Difficult to cover
  - Scars and deformity visible
  - Nerve defects (facial) obvious
- Many types of tissues required
  - Bone
  - Muscle
  - Epithelia/skin
  - Tendon
  - Nerves



Head & Neck Cancer Reconstruction

Reconstructive Ladder

- Balance between simplicity and results
- Patient considerations
  - Health status and age
  - Need for post-operative radiation
  - Available adjacent tissue and quality
  - Type of tissue needed
    - Bone, filler, epithelial lining



Skin graft/alloderm

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Local flap – Cross lip

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Regional pedicled flap reconstruction

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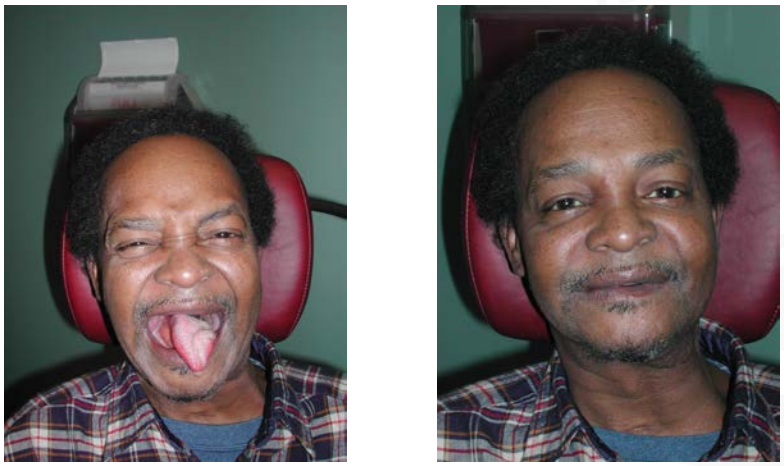
Post op: Regional flap reconstruction



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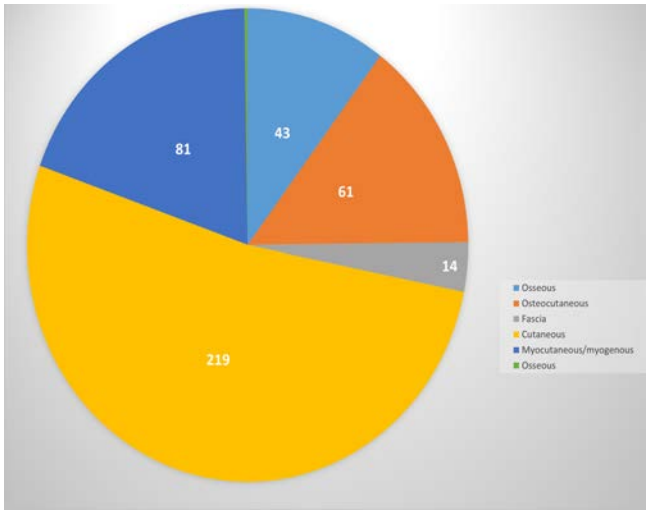
Free flaps 2019-2020



- High volume center
  - 220 flaps last year
- Facile various flaps
  - Soft tissue only
  - Bone only
  - Soft tissue and bone
  - Soft tissue, bone, skin
  - Maximize function
  - Maximize appearance

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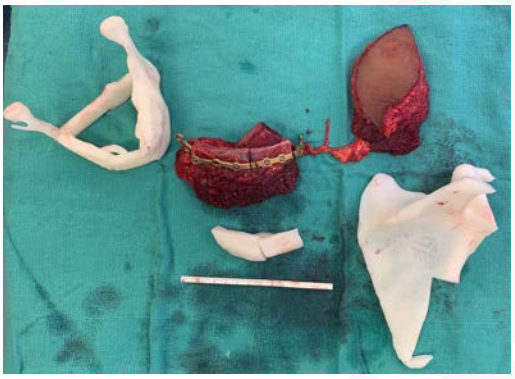
Preoperative planning: CT planning



- Cutting templates
- Pre-bent plates

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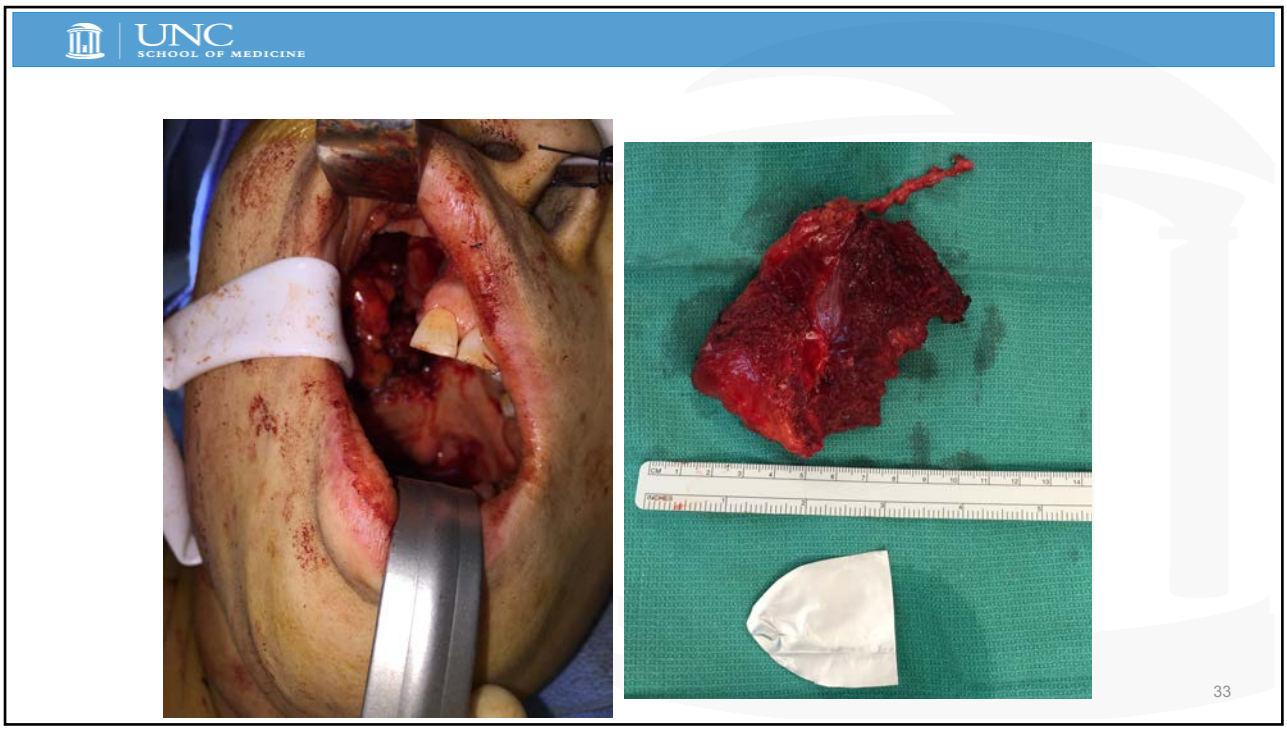

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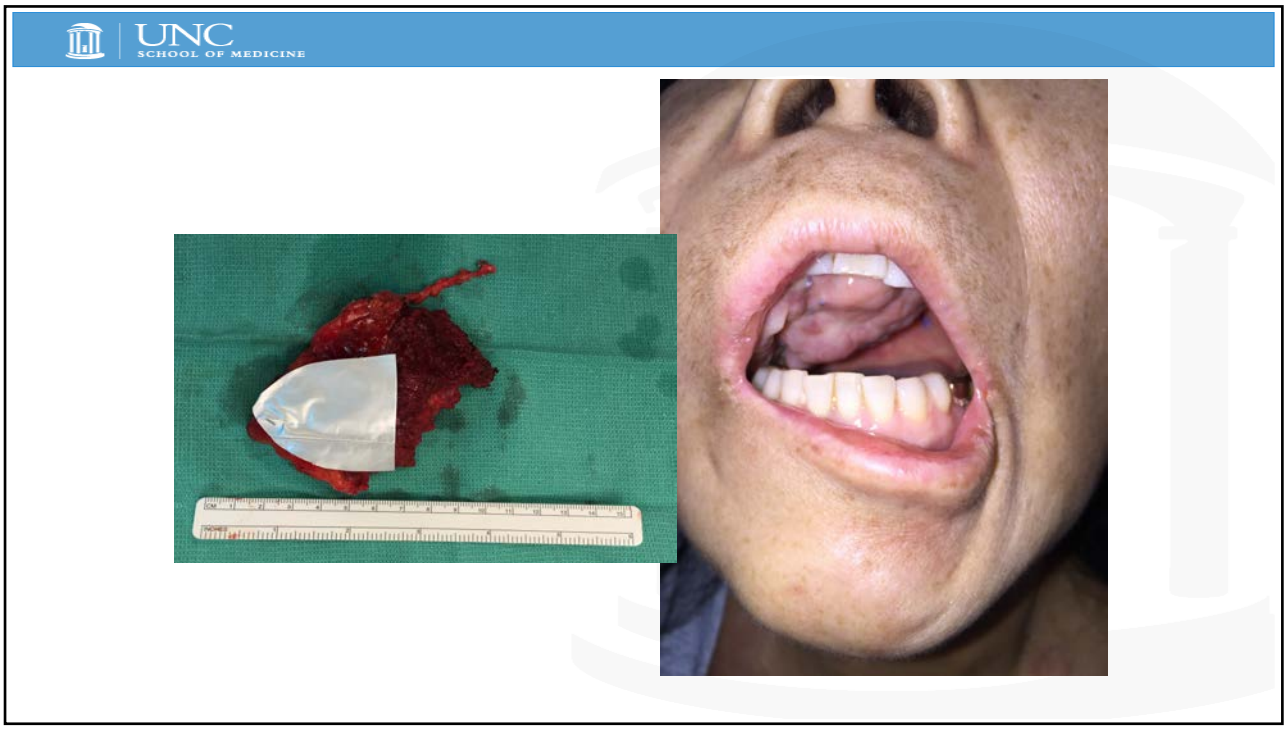

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3D CT of Scapula Tip Reconstruction - Maxillectomy

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Practice Gaps: HPV+ HNSCC

- Identify patients with good or poor outcomes
  - Currently smoking history > 10 pack years
  - Overtreating some patients / Undertreating others?
- How do we safely de-intensify therapy
  - Surgery – TORs with post op therapy guided by path
  - Radiation – decrease dose or fields
  - Neoadjuvant therapy
  - New therapies targeting molecular vulnerabilities
- Early diagnosis of HPV+ HNSCC

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De-escalation of therapy

- Decreasing dose or delivery of chemotherapy and radiation
- Minimizing invasiveness of surgery
  - Transoral robotic surgery (TORS)
- No prognostic markers to choose patients for de-escalation therapy

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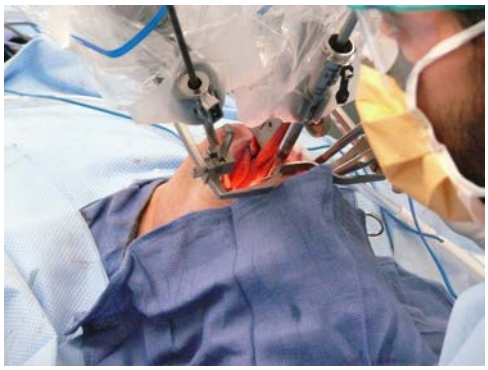
TORS for OP cancer



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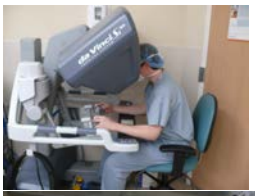
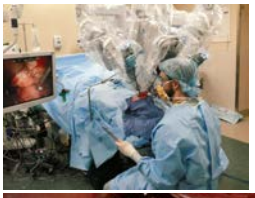
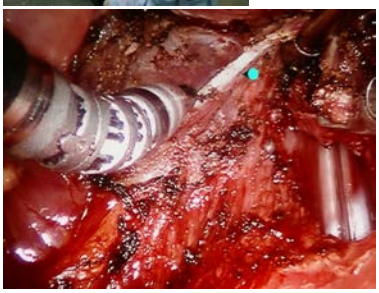
TORS: Operative view



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HPV+ OPSCC: Post TORS

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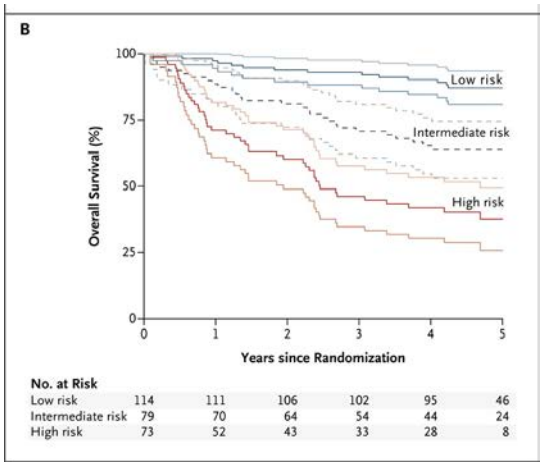
Smoking history is only indicator of survival HPV+ HNSCC



Ang KK et al. N Engl J Med 2010;363:24-35

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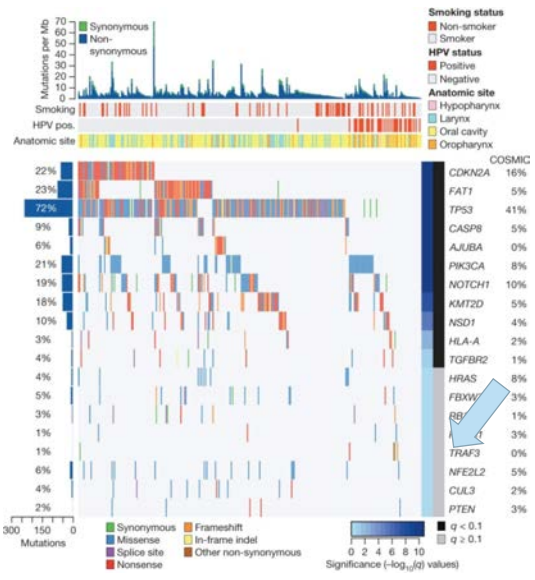
Mutated genes in HNSCC

TRAF3 (ubiquitinase)
- Regulator of NF-kB/innate immunity
- Deep deletions also found
- 1% of all HNSCC
- Clustered in HPV+ tumors
- Not found in COSMIC

CYLD (de-ubiquitinase)
- Regulator of NF-kB/innate immunity
- Deep deletions also found
- Clustered in HPV+ tumors



MS Lawrence *et al. Nature* **517**, 576-582 (2015) doi:10.1038/nature14129

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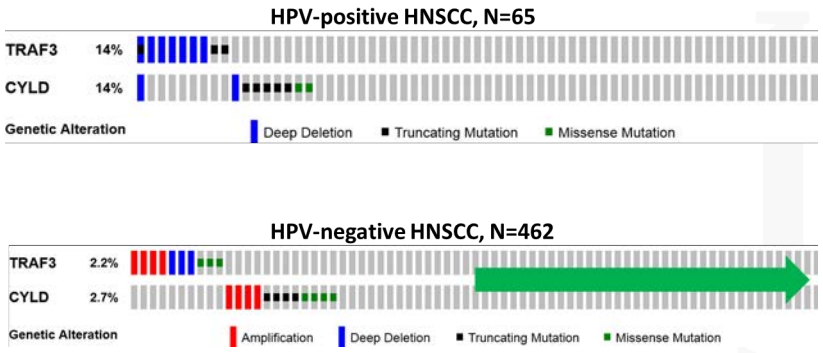
TRAF3/CYLD defects are uncommon in HPV(-) HNSCC



			Expression Compared to wt
	TRAF3		
Q211Rfs*4	FS del	ShallowDel	↓
Q320=	Splice	ShallowDel	↓
	CYLD		
S371*	Nonsense	ShallowDel	↓
K680*	Nonsense	ShallowDel	↓
N300S	Missense	ShallowDel	↓
D618A	Missense	ShallowDel	↓
E638Rfs*9	FS ins	ShallowDel	↓
S365*	Nonsense	ShallowDel	↓
C934Afs*20	FS ins	ShallowDel	↓

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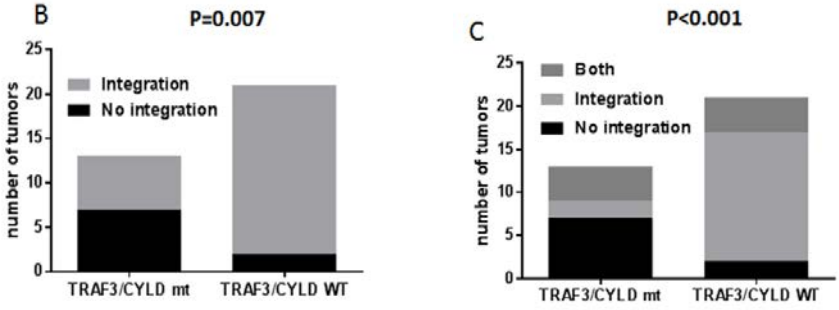
TRAF3/CYLD defects correlate with episomal HPV



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Hajek, Sewell, Kaech, Burtness, Yarbrough, Issaeva. *Cancer* 123:1778, 2017

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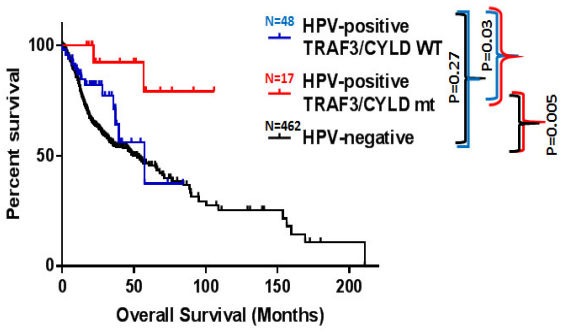
Prognostic marker of survival: HPV+ HNSCC



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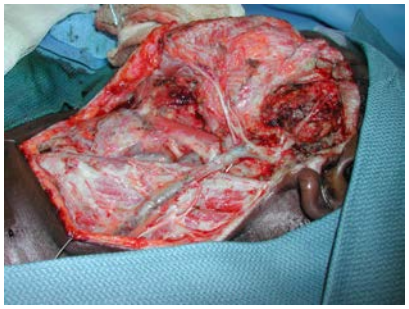
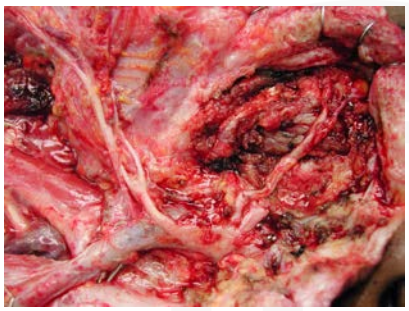
Salivary Cancer

Many types of salivary tumors

- 1st goal to remove tumor
  - 2nd goal preserve facial function
    - 3rd goal scar and contour





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Salivary Cancer

- Many tumor types
- 1st goal to remove tumor
  - 2nd goal preserve facial function

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Salivary Cancer

- Many tumor types
- 1st goal to remove tumor
  - 2nd goal preserve facial function
- But appearance important
- Typical neck face incision
  - Scar and soft tissue defect

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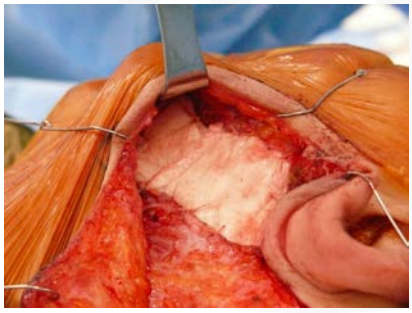
Salivary tumors/cancer

- Facelift incision



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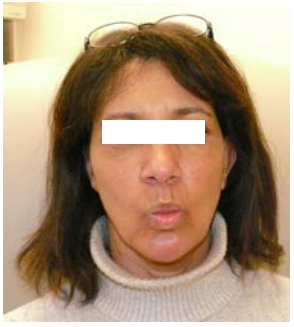
Salivary tumors/cancer



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Salivary tumors/cancer




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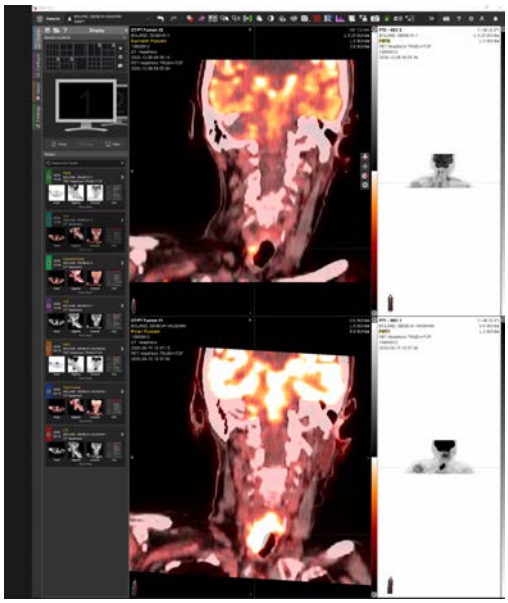
Anaplastic Thyroid

- Most aggressive thyroid cancer
- Rare, but more than 50% of thyroid cancer mortality
  - mOS 6 mos
- Associated with invasion of airway

Targeted therapy if BRAF mutant

- 45% BRAF mutant
- MEKi + BRAFi Therapy for unresectable or distant metastases
- Continue therapy until resectable



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Anaplastic Thyroid

- Integrated clinical and research team
- Multi-disciplinary endocrine tumor board
- Clinical trial opening for advanced disease Q2 2021

Jeff Blumberg
ENT

Sid Sheth
Medical Oncology

Larry Kim
Surgical Oncology

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UNC Head & Neck Oncology Lab

Natalia Isaeva
Gary Bellinger
Hina Rehmani
Damir Alzhanov
Travis Schrank
Andrew Prince
Wesley Stepp

Vaccine/Immunology/Therapy

Blossom Damania
John Serody
Jared Weiss
Wesley Stepp
Alison McBride
Cary Moody
Bhisham Chera
Gaorav Gupta
Jennifer Smith
Noel Brewer
Martha Perry

p53

Yue Xiong
Jennifer Pietenpol

Weaver Lab

Previous Lab Members

Xinyuan Lu
Hanbing An
Amy Whigham
Jonathan Law
Jialiang Wang
Adam Zanation
Brandee Brown
Carol Shores
Asel Biktasova
Michael Chang
Bea Carbone
Kathy Yu
Jonathan Moss

Yale Head & Neck and SPORE

Barbara Burtness
Karen Anderson
Joseph Contessa
Mark Lemmon
Benjamin Judson
Saral Mehra

UNC HN Surgery

Samip Patel
Mark Weissler
Trevor Hackman
Jeff Blumberg
Catherine Lumley
Travis Schrank

NF-κB

Albert Baldwin
Marty Mayo

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Otolaryngology
#10 ranked ENT department in the NATION
#1 ranked program in the Southeastern U.S.
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BEST HOSPITALS
USNews
2018-19
University of North Carolina Hospitals is ranked nationally in 5 adult specialties and 7 children's specialties.
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