Head and Neck Cancer: An Overview

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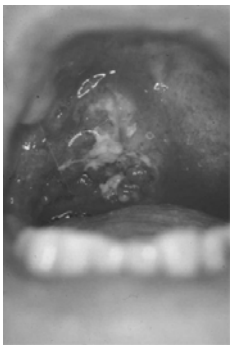
What is Head and Neck Cancer?

- **Objectives:**
  - ✓ **Discuss mucosal head and neck cancer**
  - ✓ **Epidemiology**
  - ✓ **Presentation and Diagnosis**
  - ✓ **Staging**
  - ✓ **Treatment Options**
  - ✓ **Recent Developments**
  - ✓ **Pearls for non-Otolaryngologists**

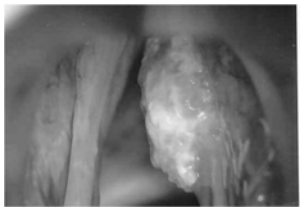


What is Head and Neck Cancer?

- **Wide range of malignant diseases involving:**
  - ✓ **Mucosal surfaces from the nares and lips down to the esophageal inlet and larynx**
  - ✓ **Salivary glands**
  - ✓ **Thyroid/parathyroid**
  - ✓ **Skin**
  - ✓ **Skull base**

Head and Neck Cancer Incidence

- **5th most common cancer worldwide**
- **Leading cause of cancer related deaths in India and eastern Europe**
- **Annual incidence of 78,000 patients with 17,500 annual deaths in the US**



Etiology

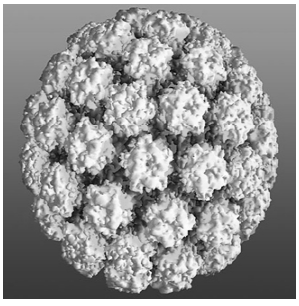
- Environmental factors
  - ✓Smoking
  - ✓ETOH
- Immunosuppression
  - ✓Congenital
  - ✓HIV
  - ✓Transplantation
- Vitamin Deficiency
- Poor Oral Hygiene and Nutrition
- Syphilis
- Previous Radiation

Clinical Presentation of Head and Neck Cancer

- Odynophagia, dysphagia, otalgia
- Hoarseness, weight loss, noisy breathing
- Nasal obstruction, epistaxis, otitis media, facial pain, loose dentition
- Cranial neuropathies, trismus, facial pain
- Neck mass

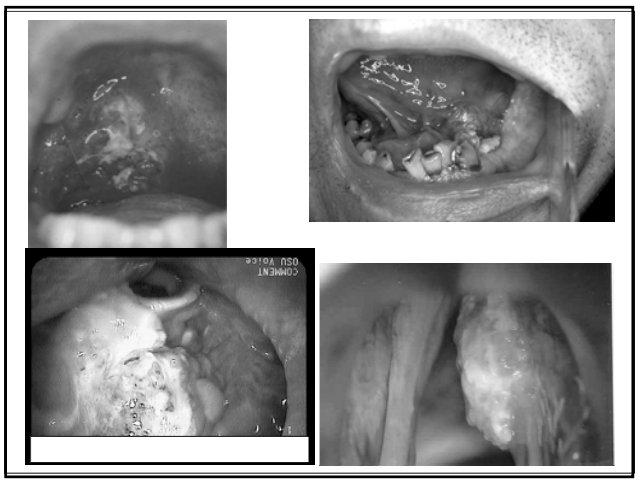
Etiology

- HPV infection
  - ✓ The incidence of these cancers is increasing dramatically
  - ✓ More common in young, white non-smoking males
  - ✓ Related to the number of oral sex, sexual partners



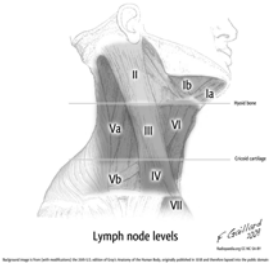
Physical Exam

- All mucosal head and neck cancers can be visualized in the clinic, but specialized equipment is often necessary
- Early detection is the key to improved survival



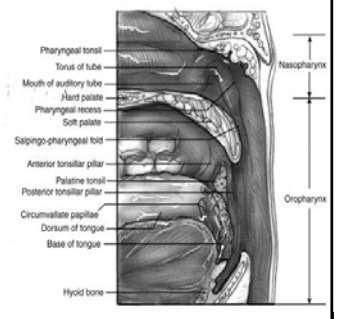
Neck Levels Correlate to Primary Site

- **Nasopharynx: level V**
- **Oral cavity: Levels I-III**
- **Oropharynx: Levels II-IV**
- **Larynx: Levels III, IV, VI, VII**
- **Thyroid: Levels Vb, IV, VI, VII**



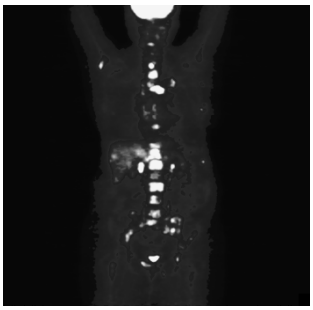
Physical Exam

- **Complete exam of all mucosal surfaces**
- **Pneumatic otoscopy**
- **Complete cranial nerve exam**
- **Neck palpation**



Adjuncts to Physical Exam

- **Imaging studies**
  - ✓ **Cxray (screening for mets)**
  - ✓ **CT scan of neck with contrast**
  - ✓ **MRI**
  - ✓ **PET or CT/PET**
- **Laboratory Evaluation**
  - ✓ **No serum markers available to date**
  - ✓ **Oral cytology and salivary cytokines**



Fine Needle Aspiration

- Simple office based procedure
- Must be performed on all neck masses
- Very sensitive and specific for squamous cell carcinomas of the head and neck

Management of Head and Neck Cancer

- The best opportunity to cure a patient is at the time of the original therapy
- Approximately 13,500 recurrences occur annually
- Salvage treatment always has inferior survival data

Staging of HNSCC

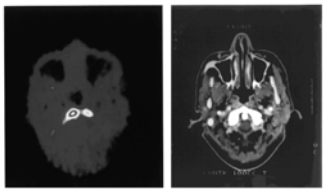
- Use TNM staging system
- Stage I: T1N0M0
- Stage II: T2N0M0
- Stage III: T3N0M0, any TN1M0
- Stage IVa: T4N0M0, any TN2-3,M0
- Stage IVb: Distant mets, Unresectable

General Treatment Principles

- Stages I and II can be treated surgically or with radiation with equivalent outcomes (except oral cavity)
- Stage III and IV disease requires multimodality therapy

Nasopharyngeal Cancer

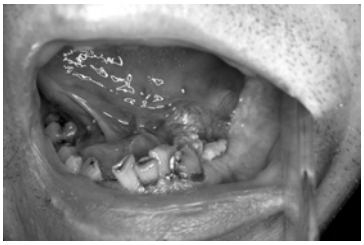
- Stage I and II
  - ✓ Radiation therapy
- Stage III and IV
  - ✓ Chemoradiation



Advances in Reconstruction Makes Primary Surgery Feasible

Oral Cavity Cancer

- Stage I and II
  - ✓ Surgery alone
- Stage III and IV
  - ✓ Surgery with appropriate reconstruction
  - ✓ Postoperative radiation or chemoradiation

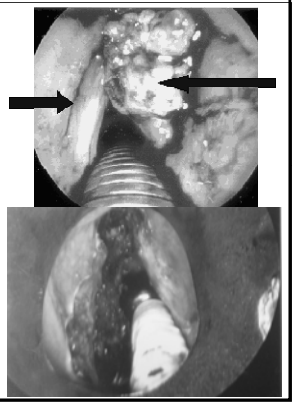


Indications for Postoperative Chemoradiation

- Positive margins on resection
- Multiple lymph nodes
- Extracapsular spread

Laryngeal Cancer

- Stage I and II Cancer
- Equivalent cure rates between surgery and primary radiation

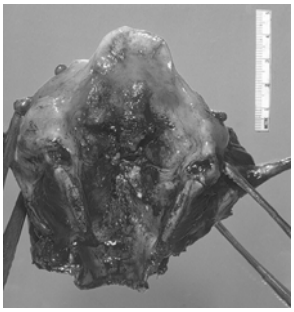


Advanced Laryngeal Cancer

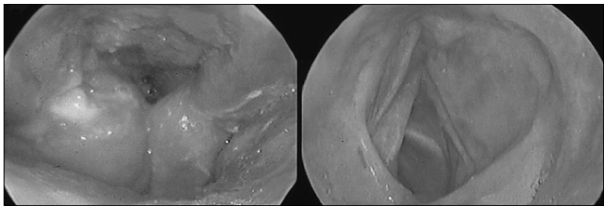
- Stage III and IV Laryngeal Cancer
- Conservation laryngeal surgery and chemoradiation therapy have resulted in a lower total laryngectomy rate

Laryngeal Cancer

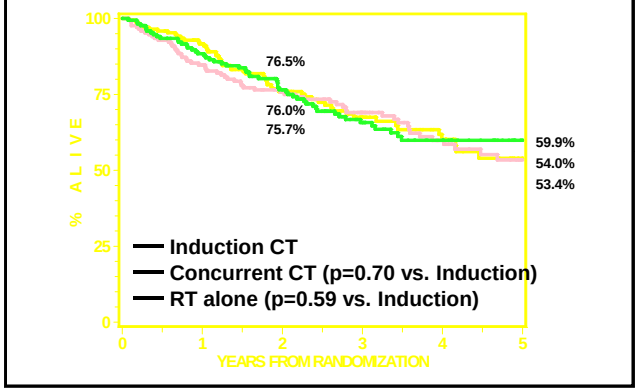
- Stage III and IV Larynx Cancer
- Total laryngectomy had been previous gold standard
- VA Laryngeal Cooperative Study and RTOG 91-11 challenged treatment paradigm



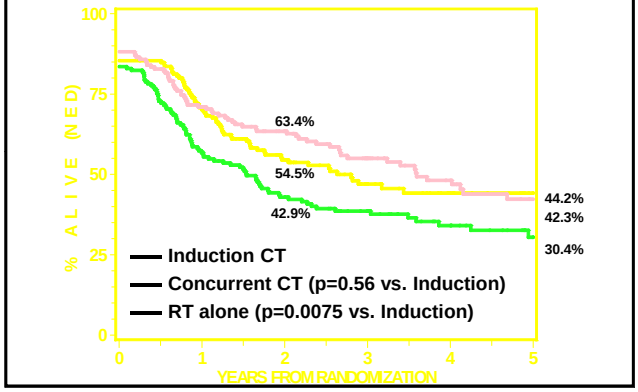
Chemoradiation Therapy



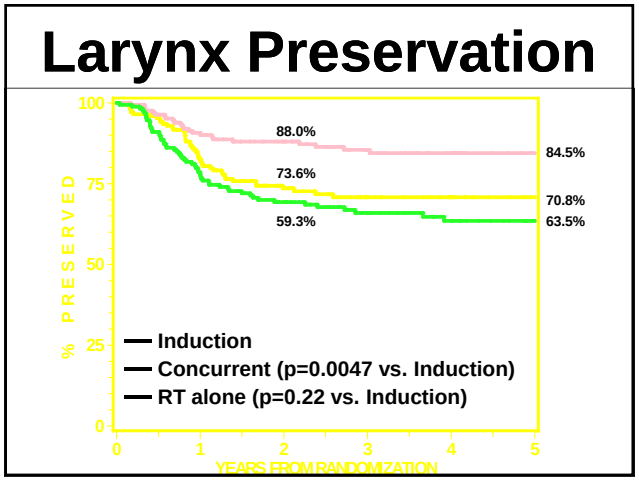
Overall Survival



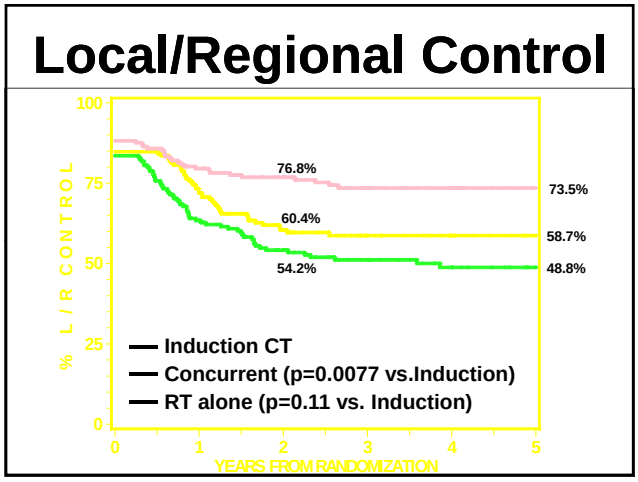
Disease-Free Survival



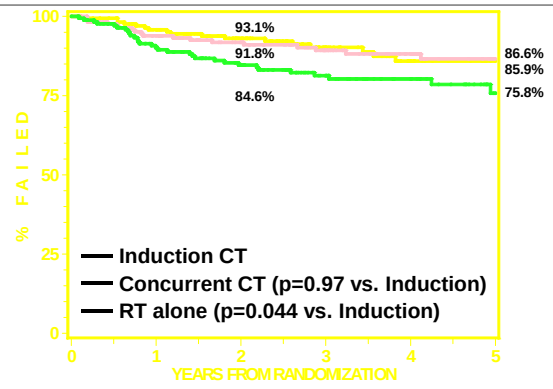
Larynx Preservation



Local/Regional Control



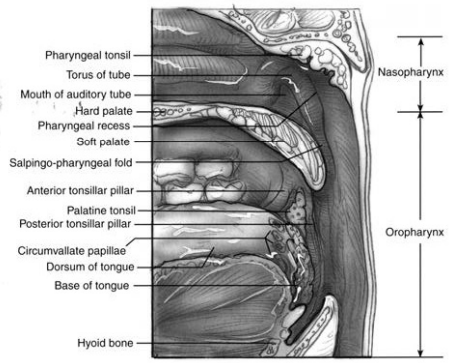
Distant Metastases



Treatment

- Stage I and II
  - ✓ lesion can be treated with primary XRT or primary surgery
- Stage III and IV
  - ✓ Surgery with post operative radiation (previous gold standard)
  - ✓ Multimodality therapy is necessary but the exact sequence is yet unclear

Oropharyngeal Carcinoma



Survival – Cancer of BOT

Rx	Trials	#	T4	Stage IV	LC	5-Yr
S +/- XRT	8	390	13		79%	
	7	500	11	31		49%
XRT +/- N.D.	9	806	13		76%	
	5	473	14	62		52%

Survival in Cancer of the Tonsil (Parsons, 2002)

Treat-ment	No. Studies	N	T4 (%)	Stage IV (%)	Local Control	5-Yr Survival
S +/-XRT	5	406	12		70%	
	7	321		44		47%
XRT +/- N.D.	12	1833	14		68%	
	14	2276		49		43%

Summary of Treatment Approaches

- Surgery with post-op XRT studies have similar outcomes to primary radiation with planned neck dissection
- Inadequate comparisons drawn with regards to swallowing outcomes and quality of life
- Primary surgery in this area often is accompanied by significant swallowing dysfunction and must be accompanied by adequate reconstruction
- Distant metastases were not addressed

Advances in Concurrent Chemo-XRT

- Improved survival over XRT alone (Calais, et al; Adelstein, et al; Pignon meta-analysis)
- Improved L/R control over XRT alone
- Increasing experience from work in larynx cancer
- Potential impact (delay) on distant metastases

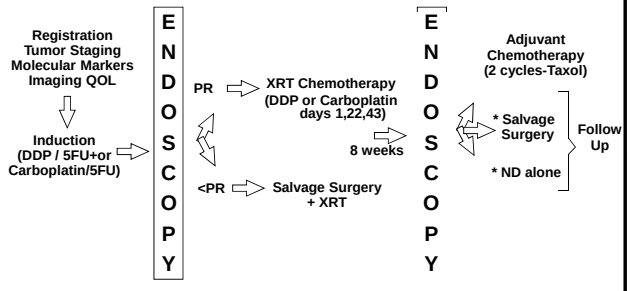
Who should we operate on…?

- Patients with small primary tumors
- Patients with large tumors that are unlikely to respond to radiation therapy
- How do we decide who won't respond to radiation therapy?

Why Induction Chemotherapy

- Best surrogate marker of radiosensitivity available
- Platinum-based regimens associated with improved survival (5% overall – Pignon, Domenge et al, p=.03)
- Early selection of patients for salvage surgery improves L/R control and minimizes morbidity and inoperability

Trial Design (UMCC 9921)



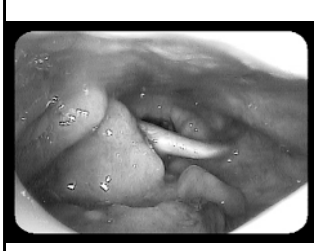
* If positive primary biopsy -- Primary site resection
If negative primary biopsy but positive node -- Neck dissection
If original neck node >3cm – Selective neck dissection
\+ Carboplatin substituted for cisplatin is renal insufficiency or significant hearing loss

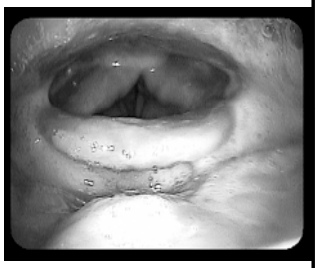
Study Results

81% responded to induction chemo

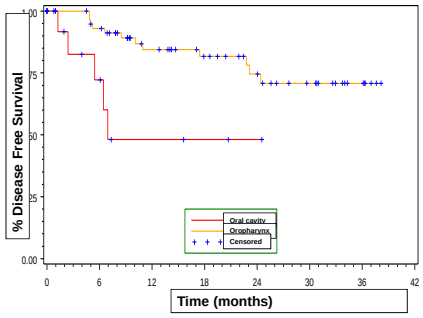
- 78.6% rate of organ preservation
- 70.4% overall survival at 4yrs
- 75.8% disease free survival at 4yrs
- No patient treated with chemo/XRT was Gtube or trach dependent
- No isolated locoregional recurrences

Pre and Post Treatment



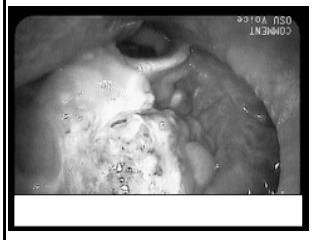


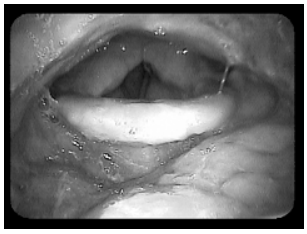
Disease Free Survival for Advanced Oropharynx and Oral Cavity Carcinoma – UMCC 9921



Oropharynx 2-Yr DFS = 71% (CI 56-86%)

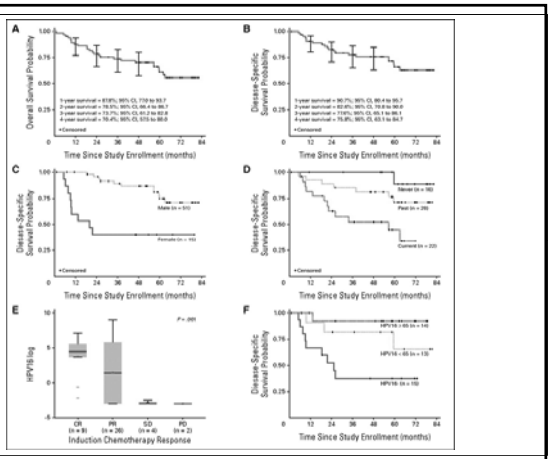
Pre and Post Treatment

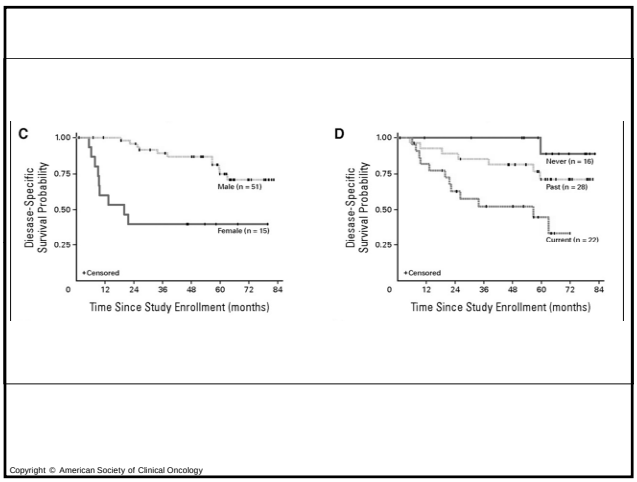


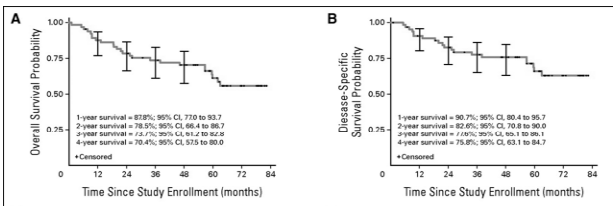


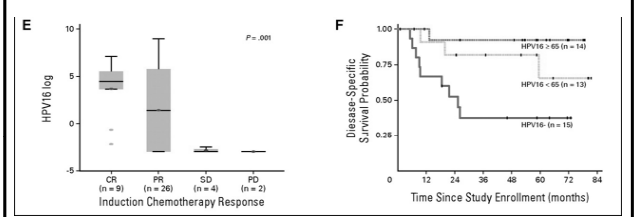
Translational Investigations in 9921

- 64% positive for HPV 16 (61.5% BOT, 68.5% tonsil)
- HPV significantly associated with young age, males and non-smokers
- HPV copy number associated with improved chemoresponsiveness, overall survival and disease specific survival
- Smoking status most important factor for survival
- Smokers are more likely EGFR positive, HPV negative

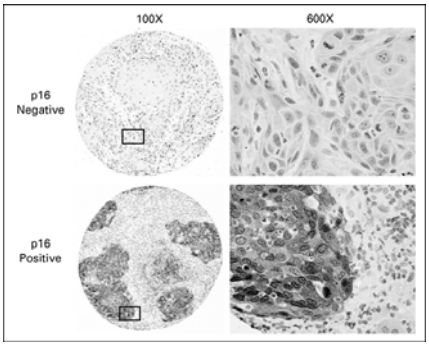








Representative images of p16 staining



Kumar, B. et al. J Clin Oncol; 26:3128-3137 2008

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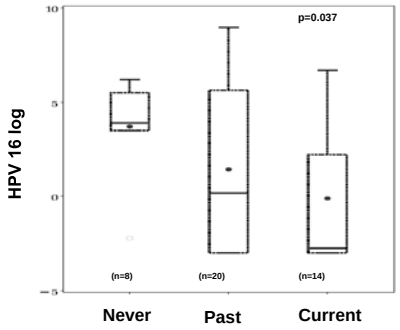
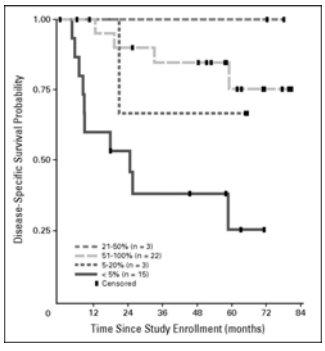
Who are the HPV + Patients



Disease-specific survival of patients according to p16 stain proportion



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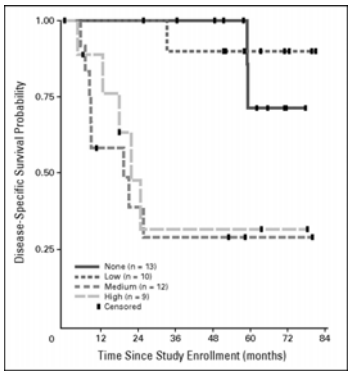
Disease-specific survival of patients according to epidermal growth factor receptor intensity



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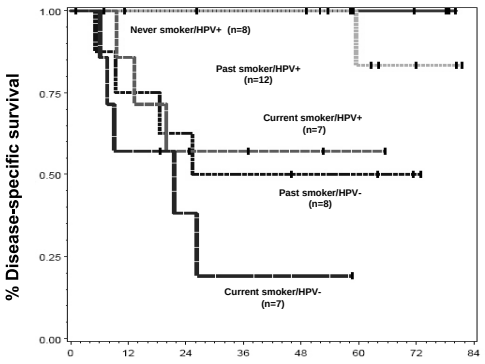
Survival Based on HPV and Smoking

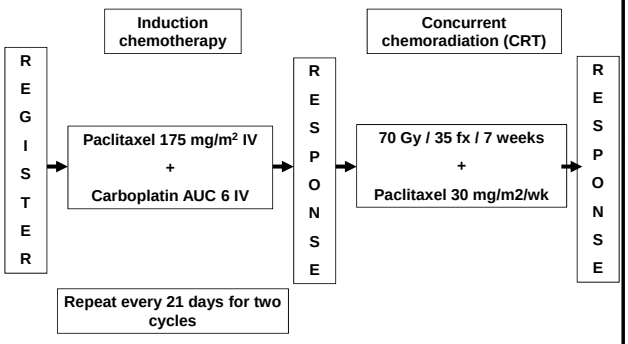


Response rates by tumor HPV status

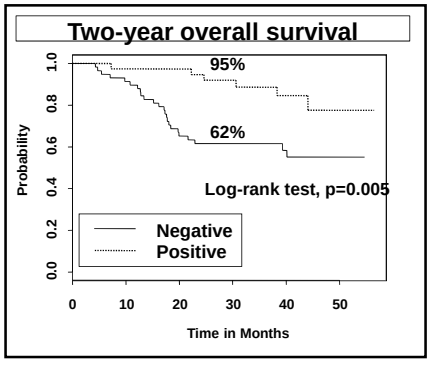
	HPV-pos	HPV-neg	p-value
Induction Complete or Partial	**82%**	**55%**	**0.01**
Protocol therapy Complete or Partial	**84%**	**57%**	**0.007**

Fakhry C et al JNCI 2008

ECOG 2399 Study Design



Tumor HPV status and survival



Fakhry C et al JNCI 2008

Survival outcomes by tumor HPV status

	HR**	95% CI
Overall survival HPV-positive tumor	**0.36**	**0.15-0.85**
Progression-free HPV-positive tumor	**0.27**	**0.10-0.75**

** Cox proportional hazard model adjusted for age, performance status, stage

Classic Head and Neck Cancer Patient

- Older, male
- Smoker, Drinker
- Malnourished
- Edentulous
- Low SES
- Keratinized Squamous Cell Carcinoma
- Because of this, NCI funding has been poor

HPV-positive HNSCC: A Distinct Clinical Entity

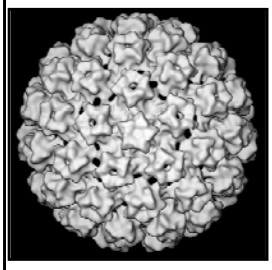
- Oropharynx
- Palatine and lingual tonsils
- Poorly differentiated (basaloid)
- Cystic metastasis
- Early T stage, advanced N stage
- Unknown primary

Gillison M et al. *J Natl Canc Inst.* 2000

Current Classic Case of Oropharyngeal Carcinoma

- Younger age
- Male
- High SES
- Risk factors: sexual activity
- Non smokers and nondrinkers
- Basaloid pathology
- Small primary tumor with cystic neck adenopathy

Human Papillomavirus

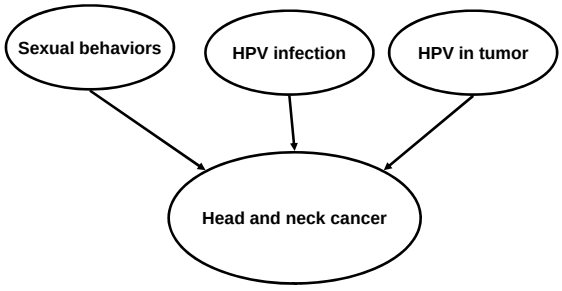


- Small, DNA viruses, protein coat
- Over 130 unique types
- Humans only known host
- Infection common
- Skin and Mucosal types
- Benign warts, precancer, cancer
- “High” and “low risk” types

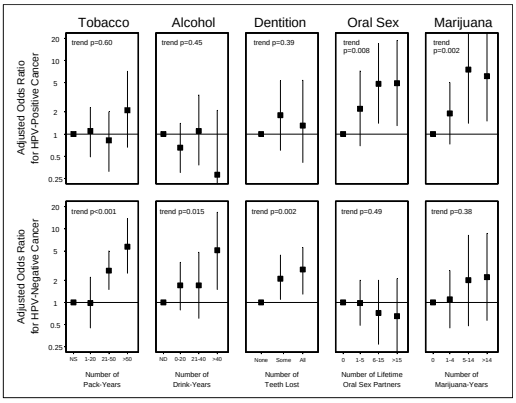
Evidence for HPV in Oropharynx Cancer as Strong as for Cervix

HPV-tumor association	Cervical Cancer	Oropharynx Cancer
High-risk DNA present	++	++
Tumor specificity	++	++
E6/E7 expression	++	++
Clonality-Copy number	++	++
Clonality-Variant analysis	++	+
Clonality- Integration	++	++
Malignant phenotype	++	+

Expected associations for HPV-caused tumors



Two different risk-factor profiles



Gillison M et al, JNCI. 2008.

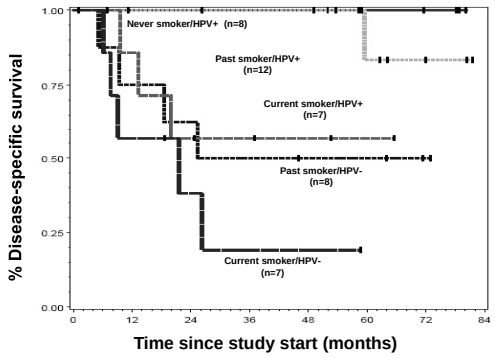
Two distinct head and neck cancers

	HPV-positive	HPV-negative
Anatomic site	Tonsil / BOT	All sites
Histology	Basaloid	Keratinized
Age	Younger	Older
Gender	3:1 men	3:1 men
SE status	High	Low
Risk factors	Sexual behavior	Alcohol / tobacco
Cofactors	Marijuana	Diet, hygiene
Survival	Improved	Worse
Incidence	Increasing	Decreasing

Incidence Trends in US

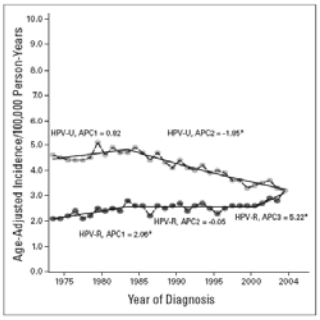
- Surveillance, Epidemiology and End Results Program (SEER), National Cancer Institute
-
- Incidence and survival of HNSCC in US from 1973-2004
- 45,769 oral (oral cavity and oropharynx) squamous cell cases
- Classified as potentially HPV-related vs. unrelated based on primary site.

Survival Based on HPV and Smoking



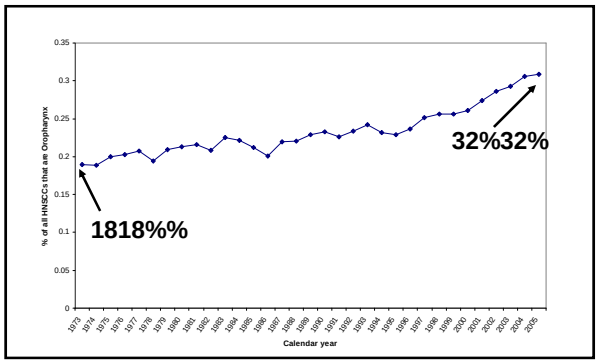
Increasing incidence of oropharynx cancers in the US

- 9 SEER registries
- 1973-2004
- 46,000 cases
- HPV-related
  - ✓ Base of tongue
  - ✓ Lingual and palatine tonsil
  - ✓ Oropharynx
- HPV-unrelated
  - ✓ Tongue
  - ✓ Gum
  - ✓ Floor of mouth
  - ✓ Palate
  - ✓ Other mouth



Chaturvedi et al. JCO, 2008

Proportion of all HNSCC that are oropharynx, U.S. 1973-2005



Chaturvedi and Gillison, unpublished

Actuarial life-table estimates of survival

Period	Two-year survival HPV-R vs. HPV-U	P-value
1973-1982	46.6 vs. 47.2%	0.71
1983-1992	56.0 vs. 49.6%	<0.01
1993-2004	69.7 vs. 50.3%	<0.01

Chaturvedi A et al, JCO 2008

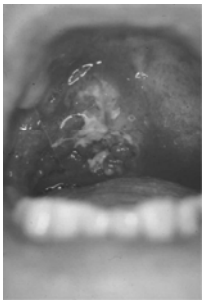
Tonsillar cancer HPV prevalence by calendar period, Swedish Cancer Registry

Period	HPV prevalence	Chi square P-value
1970-1979	7 of 30, 23%	Ref
1980-1989	12 of 42, 28%	0.79
1990-1999	48 of 84, 57%	0.0025
2000-2002	32 of 47, 68%	<0.001

Hammarstedt L et al, Int J Cancer 2006 119: 2620

Sites of Recurrence

- **Primary Site**
  - ✓ **Most common**
  - ✓ **20-30% of HNSCCa**
- **Neck**
  - ✓ **Next most common site**
  - ✓ **10-15% of recurrences**
- **Distant**
  - ✓ **Approx. 10% but rising rapidly**



Prognosis in Recurrent Head and Neck Cancer

- Generally poor
- Stell et.al reported on 515pts
  - ✓ Prognosis varies with
    - Time to first recurrence ($p<0.0001$)
    - Site of recurrence ($p<0.005$)
    - Patient performance status ($p<0.05$)
    - Recurrent stage ($p<0.05$)

Summary

- Head and Neck Cancer is a broad disease classification
- Early diagnosis is the key to improved outcomes
- Many tumors are difficult to detect on physical exam without specialized equipment
- Treatment various according to disease site
- HPV has changed the face of this cancer

Pearls for Primary Care Providers

- Refer to Head and Neck Surgeon if:
- Earache or sore throat that does not respond to ONE course of antibiotics
- Any neck mass
- Unilateral nasal obstruction/epistaxis
- Serous or acute otitis media in an adult