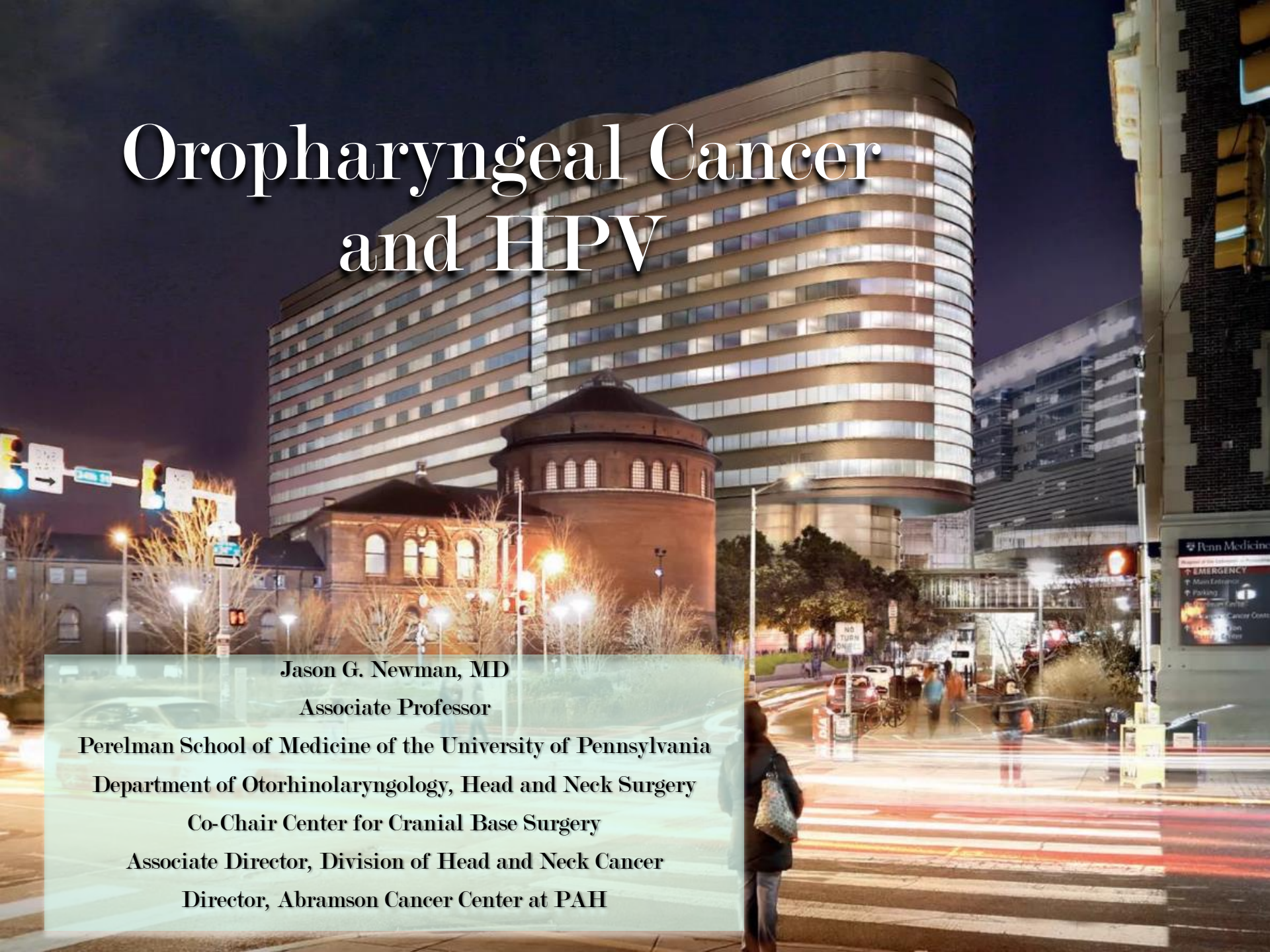
Oropharyngeal Cancer and HPV



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Disclosures

Consultant, Medtronic, Inc.

Consultant, Boulder Surgical

Medical Board, Castle Biosciences

The cancer burden

- American Cancer Society's estimate oral cavity & oropharyngeal cancers in the United States 2019:
  - 53,000 cases
  - 10,860 deaths
  - About 70-75% of oropharynx cancer caused by HPV in US
  - 15,500 men and 3,500 women with HPV related oropharynx cancer

What's the role of HPV

- Double stranded DNA virus
- Several hundred subtypes
- Unique to humans
- Type 16 and 18 are known carcinogens, but other less common ones (31,45) are also carcinogens
- Infects the basal epithelial cells
- Replicates with the host genome

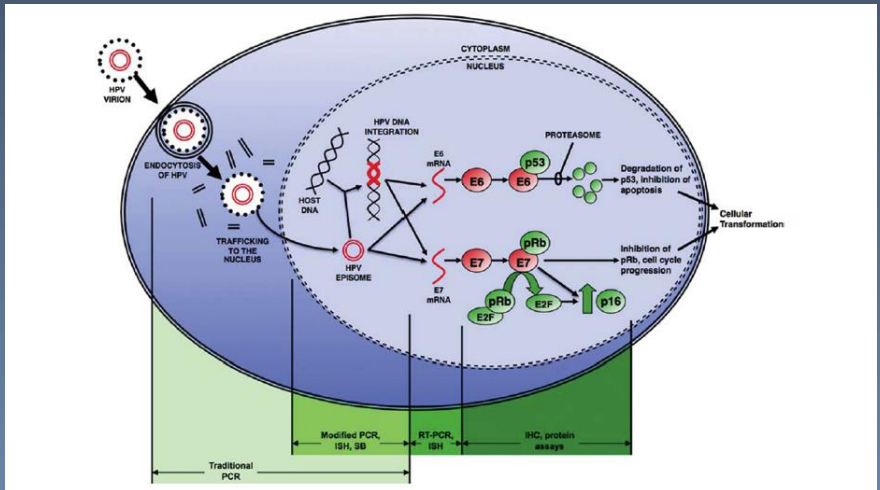
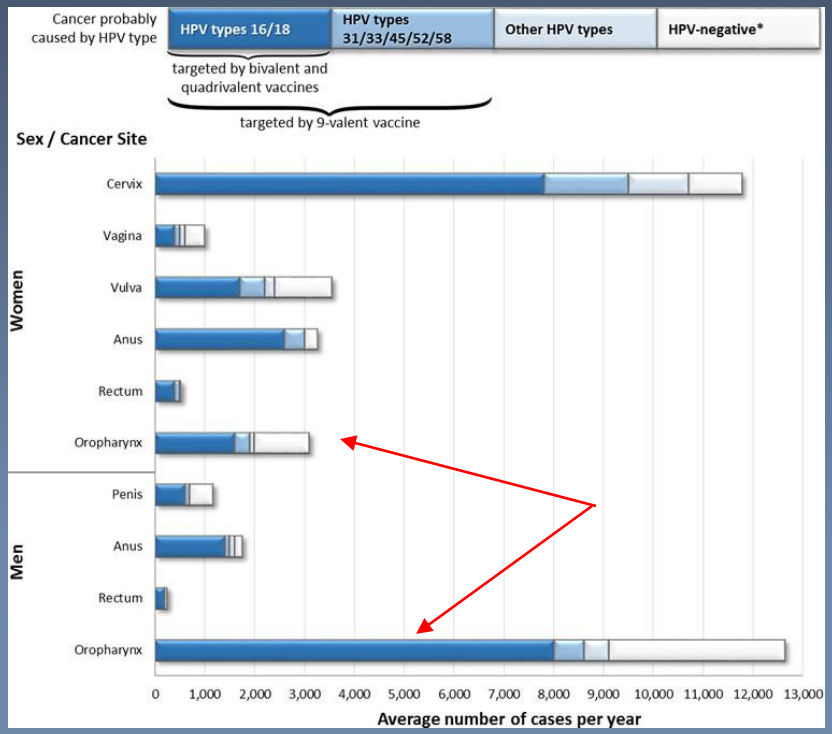


Fig. 1. Schematic of HPV infection of a mucosal cell. After virion entry via endocytosis, the virus establishes a persistent infection as a viral episome or integrates into the host genome. HPV E6 and E7 oncoproteins are expressed from both forms of the viral DNA, which lead to p53 degradation and Rb inhibition, respectively. Methods of HPV, oncogene or p16 detection are depicted with respect to stage of HPV biologic activity.

US Cancers caused by HPV



- Burden of HPV oropharynx cancer is higher than the burden of cervical cancer in the US.
- We have no screening
- The incidence continues to rise

What do we do?

- We have a vaccine! (or three)
  - Gardisil- HPV 6, 11, 16, 18
  - Gardisil 9 HPV 6,11,16,18, 31,33,45,52,58
  - Cervarix- HPV 16,18
- Over 95% effective at preventing pre-cancers and cancers (cervical and vaginal) caused by HPV
- Not effective if patient already infected
- No proof yet, but preliminary research suggests it is effective against oropharynx cancer

Need to improve public awareness

- This is a cancer vaccine not just an STD vaccine!
  - AAP and CDC- noted vaccine curves have flattened
- Vaccinate boys and girls
  - Higher incidence of this cancer in men
- According to the CDC, estimated 44,000 HPV related cancers in 2016
  - 25,000 in women (3,500 oropharynx)
  - 19,000 in men (15,500 oropharynx)

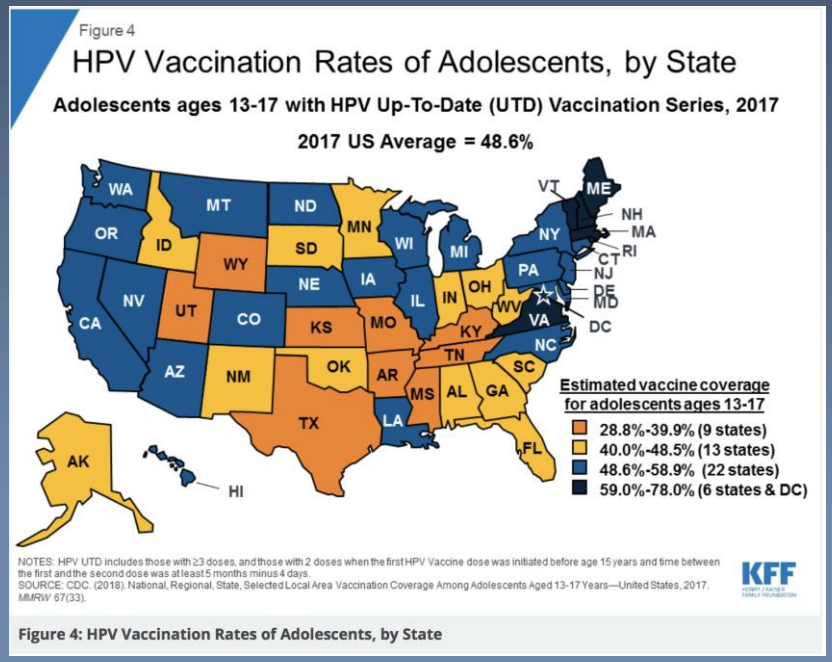


Figure 4: HPV Vaccination Rates of Adolescents, by State

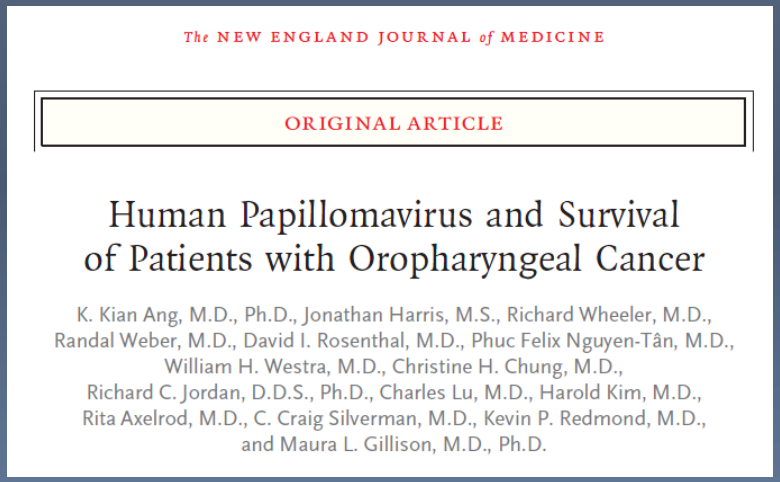
HPV Recommendations by CDC

- Girls AND boys receive three doses of vaccine at ages 11-12
- Can start as early as age 9, but should be done before age 13
- Also recommended for women until age 26, and men until age 21
- All health care providers should be advocates for HPV vaccination
- HPV vaccination is CANCER PREVENTION
- Vaccination now considered under some circumstances from age 26-45

How does this affect Head and Neck Cancer?

- Forced to reconsider some of our most routine "truths" in head and neck cancer
  - Patient demographics
  - Risk factors
  - Results of previous studies (race, gender, new drugs or surgeries, different demographics or countries)
  - Role of staging, nodes
  - Role of Extra-capsular spread (ECS)

Improved prognosis



The NEW ENGLAND JOURNAL of MEDICINE

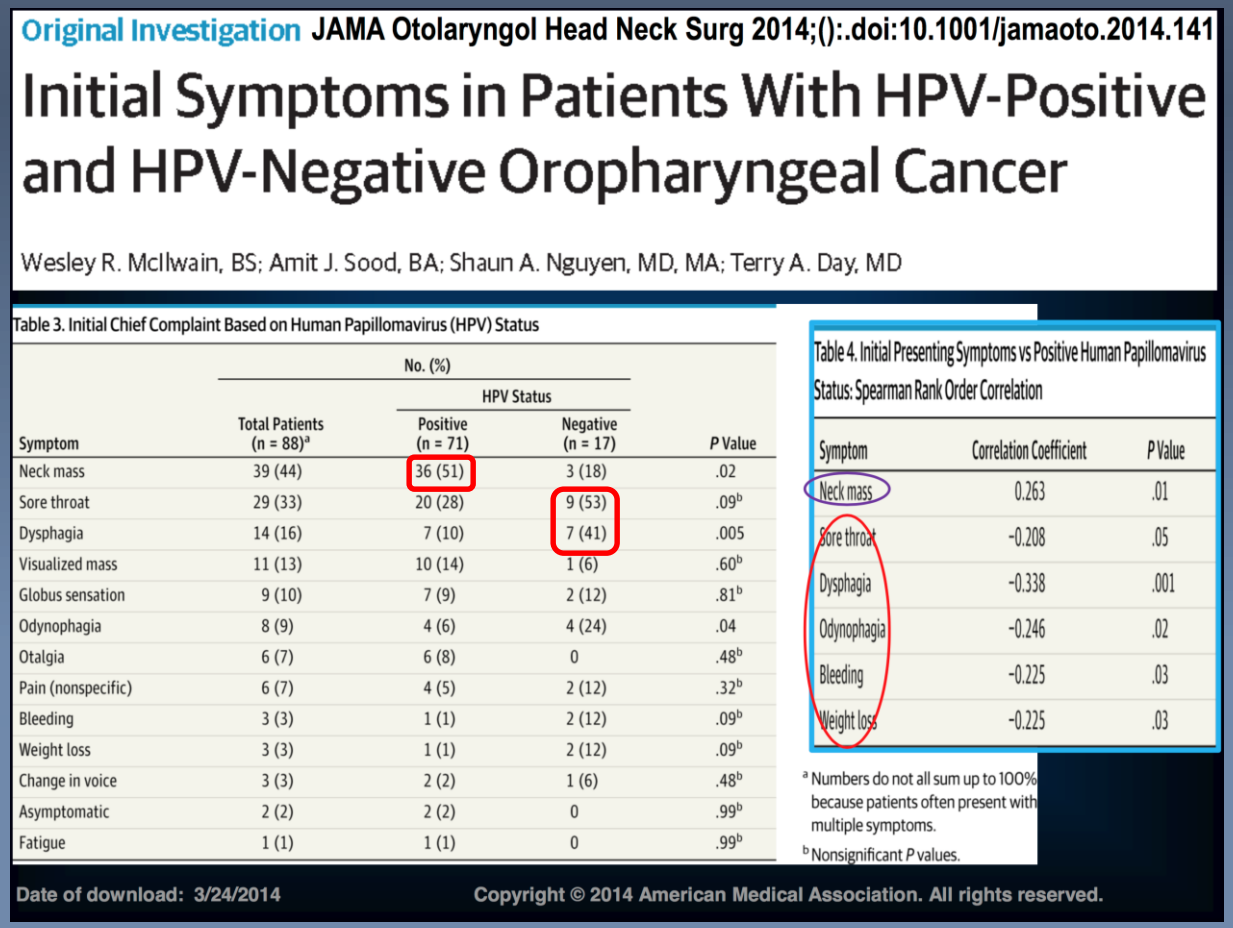
ORIGINAL ARTICLE

Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

K. Kian Ang, M.D., Ph.D., Jonathan Harris, M.S., Richard Wheeler, M.D., Randal Weber, M.D., David I. Rosenthal, M.D., Phuc Felix Nguyen-Tân, M.D., William H. Westra, M.D., Christine H. Chung, M.D., Richard C. Jordan, D.D.S., Ph.D., Charles Lu, M.D., Harold Kim, M.D., Rita Axelrod, M.D., C. Craig Silverman, M.D., Kevin P. Redmond, M.D., and Maura L. Gillison, M.D., Ph.D.

- RTOG 0129 (2010)
  - Accelerated fraction RT and platinum compared to standard RT with platinum
  - Controlled for HPV
  - Survival (regardless of arm) was significantly different in HPV+ (82 vs. 57%)

Presentation



Original Investigation JAMA Otolaryngol Head Neck Surg 2014;():.doi:10.1001/jamaoto.2014.141

Initial Symptoms in Patients With HPV-Positive and HPV-Negative Oropharyngeal Cancer

Wesley R. McIlwain, BS; Amit J. Sood, BA; Shaun A. Nguyen, MD, MA; Terry A. Day, MD

Table 3. Initial Chief Complaint Based on Human Papillomavirus (HPV) Status

Symptom	No. (%) Total Patients (n = 88)[a]	HPV Status Positive (n = 71)	HPV Status Negative (n = 17)	*P* Value
Neck mass	39 (44)	36 (51)	3 (18)	.02
Sore throat	29 (33)	20 (28)	9 (53)	.09[b]
Dysphagia	14 (16)	7 (10)	7 (41)	.005
Visualized mass	11 (13)	10 (14)	1 (6)	.60[b]
Globus sensation	9 (10)	7 (9)	2 (12)	.81[b]
Odynophagia	8 (9)	4 (6)	4 (24)	.04
Otalgia	6 (7)	6 (8)	0	.48[b]
Pain (nonspecific)	6 (7)	4 (5)	2 (12)	.32[b]
Bleeding	3 (3)	1 (1)	2 (12)	.09[b]
Weight loss	3 (3)	1 (1)	2 (12)	.09[b]
Change in voice	3 (3)	2 (2)	1 (6)	.48[b]
Asymptomatic	2 (2)	2 (2)	0	.99[b]
Fatigue	1 (1)	1 (1)	0	.99[b]

Table 4. Initial Presenting Symptoms vs Positive Human Papillomavirus Status: Spearman Rank Order Correlation

Symptom	Correlation Coefficient	*P* Value
Neck mass	0.263	.01
Sore throat	-0.208	.05
Dysphagia	-0.338	.001
Odynophagia	-0.246	.02
Bleeding	-0.225	.03
Weight loss	-0.225	.03

[a] Numbers do not all sum up to 100% because patients often present with multiple symptoms.

[b] Nonsignificant *P* values.

HPV and Management of OP Cancer

- Studies imply we should intensify treatment for HPV negative patients, and de-intensify for HPV positive (smoking?)
- NCCN currently has no recommendations for how to do this
- New staging system
  - Does not address treatment, only outcomes
  - “Stage using AJCC 8, treat using AJCC 7”

How Should We Treat These Cancers?

Cochrane Database

Summary of findings for the main comparison. Minimally invasive surgery versus radiotherapy/chemoradiotherapy for small-volume primary oropharyngeal carcinoma

Minimally invasive surgery versus radiotherapy/chemoradiotherapy for small-volume primary oropharyngeal carcinoma

Patient or population: patients with small-volume primary oropharyngeal carcinoma

Settings: inpatient

Intervention: transoral, minimally invasive surgery (transoral robotic surgery/transoral laser microsurgery) with or without adjuvant radiotherapy or adjuvant chemoradiotherapy

Comparison: primary radiotherapy with or without induction or concurrent chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Primary radiotherapy ± induction or concurrent chemotherapy	Transoral, minimally invasive surgery ± adjuvant radiotherapy or adjuvant chemoradiotherapy				
Overall survival	No data	No data	No data	No data	—	—
Locoregional control	No data	No data	No data	No data	—	—
Progression-free survival	No data	No data	No data	No data	—	—
Gastrostomy rate (at 1 year)	No data	No data	No data	No data	—	—
Tracheostomy rate	No data	No data	No data	No data	—	—
Swallowing function (MDADI)	No data	No data	No data	No data	—	—
Quality of life (EORTC QLQ-C30 and H&N35)	No data	No data	No data	No data	—	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **EORTC:** European Organisation for Research and Treatment of Cancer; **MDADI:** MD Anderson Dysphagia Inventory

*

Minimally invasive surgery versus radiotherapy/chemoradiotherapy for **small-volume** primary oropharyngeal carcinoma.
Howard J, Masterson L, Dwivedi RC, Riffat F, Benson R, Jefferies S, Jani P, Tysome JR, Nutting C.
Cochrane Database Syst Rev. 2016 Dec 11;12:CD010963. doi: 10.1002/14651858.CD010963.pub2. Review.

Current Trials

Table 1
Selection of treatment de-escalation trials for HPV-driven oropharyngeal cancer (details available at www.clinicaltrials.gov).

Identifier	Phase	Population	Intervention
Substitution of cisplatin by cetuximab			
NCT01302834[a] RTOG 1016	III	N = 987 Stage III-IV	RT (70 Gy) with Cisplatin (100 mg/m^2 X2) or weekly Cetuximab
NCT01874171[a] De Escalate HPV	III	N = 304 Stage III-IVa	RT (70 Gy) with Cisplatin (100 mg/m^2 X3) or weekly Cetuximab
NCT01855451	III	N = 200 Stage III-IV	RT (70 Gy) with weekly Cetuximab or weekly Cisplatin (40 mg/m^2)
Induction chemotherapy followed by lower radiation dose in good responders			
NCT01084083[a] ECOG 1308[25]	II	N = 80 Stage III-IV	Paclitaxel, cisplatin and cetuximab followed by low (54 Gy) or standard dose IMRT with cetuximab depending on the response to IC
NCT01706939 Quarterback trial	III	N = 365 Stage III-IV	3 Cycles TPF followed by low (56 Gy) or standard dose (70 Gy) IMRT with weekly cetuximab + carboplatin or carboplatin only, depending on the response to IC
Induction chemotherapy followed by reduced (chemo)radiation dose and volume in good responders			
NCT02258659[a,b] OPTIMA trial	II	N = 62 Stage III-IV	Patients (pts) are classified as low-risk (≤T3, ≤N2B, ≤10 PYH) or high-risk (T4 or ≥N2C or >10 pack/years) All pts receive 3 cycles of carboplatin and nab-paclitaxel and dose/volume adapted radiotherapy 1) Low-risk pts with ≥50% response received low-dose radiotherapy alone to 50 Gy 2) Low-risk pts with 30–50% response OR high-risk pts with ≥50% response received low-dose chemoradiotherapy to 45 Gy 3) All other pts, i.e. poor responders, receive regular-dose CRT All pts also received de-escalated RT volumes limited to the first echelon of uninvolved nodes. CRT consisted of paclitaxel, 5-FU, hydroxyurea, and 1.5 Gy twice daily RT every other week. Primary site biopsy and neck dissection performed after de-escalated treatment for pathologic confirmation
Radiation therapy alone (standard or reduced dose)			
NCT02254278[a] NRG HN002	II	N = 295 Stage III-IV	Reduced dose IMRT (60 Gy) with or without cisplatin (40 mg/m^2)
Upfront surgery			
NCT01898494 ECOG 3311	II	N = 377 Stage III-IVa	Transoral surgery followed by pathological risk stratification: – Low-risk patients do not have adjuvant therapy – Intermediate-risk patients are randomized between 50 and 60 Gy – High-risk patients undergo RT (66 Gy) with weekly cisplatin (40 mg/m^2)

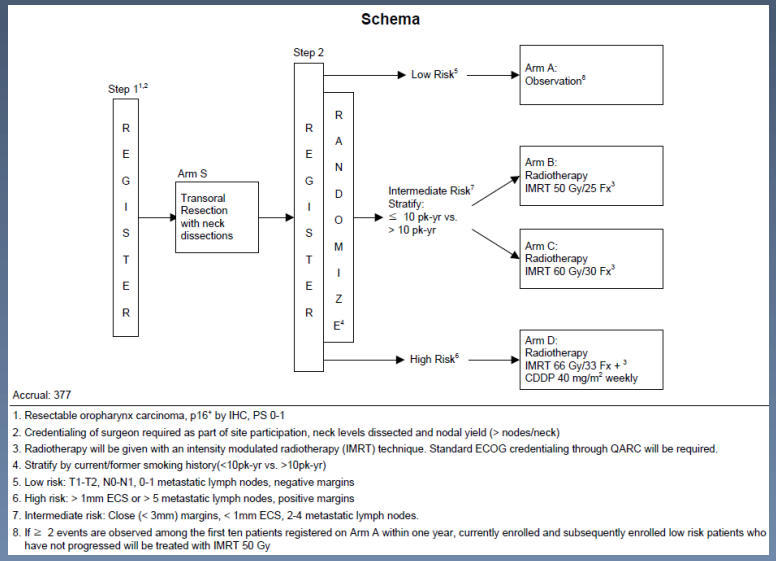
[a] Accrual completed.
[b] Very preliminary data [52] (1 year median follow-up) were presented during ASCO 2017 showing promising rates of response to induction chemotherapy and high rates of pathological response after dose reduced radiotherapy. Severe mucositis and PEG tube dependency at 3 months post RT were correlated with RT dose ($p = .03$ and $<.001$ respectively). Longer follow-up needed to consider survival results.

HPV Stratification Studies: Non-Surgical

- ECOG 1308
  - HPV + patients
  - Induction chemo with deintensification of RT for cCR
  - For cCR (70% of patients) 2 yr PFS and OS of 96% and 96% in patients <T4,<N2C,<10 Pack years smoking
- Quarterback
  - TPF, then randomize to standard or deintensified RT with carboplatin
  - Just published: 23 patients, similar 3 yr PFS/OS (87.5% vs 83.3%). 50% of failures in high risk HPV variants.
  - Conclusion: rdCRT after IC may be appropriate. HPV variant testing and smoking relevant
- RTOG 1016
  - HPV + patients
  - Platinum based CRT vs RT with cetuximab
  - Results favor platinum
- De-Escalate HPV
  - Similar to 1016
  - Results favor platinum

HPV Stratification Studies: Surgical

- ECOG 3311
  - HPV + patients
  - Randomized Phase II Trial
  - Transoral surgery then randomize intermediate group to standard vs de-intensified RT
  - Completed enrollment



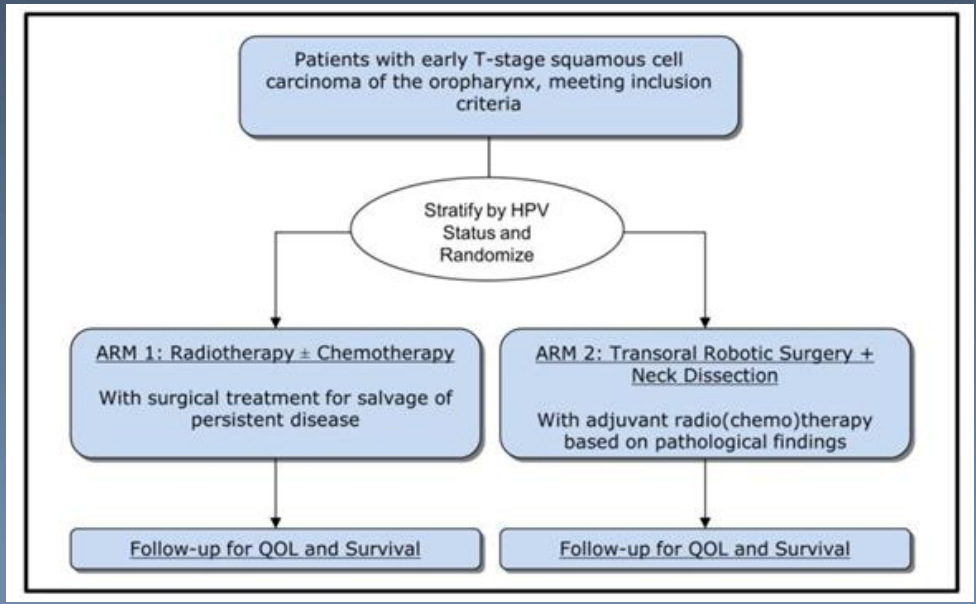
ECOG 3311 Schema

HPV Stratification Studies: Surgical

- ADEPT
  - Adjuvant De-escalation, Extracapsular Spread, P16+, Transoral (ADEPT)
  - Patients can randomize or choose
  - Does ECE matter in HPV+ HNSCCa?
  - Completed Enrollment

HPV Stratification Studies: Randomized

- ORATOR- Randomize primary TORS with primary CRT
- Non-US trial
- 68 patients
- Primary endpoint- QOL at 1 year



ORATOR Schema

Results

- Swallowing related scores were better in RT arm at 1 year (not a clinically meaningful difference)
- Toxicity patterns were different
- Patients should be informed of both options

- Caveats
  - After a bleeding death, all surgical patients were recommended for a tracheostomy.
  - Wider than average margins
  - 6 centers, unclear level of expertise/volume

Outcomes

- Survival
- Adverse Events
- Swallowing/QOL

THE Laryngoscope
FOUNDED IN 1896

Head and Neck

A systematic review of transoral robotic surgery and radiotherapy for early oropharynx cancer: A systematic review

John R. de Almeida MD, MSc, James K. Byrd MD, Rebecca Wu BSc, Chaz L. Stucken MD, Uma Duvvuri MD, PhD, David P. Goldstein MD, MSc, Brett A. Miles MD, DDS, Marita S. Teng MD, Vishal Gupta MD, Eric M. Genden MD ... See fewer authors

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February 2015, Volume 272, Issue 2, pp 463–471 | Cite as

Functional outcomes after TORS for oropharyngeal cancer: a systematic review

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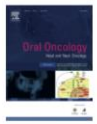
Katherine A. Hutcheson, F. Christopher Holsinger, Michael E. Kupferman, Jan S. Lewin

ELSEVIER

Oral Oncology
Volume 50, Issue 8, August 2014, Pages 696-703



Review

Oncologic, functional and surgical outcomes of primary Transoral Robotic Surgery for early squamous cell cancer of the oropharynx: A systematic review

Kate Kelly [a], Stephanie Johnson-Obaseki [b], Julie Lumingu [c], Martin Corsten [d]

Decision-making

PRACTICE GUIDELINES

ACR Appropriateness Criteria® Locoregional therapy for resectable oropharyngeal squamous cell carcinomas

Jonathan J. Beitler, MD, MBA,[1]* Harry Quon, MD, MS,[2] Christopher U. Jones, MD,[3] Joseph K. Salama, MD,[4] Paul M. Busse, MD, PhD,[5] Jay S. Cooper, MD,[6] Shlomo A. Koyfman, MD,[7] John A. Ridge, MD, PhD,[8] Nabil F. Saba, MD,[9] Farzan Siddiqui, MD, PhD,[10] Richard V. Smith, MD,[11] Francis Worden, MD,[12] Min Yao, MD, PhD,[13] Sue S. Yom, MD, PhD,[14] Expert Panel on Radiation Oncology – Head and Neck

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- There is no Level 1 evidence*
- Multi-D tumor board including surgeon
- Determine unresectability
- HPV and smoking are relevant
- T1-2, N0-N3, surgery or RT
- T3-4, primary RT ***

Counseling patients

- 85-90% of humans will be infected with the HPV virus
- Most people clear it within 1-2 years of infection
- Virus, like many viruses, can remain dormant and then resurface
- Vaccinate your kids/grandkids/relatives

Conclusion

- HPV testing should be considered a reflex test
  - All head and neck SCCa
  - All head and neck unknown primary
  - Subtype testing should be considered
- Counsel patients
- Counsel dental community, doctors and media
- Refer to Multidisciplinary Center
- Participate in clinical trials

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Thanks