Human Papillomavirus in Head and Neck Cancer

Adam L. Holtzman, M.D.

ACLI Medical Section Meeting 2019
Disclosures

Employment Relationship
• University of Florida

Compensation, Remuneration, Funding
• None applicable

Ownership or Investment Interests
• None applicable

Leadership Positions
• Only within UF
Disclosures

Hang out at your own risk
In this talk

HPV: background

Head and neck cancer

HPV in head and neck cancer

Treatment decisions
What we won’t discuss today

Head/neck cancers other than squamous cell carcinoma (SCCa)

Detailed molecular biology
Background: HPV
What is human papillomavirus (HPV)?

Double-stranded DNA virus

Highly species specific

About 200 varieties in humans
Only 13 cause cancer:

- HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68

- HPV 16 and 18 cause 63% of HPV-associated cancers
- HPV types 31, 33, 45, 52, and 58 cause an additional 10%

- HPV 16 is the most likely to both persist and to progress to cancer
What is human papillomavirus (HPV)?

Recall that HPV is also responsible for genital warts

- “Low-risk” strains, such as HPV 6 and 11, cause about 90%

If there is any connection to cancer it’s weak
What is human papillomavirus (HPV)?

Non-sexually transmitted warts are also from HPV

- HPV 1, 2 & 4: plantar and common warts
- HPV 3 & 10: flat warts
- HPV 2 & 7: butcher’s warts
- HPV 6&11: recurrent respiratory papillomatosis
How do people get HPV?

Respiratory form transmitted during childbirth

Casual contact and shared objects sufficient

Genitourinary and oral infections through intimate skin-skin or –mucosa contact

Essentially everyone who has sex gets HPV
How do people get HPV?

Most infections resolve within 12-24 months
Can have latent period with symptoms months+ later

There is some suggestion that the virus can reactivate later in life
Connection to cancer unclear
How can we prevent transmission of HPV?

Condoms reduce transmission but don’t eliminate
  • Uncovered skin is sufficient

The only real solution is the **vaccine**:

Gardasil 9  (earlier versions: Gardasil and Cervarix)
  • HPV 16 and 18 - most common in cancer
  • HPV 31, 33, 45, 52, and 58 - cancer
  • HPV 6 and 11 - 90% of genital warts

Ages 9-14:  2 shots (6 months apart)
Ages 15-45: 3 shots (2, 4 months apart)

~100% effective in preventing cancer and warts if given BEFORE SEXUAL CONTACT

0% effective if given after exposed to virus
How does HPV cause cancer?

Virus makes proteins E6 and E7 that make human cells live longer
  • Turn off brakes on the cell cycle (ex. p53 and pRB)

These same proteins cause human DNA to mutate more
  • Inhibit DNA repair
  • Suppress apoptosis
How does HPV cause cancer?

HPV performs lateral gene transfer, but no evidence cancer results from this.

Fun fact: As much as 8% of the human genome is ancient viruses passed down in this way.
How does HPV cause cancer?

Co-risk factors
• #1: Smoking
• #2: Alcohol

Pooled data: 11,221 cases and 16,168 controls

Calculated population attributable risks:

Alcohol* or tobacco: 72% (95% CI 61-79%)
• 4% alcohol alone
• 33% tobacco alone
• 35% alcohol and tobacco combined
• 74% for men
• 57% for women

• 33% for cases <45 years
• 73% for cases >60 years
• 84% in Europe
• 83% in Latin America
• 51% in North America

*3+ drinks per day Hashibe J Nat Can Inst 99(10) 2007
How does HPV cause cancer?

Co-risk factors

#1: Smoking
#2: Alcohol
Poor hygiene
Mechanical irritation
Gastroesophageal reflux
Chronic infection
Immunosuppression
Poor nutrition
Wood dust
Metal vapors

Nasopharynx cancer: Epstein-Barr Virus (EBV)
Specific subtype that resembles lymphoma
Extremely common in Asia
Rare here EXCEPT in Asian immigrant population
Which cancers?

1. HPV causes **all** or many
   - Uterine cervix
   - Anal canal
   - Penis
   - Vagina, vulva

2. HPV causes **some**, presence is **prognostic**:
   - Oropharynx

3. HPV sometimes present, **role unclear**:
   - Skin: basal, squamous, and melanoma
   - Oral cavity
   - Larynx, hypopharynx
   - Nasopharynx
Worldwide picture quite different from U.S.

Routine Pap testing and now vaccine have changed the HPV landscape.
Head & neck cancer
Cancers of the head and neck

65,000 in U.S. in 2017

Average age at diagnosis is 62

> 90% are squamous cell carcinoma

> 75% associated with tobacco exposure and/or alcohol

Overall declining as smoking does

However rise in rates of HPV-associated cancers rising
Cancers of the head and neck

About 70% test positive for HPV

2008-2012:
12,638 of 15,738 HPV positive were in males

1988 – 2004 there was a **225%** increase in HPV-positive cancers
Cancers of the head and neck: Treatment

Surgery
Radiation therapy
Chemotherapy

Can sometimes omit chemo
• If small
• If not in lymph nodes

Can sometimes omit a local therapy
• Done empirically – depends on site
Oropharynx vs oral cavity: a lesson in biology

Orophx: Radiation is primary treatment
OrCav: Surgery is primary treatment

Oral cavity has worse cause-specific survival

Orophx: HPV status prognostic
OrCav: HPV does not affect outcomes

Rusthoven Cancer 112(2) 2008
An example of why you should not extrapolate

Tonsil versus retromolar trigone

Tonsil region:
- LRC at 5 years: 75%
- Best first treatment: radiotherapy
- HPV prognostic

Mendenhall Am J Oncol 18(11) 2000

RMT:
- LRC at 5 years: 60%
- Best first treatment: surgery
- HPV not prognostic

Hitchcock Am J Otol 36(20) 2015
HPV in head and neck cancer
How we learned about HPV: cervical cancer

Early testing poor – hard to establish relationship
As soon as testing reliable, used for screening
Immediate work on vaccine begun

What about those other mucosal squamous cancers?

Later converted to testing p16 instead of HPV DNA
p16 protein expression changed by HPV
p16 test shown to be just as reliable
Test much cheaper
We learned HPV was present in H&N cancers

Published in 2000.

Relationship not understood. Causal? Associative?

They did know oropharynx was the site where it mattered

Gillon et al looking for HPV in different sites
Where it got traction: a big study rescued

RTOG 0129
Oral cavity, oropharynx, hypopharynx, larynx: 721 patients
Testing different methods of radiotherapy
**Negative study** - no difference in outcomes – big problem for authors

**BUT**
HPV status determined in 74.6% of oropharynx patients
Where it got traction: a big study rescued

RTOG 0129

HPV status determined in 74.6% of oropharynx patients

HPV+ more common in
• non- or light smokers
• younger age
• Caucasians
• smaller primary tumors at diagnosis
Where it got traction: a big study rescued RTOG 0129
HPV(+) and HPV(-) arms balanced for other factors

3 year overall survival: 84% vs 51%
3 year progression-free survival: 74% vs 38%
Where it got traction: a big study rescued

Recursive partitioning analysis used to create risk groups

**Smoking remained a powerful predictor of survival**
HPV negative OPX SCCA

Smoker
Median age early 60s
Less likely to be white
Diagnosed at later stage

No gender difference (~80% male both)

HPV positive OPX SCCA

Non-smoker
Median age early 50s
More often white
Diagnosed at early stage
Now our staging system is broken! AJCC 7th Ed.

For HPV(+) SCCa of the oropharynx, stage was no longer predictive of outcome

O’Sullivan Lancet Onc 2016
**Improved staging for oropharynx: AJCC 8th Edition**

Different staging for HPV(+) and HPV(-)

---

<table>
<thead>
<tr>
<th>N Category</th>
<th>N Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative; or metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative; or metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in any lymph node(s) and clinically overt ENE-positive</td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in any node(s) and clinically overt ENE-positive</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis in any node(s) and clinically overt ENE-positive</td>
</tr>
</tbody>
</table>

So for example, multiple ipsilateral nodes is staged:
HPV(+): N1
HPV(-): N2b (or N3b if cancer outside node!)
Improved staging for oropharynx: AJCC 8th Edition

<table>
<thead>
<tr>
<th>T CATEGORY</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>NA</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>T1</td>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>T2</td>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>T3</td>
<td></td>
<td>II</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>T4</td>
<td></td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
</tbody>
</table>

*Any M1 is stage IV.

No Stage IV Subdivision

---

<table>
<thead>
<tr>
<th>T CATEGORY</th>
<th>N0</th>
<th>N1</th>
<th>N2a,b,c</th>
<th>N3a,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td></td>
<td>I</td>
<td>IVA</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td></td>
<td>II</td>
<td>IVA</td>
<td>IVA</td>
</tr>
<tr>
<td>T3</td>
<td></td>
<td>III</td>
<td>IVA</td>
<td>IVA</td>
</tr>
<tr>
<td>T4a</td>
<td></td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
</tr>
<tr>
<td>T4b</td>
<td></td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
</tr>
</tbody>
</table>

*Any M1 is stage IVC.
We’re learning there is more to the story

8 years since HPV identified as a key factor
5 years since routinely tested

Outcomes remain excellent for HPV(+)

Same rate of distant mets as HPV(-): ~10%

Unusual pattern of distant metastasis
  • More often multi-organ
  • Especially in bone
  • LATE: many after 3 years (versus >90% within 2y)
  • Have better salvage rates (11% vs 4% @2 years*)

*Huang Oral Oncology 49(1) 2013
If this cancer recurs, can they be salvaged?

Overall salvage rate in those without distant mets = 12%

<table>
<thead>
<tr>
<th>Site of Recurrence</th>
<th>No. of Patients</th>
<th>Procedure Success (successful/attempted)</th>
<th>Salvage Success (successful/all LR recurrences)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary site only</td>
<td>85</td>
<td>50% (15/30)</td>
<td>18%* (15/85)</td>
</tr>
<tr>
<td>Neck only</td>
<td>36</td>
<td>10% (1/10)</td>
<td>3%* (1/36)</td>
</tr>
<tr>
<td>Primary and neck</td>
<td>16</td>
<td>0% (0/3)</td>
<td>0% (0/16)</td>
</tr>
<tr>
<td>Total</td>
<td>137</td>
<td>37% (16/43)</td>
<td>12% (16/137)</td>
</tr>
</tbody>
</table>

Abbreviation: LR, local-regional  
*p=0.02
Rates of HPV(+) oropharynx cancer are rising

Many theories, little data
HPV is present in SCCa in other sites

Skın
Oral cavity  \}  No apparent connection to outcomes

Hypopharynx
Larynx  \}  May be prognostic but unproven
How does HPV impact treatment decisions?
Initially, enthusiasm for surgery as monotherapy

Trans Oral Robotic Surgery (TORS)

Was hope that we could offer surgery alone

Early data from ongoing trials shows ~90% of people still need radiation

RT versus RT and surgery:

- same cure rate
- side effects both treatments >>>> one treatment
What’s new in HPV(+) SCCa? De-intensification

Multiple institutions (including UF) looking at less treatment in HPV(+) 60 Gy instead of 70 Gy radiotherapy

Same cure rate, significantly decreased toxicity
Why should the ACLI Medical Section care about 10 Gy?

Cost of treatment (time)
Cost of managing short- and long-term effects (both $ and morbid/mort)

Probability of dysphagia versus volume irradiated and dose – Red >62 Gy, Blue <62 Gy

Doses in patients with and without side effects during head/neck cancer treatment
What about chemo – do HPV(+) still need it?

The jury is still out on this

Culturally, oncology research is pro-chemo

We suspect HPV(+) outcomes may not be improved as much with chemotherapy

Nobody is testing this at present
People with HPV(+) oropharynx cancer, compared to other head and neck cancers:

Have much better overall and disease-free survival

Are diagnosed 10-15 years earlier, on average

Have great outcomes even with extensive lymph node disease

May experience recurrence >3 years, especially distant mets
  • More often salvaged when they do, but rate still low
Objectives of this talk

1) Discuss the epidemiology of oral HPV infection and HPV-related oropharyngeal cancers

2) Discuss diagnostic and clinicopathologic features of HPV-related oropharyngeal cancers

3) Discuss the updated AJCC staging criteria for HPV-related oropharyngeal cancers

4) Compare and contrast treatment options and prognosis for HPV-related oropharyngeal cancers with those for other oropharyngeal cancers