MANAGEMENT OF LOCALLY ADVANCED OROPHARYNGEAL CANER: HPV AND NON-HPV MEDIATED CANCERS

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Goals

• Overview of etiologies and diagnostic workup for a patient presenting with concern oropharyngeal cancer

• Discuss the role Human Papilloma Virus (HPV) plays in causing oropharyngeal cancer

• Overview of potential treatment for patients with locally advanced head and neck cancer
  • Surgery, radiation, chemotherapy or multi-modality therapy

• Discuss how treatment options in future may be able to tailored to patient who are HPV+ vs. HPV-

Clinical Presentation

• 50yo white male
• History of Present Illness
  • Presented with complaints of newly found R sided neck mass
Clinical Presentation

- 50yo white male
- History of Present Illness
  - Presented with complaints of newly found R sided neck mass
  - Fast onset—noticed within a day
  - About 5cm in size
  - No associated pain
  - No fevers
  - No dysphagia or odynophagia
  - No changes in voice quality or character
  - No headaches or cranial nerve findings
  - Weight stable

Other Pertinent History

- Substance use
  - Tobacco: Smoked in the past about 1/2 pack per day for 10 years
  - quit 10 years ago
  - EtOH: occasional use
- Past Medical History:
  - Otherwise healthy
  - Not on any medications
- Mass in R neck persisted for about 1 week and he saw his PCP
  - Had trial of antibiotics and mass did not change in size

CT of Neck

CT scan showed largest LN in mid-R neck with concern for enlarged LNs bilaterally in the upper neck and fullness in the R base of tongue
PET-CT imaging showed Right BoT activity

Base of Tongue and Oral tongue

Head and Neck Anatomic sites
Oropharyngeal cancer

- Typically cancer of the tonsils or base of tongue
- Squamous cell carcinomas are vast majority of cases
  - Lymphomas or atypical solid tumors possible
- Region has a rich lymphatic supply and thus typically LNs are clinically involved or subclinically involved
  - Must consider bilateral cervical LNs at risk in many cases

Biopsy of Right BoT lesion and LN

- Invasive squamous cell carcinoma, poorly differentiated

Biopsy of Right BoT lesion and LN

- SCCa stained intensely positive for p16 and p53 overexpression and was positive for HPV viral DNA
  - p16 isn’t a HPV gene but is upregulated during HPV infection
Human Papilloma Virus

- DNA based virus that is hosted by humans
- Over 200 different strains have been discovered
- Infect epithelial cells: skin and mucosal membranes
- Ubiquitous: Almost every person has been exposed/infected
- Transmitted by direct skin to skin contact, typically a sexually transmitted disease
- Great majority of the time the HPV is cleared by the host
  - >99% clearance rate
- High risk and low risk strains
  - Low risk: HPV 6 and 11 → cause of genital warts
  - High risk: HPV 16 and 18 → cause of cancer

High Risk HPV has genes that help lead to cancer

- E6: binds to p53 which makes it so p53 cannot cause apoptosis and regular cell cycle
- E7: binds to Rb so it cannot regulate cell cycle
- Allows for cells to continue to divide unchecked which allows virus to be replicated by the growing cells
HPV uses epithelium to replicate and become able to cause new infections

High Risk HPV is an important cause of cancer
- Between 2006 and 2010 about 33,200 HPV-associated cancers were reported by the CDC
  - 20,600 in women: cervical cancer most commonly
  - 12,600 in men: oropharyngeal cancer most commonly
- In general HPV causes approximately,
  - 90% of cervical cancers
  - 90% of anal cancers
  - 70% of vaginal and vulvar cancers
  - 60% of penile cancers
  - 70% of oropharyngeal cancers
- Infection with HPV 16 leads to a 14-fold increased risk of developing SCCa of the oropharynx

Rates of HPV+ H&N cancers are rising
Two Routes to Head and Neck SCC Cancer

<table>
<thead>
<tr>
<th>Anatomic site</th>
<th>HPV-positive</th>
<th>HPV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsil / BOT</td>
<td>Basaloid</td>
<td>Keratinized</td>
</tr>
<tr>
<td>All sites</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>High</td>
<td>3:1 men</td>
<td>Low</td>
</tr>
<tr>
<td>Sexual behavior</td>
<td>Marijuana?</td>
<td>Alcohol / tobacco</td>
</tr>
<tr>
<td>Improved</td>
<td>Diet, hygiene</td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>Increased</td>
<td>Decreasing</td>
</tr>
</tbody>
</table>

Treatment of oropharyngeal cancer

- Will focus today on local-regionally advanced SCCa
- Ultimately treatment must be personalized to the patient, the type of cancer, stage of cancer, and patient comorbidities
- Need to provide curative treatment to give person best chance of long term disease free survival while minimizing long term morbidity/organ dysfunction
  - Speech
  - Swallow
  - Breathing
- At this point in time, HPV + and HPV – cancers are treated the same, though outcomes are different
  - And this may change in future

Oropharyngeal cancer staging
Our patient had a 3cm lesion and LNs on both sides of neck. Stage IVa is T2N2cM0. In head and neck cancer, Stage IV does **not** have to mean distant metastatic disease that is not curable. (that would be Stage IVc)
Surgical Options

- Surgery can be considered to the primary tumor site and/or the involved neck(s)
- Radical tonsillectomies can be open or transoral or now even robotic-assisted
- Removes majority of cancer cells
- Need to ensure tissue function remains

Neck Dissection

Adjuvant therapy

- Surgery alone is typically not enough
- In local-regionally advanced SCCa, surgery is followed by adjuvant treatment to clean up microscopic cancer cells
- Radiation alone is given adjuvantly even if all gross disease was resected if risk factors found
  - T3 or T4 disease
  - N2 or N3 disease
  - Perineural invasion
  - Lymphovascular space invasion
  - Low-lying LNs found (levels IV or V)
- Radiation concurrent with chemotherapy is given when surgical findings includes
  - Extracapillary extension of disease
  - Positive surgical margins
Definitive Radiation with chemotherapy

- Radiation can provide definitive therapy that is non-surgical
- Need to treat areas known to be involved with cancer
  - Primary tumor site and pathologically involved LNs
- Also need to treat areas that may harbor micrometastatic disease that is subclinical
  - Remaining LN regions on the involved side of neck
  - Most often LN regions on contralateral side of neck
  - Risk of contralateral LN involvement is >15%
- Local-regional control of disease as measured by DFS and OS is improved if chemotherapy is given concurrently with radiation

Radiation Treatment Planning

- Need to deliver high dose radiation to areas involved/at risk while sparing normal tissue
  - Parotids
  - Spinal cord
  - Oral cavity
  - Uninvolved soft tissues
- IMRT greatly helps
  - VMAT (arc therapy)
Radiation Treatment Planning

Outcomes of HPV+ SCCa

- Once the link between HPV and oropharyngeal cancers was made, it was noted that these patients as a group were doing better with treatment
  - Wasn’t clear if this was because they were younger, non-smokers, healthier people at baseline or if the HPV + was the reason
- RTOG 0129 was a trial comparing chemotherapy concurrent with two different types of radiation fractionation
  - Post-hoc analysis (out the initial 720 patients)
  - 433 patients had oropharyngeal cancer
  - 317 of these had been tested for HPV status
  - 83% were positive for HPV and p16 staining

HPV Status predicts OS to treatment with definitive chemoradiation

Smoking history reduces HPV+ benefit

Table 2. Hazard Ratios for Overall and Progression free Survival, According to Patient Group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients, With Data Imputed (N=173)</th>
<th>All Patients, With Data Imputed (N=173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis</td>
<td>Overall Survival</td>
<td>Overall Survival</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>P value</td>
</tr>
<tr>
<td>Treatment assignment (unadjusted)</td>
<td>1.24 (0.61–2.55)</td>
<td>0.61</td>
</tr>
<tr>
<td>Age (in years)</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>Race (non-Hispanic vs. Hispanic)</td>
<td>1.39 (0.70–2.79)</td>
<td>1.39 (0.70–2.79)</td>
</tr>
<tr>
<td>Stage (I vs. II–III)</td>
<td>0.63 (0.39–1.01)</td>
<td>0.63 (0.39–1.01)</td>
</tr>
<tr>
<td>Smoking status (never vs. current)</td>
<td>0.70 (0.40–1.22)</td>
<td>0.70 (0.40–1.22)</td>
</tr>
<tr>
<td>HPV status (high vs. low)</td>
<td>0.41 (0.21–0.81)</td>
<td>0.41 (0.21–0.81)</td>
</tr>
</tbody>
</table>

No. of patients: 173

Smoking history reduces HPV+ benefit

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>2yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>95%</td>
</tr>
<tr>
<td>Current</td>
<td>80%</td>
</tr>
<tr>
<td>High school</td>
<td>71%</td>
</tr>
<tr>
<td>Any other</td>
<td>63%</td>
</tr>
</tbody>
</table>

HPV+ oropharyngeal SCCa

- This is a cancer that is increasing in incidence
- This is a cancer that has relatively good outcomes/cure
- Patients with HPV+ cancer typically are younger and thus have fewer medical comorbidities
  - This cancer is the greatest risk to their life
- If this is a cancer that most likely will be cured long term AND this is a group that has an reasonable expected lifespan, . .
- They are going to have to live with the consequences of treatment for a long time
  - Deal with treatment mediated morbidity and could perhaps how this may impact mortality

Long term Radiation Side effects

- Dry mouth
- Risk of cavities
- Stiffness/fibrosis of nck
- Lymphedema in neck
- Lymphedema in supraglottic larynx
- Altered swallowing
- Risk for aspiration
- Altered taste
- Narrowed airway
- Vascular disease
- Secondary cancers

Can Treatment of HPV+ SCCa be deescalated?

- ECOG 1308, phase II trial reported at ASCO in 2014
- 90 patients with oropharyngeal HPV+ SCCa
De-escalated radiation therapy for HPV+ oropharyngeal SCCa: ECOG 1308

- Tumor and Nodal stage:
  - T4-10%, T3-17%, T2-50%, and T1-23%;
  - N0,1-16%, N2a,b-54%, N2c-31%.
- Median age 57yrs.
- 46% never smoked and 84% not current smokers.
- Induction chemotherapy and Cetuximab-IMRT was well tolerated:
  - 96% received all 3-cycles of induction chemo.
  - 71% had clinical CR
  - 62 pts (78%) received Cetuximab-IMRT

Deescalated radiation therapy for HPV+ oropharyngeal SCCa: ECOG 1308

- For all reduced dose IMRT pts
  - 23mo PFS is 84%,
  - primary site LC 94%,
  - nodal control 95%
  - distant control 92%.
- Post-XRT neck dissection needed in 8 low dose patient (4 positive for disease) as opposed to 3 (1+) with standard XRT

**Conclusions:** Patient who had complete clinical response to induction chemotherapy received reduced XRT-dose with cetuximab and this produced high tumor control rates. Late toxicities were minimal.

- Low dose pts achieved 84% PFS at 23mo and 95% 2-yr survival.
- Pts with <10yrs smoking, T1-3 and N0-2b disease achieved 96% PFS.
- Further studies of reduced-dose IMRT in chemoresponsive HPV+ pts are warranted.

HPV+ SCCa treatment options

- Further work will be undertaken to determine further treatment de-escalation
  - Need to ensure that treatment is just as efficacious
  - Need to be mindful of other completing risk factors that may be negative prognostic factors (ie smoking).
- There is currently no recommended screening available
  - Oropharyngeal screening would be invasive
- Prevention of developing SCCa would be preferable
HPV epidemiology

- HPV is prevalent
- 7% of US population aged 14-69 had active infection
  - Bimodal distribution: Peak at 30-34yo and again 60-64yo
- 1% of US population had high risk HPV-16
- Risk factors included age, gender, # sexual partners, extent of smoking


HPV vaccine

- FDA has approved vaccinations to prevent HPV infections by certain HPV subtypes
  - Gardasil protects against HPV 16, 18, 6, 11
  - Cervarix protects against HPV 16 and 18
- Approved for both boys and girls
  - Given as a series of 3 shots (over 6 months) at ages 11-12
  - Can be given to older young adults based on risk factors
- Approved to significantly reduce chance of cervical cancer, anal cancer, and genital warts
  - Prevention of oropharyngeal SCCa will occur as well
  - Perhaps even more dramatically as a greater percentage of oropharyngeal SCCa are HPV16 mediated than cervical cancer

Wrap up of Clinical Vignette

- 50yo male with minimal smoking history now with Stage IVa, cT2N2cM0, Stage IVa squamous cell carcinoma of the R BoT with involved LNs in the upper and mid R neck and upper L neck
- Current standard of care non-surgical treatment would be high dose radiation to primary tumor site and bilateral neck concurrent with chemotherapy
  - 70Gy to gross disease in R BoT and involved LN
  - 50Gy to lymph node areas at risk but not grossly involved
  - Cisplatin q3weeks 100mg/m2 concurrently
- He has >80% chance of being disease free at 3 years
- He has 100% chance of having acute effects of treatment as well as long term changes to his body from treatment.
Summary

- Human papilloma virus (HPV) is a ubiquitous human virus with high risk subtypes that can increase risk of developing epithelial cancers
  - Oropharyngeal, cervical, anal, vaginal, vulvar
- HPV is shifting the epidemiology of head and neck cancers
  - Oropharyngeal cancers are on the rise while rates of other H&N cancer sites are falling
- HPV is shifting the demographics of those developing H&N cancer
  - Trending toward younger, non-smoking, males likely in otherwise good health with higher social-economic status

Summary

- HPV mediated oropharyngeal cancers typically are more locoregionally advanced
  - Thus typically require aggressive multi-modality treatment
- Need to provide needed aggressive care that cures the cancer but treatment needs to minimize acute and long term side effects
  - Speech, swallow, breathing, etc.
- Typically one considers
  - Surgical intervention followed by adjuvant therapy based on pathologic findings
  - Radiation vs. chemo-radiation
  - Definitive radiation concurrent with chemotherapy as non-invasive curative treatment with excellent results

Summary

- HPV mediated SCCa of the oropharynx are more likely to respond favorably to treatment and provide long term cure
  - This benefit is blunted or negated by extensive smoking history
- In appropriately selected HPV+ patients, treatment de-escalation is being actively studied and will continue to be an emphasize of future clinical trials
  - Can we be less aggressive with treatment in order to spare acute and long term toxicities while not compromising cure rates?
- HPV is incredibly prevalent in human society
  - We now have FDA approved vacciations targeting high risk HPV subtypes
  - Hope to see incidence of HPV mediated cancers decrease over the next decades
Questions? Thank You