Head and Neck Cancer: 2016
It’s Not What You Think!

New Treatments, Improved Outcomes, and
A Sexually Transmitted Disease?

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Massachusetts General Hospital
None of the planners or presenters of this session have disclosed any conflict or commercial interest.
• **OBJECTIVES:**

1. Learners will be able to identify the most common head and neck cancers

2. Learners will be able to relate significance of HPV and EBV in relation to management of head and neck cancers
HEAD AND NECK CANCER: 2014

• What is Head and Neck Cancer
  – Why increasingly relevant
  – The Old and the New

• Standard Treatment and Getting Patients Through It
  – Surgery and Radiation Therapy
  – Roles for Medical Oncology and Supports Staff

• HPV-Associated Head and Neck Cancer
  – Epidemiology, Treatment, Outcomes, Counseling and Prevention
Why is Head and Neck Cancer Relevant?

- A disease of high morbidity or mortality
- Morbidity related to problems experienced by all patients
  - Functional, cosmetic, psychological
- Multidisciplinary treatment and “team play” can enhance curative potential and lessen morbidity
  - Physician staff can create a care plan, but ….
  - RNs, NPs, SLPs, LSWs, Nutritionists are vital to getting pt through complex treatment programs
- Work is never over!
  - HPV-associated oropharynx cancer, 4% annual increased in young males
  - Of all “cured cancer patients”, 3% have had head and neck cancer
  - “New” prevention therapy: HPV-vaccination
Head and Neck Cancer: **Anatomy**

- Head and neck cancer as a phrase, commonly refers to squamous cell cancers (SCC) of upper aerodigestive tract
  - SCC HN for 85-90% of cases (thyroid cancer excluded)
  - Commonly subdivided into 7 anatomic subsites
Oral Premalignant Lesions: **Leukoplakia**
Oral Premalignant Lesions: Erythroplasia
Invasive Oral Cancers
Non-Hodgkin’s Lymphoma of Tonsil
Hypopharyngeal Cancers
HN Cancer: National Perspective

- Ninth most common cancer in United States
  - About 5th most common cancer in males …
    - Cancers of prostate, lung, colon, bladder more common
  - In 2015: 59,340 cases, 9,300 deaths

- National Trends
  - Incidence and mortality rates recently falling, HOWEVER…
    - Thyroid cancer and HPV+ OPCA increasing
  - Prevalence slightly up owing to aging population and HPV+ OPCA
  - Overall trends parallel those for lung cancer
  - Challenges: Significant gender and race differences
    - Increasing incidence in young males likely related to HPV
Lung Cancer Incidence and Tobacco Use in U.S. 1900-1999

- Per capita cigarette consumption
- Male lung cancer death rates
- Female lung cancer death rates

Graph showing trends in per capita cigarette consumption and age-adjusted lung cancer death rates from 1900 to 1999.
HPV Trends:
Magnitude of change in last 2 decades extremely dramatic

• Chaturvedi, NCI, ASCO, June 2011
  – SEER data 1984-2004, and analysis of 271 oropharyngeal cancer cases during that period
    • 225% increase in HPV+ cancers
    • 50% decrease in HPV- cancers
    • By 2020, number of HPV-related oropharyngeal cancer in men will exceed cervical cancer
Head and Neck CA: International Perspective

- Sixth most common cancer worldwide
  - 600,000 cases annually (8%)
- Third most common cancer in developing countries
- Impact society measured by:
  - Prevalence
  - Overall mortality
  - Morbidity experienced by cured patients
- “International” associations ........
HN Cancer Factoid:
What do these places have in common?

Southern China
Greece
North Africa
Alaska
Risk Factors for HN Cancer

- Mucosal carcinogens: Alcohol and tobacco
- Occupational carcinogens: Asbestos (larynx); nickel refining, wood dust, leather tanning (nasal cavity & sinus)
- Infectious: EBV (NPC); HPV (OP, subtypes 16 and 18)
- Misc:
  - Previous HNCA or “premalignant lesion”
  - Radiation exposure (solar or nuclear)
  - “Immunosuppression” (e.g. post-transplant, chronic leukemia, etc.)
HN Cancer Factoid:
What do these places have in common?
What is HPV?
- DNA (double-stranded) virus containing 7900 bps
- > 140 subtypes
- Remarkable tropism for specific epithelial surfaces
  - HPV 16 and 18: Cervical cancer, OP-HNCA
    - Also Vulvar, Peri-anal, Penile cancers
  - HPV 9 and 11: Genital warts & Laryngeal Resp Papillomatosis
    - Commonly subdivided into “high risk” and low risk” subtypes
      - High risk subtypes with significant carcinogenic potential
        - HPV 16, 18, 31, 33, 35
Changing Face of Head and Neck Cancer

- An 65-85 yo man with history of alcohol and tobacco abuse
Changing Face of Head and Neck Cancer

- A younger man with history of alcohol and tobacco abuse, and past oral HPV infection
• An even younger man the in prime of life with a loving family and no history of alcohol and tobacco abuse
SCCHN 2015: Two “common” biologically distinct diseases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EtOH / Tobacco</th>
<th>HPV-16/18 Related (also 31, 33, 35)</th>
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<tbody>
<tr>
<td>Association</td>
<td>80-85%</td>
<td>15-20%</td>
</tr>
<tr>
<td>Most Common Site</td>
<td>Larynx / Oral Cavity</td>
<td>Oropharynx</td>
</tr>
<tr>
<td>Risk Factor</td>
<td>EtOH / Tobacco</td>
<td>Sexual Behaviors</td>
</tr>
<tr>
<td>Incidence</td>
<td>Decreasing</td>
<td>Increasing, 4% annually</td>
</tr>
<tr>
<td>Prevalence</td>
<td></td>
<td>Academic Centers: ~50% cases</td>
</tr>
<tr>
<td>Male : Female Ratio</td>
<td>3 : 1</td>
<td>3 : 1</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Keratinizing</td>
<td>Often Non-Keratinizing. Basaloid</td>
</tr>
<tr>
<td>Genetic Phenotype</td>
<td>p53 abnormal</td>
<td>p53 and pRb degraded</td>
</tr>
<tr>
<td>Sensitivity to Tx</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>Stage III-IV Survival</td>
<td>35-40%, 3 yrs</td>
<td>80-85%, 3 yrs</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Risk for 2nd Primary</td>
<td>High, 2-4% / yr</td>
<td>Unclear, very low, &lt;&lt; 2-4%</td>
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SCCHN 2015: Two “common” socially distinct diseases

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<tr>
<td>Age of patient</td>
<td>55 - 75</td>
<td>45 - 65</td>
</tr>
<tr>
<td>Risks factors</td>
<td>EtOH / Tobacco</td>
<td>Increasing None</td>
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<tr>
<td>Social / Economic Status</td>
<td>Low – Middle</td>
<td>Middle - High</td>
</tr>
<tr>
<td>Fiscal / Social Burden</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>Primary lesion ≥ Neck lesion</td>
<td>Neck Lesion ≥ Primary lesion</td>
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Head and Neck Cancer: Treatment

- Treatment planning by MD staff relatively straightforward.
- Getting patients through planned treatment challenging:
  - Control of pain, nutrition, secretions is frequently difficult.
  - In recent co-operative group trials:
    - Up to 40% pts do not complete chemo.RT “per protocol”.
    - Rate of permanent g-tube retention, up to 10%.
  - Rate of compliance to protocol treatment, and g-tube removal higher in centers with experienced support staff.
- Value of support staff in HNCA care... “priceless”.
Definitive Head and Neck Cancer Therapy

- **Principles of HN Surgery:**
  - As a single agent, more effective than radiation
  - Surgery is “default” consideration and indicated when:
    - Lesion resectable (clear margins possible) with “acceptable” morbidity, and when …
    - Lesion not uniquely radio-sensitive (HPV-associated lesions)
  - Primary site & neck disease treatment often “different”
    - Small volume primary with large neck lesion
      - Primary lesion: RT
      - Neck lesion: RT, then S (neck dissection)
Definitive Head and Neck Cancer Therapy

- **Principles of Radiation Therapy**
  - More better
    - RT delivered to maximal normal tissue tolerance
    - Definitive RT: 70 Gy, 200 cGy daily for 7 wks
    - Post-op RT: 60 Gy
  - When S & RT planned, preferred sequence: S → RT
  - Altered dose-fractionation schedules
    - AKA: “accelerated” or hyperfractionated schedules:
      - Slight increase in local control but not overall survival
  - RT with concurrent chemotherapy:
    - Increases local toxicity, but clear increase in local control, OS
    - Less distant metastases in some studies
• Limited HNCA: T1-2N0-1, or T3N0 exophytic tonsil lesions

• Therapy relatively standardized, site-specific
  – Survival 60%-90%

• Resectable lesions: Results surgery vs. RT, similar
  – Treatment decision biased toward least morbid

• Relative sites of failure:
  – Local-regional  95%
  – Distant  5%

• Failure after 3 yrs is uncommon (<10%)

• Major concerns: Control of late treatment-related morbidity
  Detection 2nd primary carcinomas
HN Cancer: Traditional Therapy & Natural History

- Advanced (M0) disease: T3-4 N2-3
- Biologically, a very different disease
- Survival, 10%-50%
- Therapy is maximal
- Relative sites of failure:
  - Local-regional 75%
  - Distant 25%
- Despite therapy, outcome frequently limited to situation of high mortality or high morbidity
# Advanced HN Cancer Management by Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Resectable with Acceptable Morbidity</th>
<th>RT Sensitivity</th>
<th>RT Toxicity</th>
<th>Potential for Salvage Surgery</th>
<th>“Default” Initial LR Treatment</th>
<th>Role of Medical Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Cavity</td>
<td>Yes</td>
<td>+</td>
<td>++++ (pain)</td>
<td>10%-30%</td>
<td>S/RT</td>
<td>? Post-op C._RT</td>
</tr>
<tr>
<td>Larynx</td>
<td>No</td>
<td>+</td>
<td>++</td>
<td>50-60%</td>
<td>C._RT</td>
<td>C._RT</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>No</td>
<td>+ and +++</td>
<td>+++ (pain)</td>
<td>30%</td>
<td>C._RT</td>
<td>C._RT</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>No</td>
<td>+</td>
<td>++</td>
<td>30-50%</td>
<td>C._RT</td>
<td>C._RT</td>
</tr>
<tr>
<td>NPC</td>
<td>Unresectable</td>
<td>+++</td>
<td>+</td>
<td>0-5%</td>
<td>C. RT</td>
<td>C. RT</td>
</tr>
<tr>
<td>PNS/NC</td>
<td>Yes</td>
<td>+ and ++</td>
<td>+</td>
<td>10%</td>
<td>S.RT</td>
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**Notes:**
- **RT Sensitivity:**
  - +: Moderate
  - ++: High
  - +++: Very High
  - ++++: Extremely High
- **RT Toxicity:**
  - +: Low
  - ++: Moderate
  - +++: High
  - ++++: Very High
- **Potential for Salvage Surgery:**
  - 10%-30%: Low
  - 50-60%: Moderate
  - 30-50%: High
  - 0-5%: Very High
- **Role of Medical Oncology:**
  - ? Post-op C. RT: Unresolved
Advances in HN Surgery

- Surgical Oncology: has developed ...
  - Strategies allowing “primary site” & “neck” preservation
  - Improved reconstructive techniques
    - Free flaps
    - Voice restoration via tracheo-esophageal puncture

Tracheo-Esophageal Puncture (TEP)
Advances in HN Radiation Therapy

- Radiation Oncology: has developed ...
  - Improved treatment simulators
  - Effective radiation sensitizers
  - Highly Conformal Radiation Therapy techniques
    - Proton beam radiation: highly focused, not readily available
    - Intensity Modulated Radiation Therapy (IMRT)
Chemotherapy for Head and Neck Cancer

- Chemotherapy is active against HNCA
- Responses are at times quite dramatic
## Opportunities for Medical Intervention

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<th>Outcome</th>
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Adjuvant Therapy for Head and Neck Cancer

• Potential Advantages
  – Treats persistent “high-risk” microscopic disease
  – Generally well tolerated, 3-6 month course of therapy

• Standard of care in oncology
  – Breast cancer, NSCLC, colo-rectal cancer
  – Reduces risk of systemic relapse ~20-30%
  – Value is control of local-regional relapse limited

• Re SCC HN:
  – Classical adjuvant: limited experience owing to toxicity
  – Some experience as post-op chemo.RT
EORTC Phase III Trial of Cisplatin and Post-op Radiotherapy

- Intergroup study 22931: 334 patients (follow up 26.6m)

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<tr>
<th>Stage III-IV</th>
<th>S U R G E R Y</th>
<th>+ Margin or ECE or LVI or PNS</th>
<th>RANDOMIZE</th>
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<tr>
<td>“Standard” Post-Op RT</td>
<td>60-66 Gy / 30-33 fx</td>
<td></td>
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<tr>
<td>“Standard” Post-Op RT with CDDP 100 mg/m2 q21d x 3</td>
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- Outcome (median follow up 5yrs):
  - OS (5 yr) 40% RT 53% C/RT p = .04
  - PFS (5 yr) 36% 47% p = .02

- Marked increase in “functional” toxicity with combined therapy
- Compliance to radiation: no major difference
- Compliance to chemotherapy: 65%, 2 cycles; 50%, 3 cycles

Bernier, NEJM 350:1945, 2004
Adjuvant Therapy for HN Cancer: Advantages and Evidence-Based Results

• Chemoradiotherapy
  – Improved LR control and DFS in 3/3 studies; OS in 2/3
    • Survival benefit lost in long-term follow up of these studies
  – Significant increase in local toxicity
  – Grouped results of EORTC & RTOG Trials (Bernier, HN 2005)
  • Risk Reduction: Local-Regional Control ~42%
    Disease Free Survival ~23%
    Overall Survival ~28%

• Indications for treatment
  – Major: Positive primary margin or ECE in neck
  – Minor: Peri-neural invasion, LVI, level IV-V adenopathy
  – Adenopathy without ECE: No clear benefit!!!
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Induction Therapy for HN Cancer: History, Advantages, Disadvantages

• “Oldest” method for chemotherapy in definitive treatment
  – First phase III trial conducted in early ‘60s
  – Only 1 positive, prospective, peer-reviewed phase 3 trial (subset only)

• Postulated advantages: to improve local control and OS
  – Regression of disease prior to S/RT obvious (risk / benefit unknown)
  – Identifies patients with resectable disease who might avoid surgery ("primary site preservation")
  – Early treatment of occult micro-metastases (probably true)

• Common therapy for advanced bladder, gastric and breast cancers

• Potential disadvantage
  – Delays S/RT, most active “single agents” for SCC-HN
Indications: Induction Therapy for HN Cancer

• Biologic:
  – After >50 yrs of study, still not a standard therapy for HNCA
  – In meta-analyses, increases in overall survival, ~5%
  – Benefit quite small c/w preferred alternative, chemotherapy with RT

• Practical: in selected patients with very advanced disease
  – Allows disease control while buying time of 3-6 wks …
    • To organize complicated surgical or radiation treatment plans
    • To make dental referral for evaluation, esp if extractions needed
    • To facilitate disease regression in those who are grossly aspirating, or those who can’t lie flat as needed for RT
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Concurrent Chemo/RT for HN Cancer
Evidence-Based Results

- Multiple phase III trials indicate
  - Local control & survival improved with chemo/RT
  - Dramatic increase in local toxicity
  - Primary site preservation is possible
  - Some reduction in distant relapse with Cisplatin q3wk

- Meta-analysis (Monnerat, Annals of Oncology, 2002)
  - RR reduction 19% ± 3%
  - 8% survival benefit at 5 yrs (p = <.0001)

- “Optimal” regimen of concurrent therapy unknown
INT-R91-1
A Phase III Trial of Larynx Organ Preservation

- 547 patients; 3.8 year median follow up
- Intermediate stage (65% stage III; 28% N₂-₃)
- Stage III/IV included (only T2-3, low risk T4)

Forastiere, NEJM 349:2091, 2003
INT-R91-1: Laryngeal Preservation Rate
A Phase III Trial of Larynx Organ Preservation

Forastiere, NEJM 349:2091, 2003
Few published trials exclusively designed for OPCA

- GORTEC trial (Calais et al, JNCI, 1999): N = 226 oropharynx pts

STAGE 3/4 OROPHARYNX CARCINOMAS n=226

Randomized: 115
Eligible: 113
Treated: 112

Randomization

ARM A

70 Grays
2 Grays/fraction
7 weeks

ARM B

70 Grays, 7 weeks
+ Carboplatin
+ FU
Weeks 1, 4, 7

Randomized: 111
Eligible: 109
Treated: 108

Denis F et al. JCO 2004;22:69-76
Oropharyngeal Cancer: Management with Chemo.RT

- GORTEC trial (Calais et al, JNCI, 1999): N = 226

Overall Survival

Local-Regional Control

Denis F et al. JCO 2004;22:69-76
Best Regimen of Chemotherapy with RT?

Academic Standards:
- Cisplatin 100 mg/m² q21d x 3 with RT Yes
- Cetuximab IV qwk x 7-8 with RT Yes

Other Practice Standards:
- Cisplatin 30-40 mg/m² q7d x 7 No
- Cisplatin / FU infusion q21-28d x 2 Yes
- Carboplatin / FU infusion q21-28d x 2 Yes Yes
- Carboplatin / Paclitaxel q7d x 7 No, but …...

At this time, no clear “best” therapy for all patients
Are the Acute Toxicities of Chemo.RT Uniform?

• Regimen makes of difference:
  • Cetuximab least, then “platins”
  • Addition of FU or taxanes escalates toxicity further

• Site makes a difference:
  % Needing G-tubes
  • Oral cavity worst, than 90%
  • Hypopharynx or Larynx, 50-65%
  • Nasopharynx and sinuses least 10-20%

• What is time course for mucositis during RT?
FIRST THIRD:
Easier than expected!
Mild altered taste
Mild oral dryness
G-tube discussed ...

SECOND THIRD:
As expected:
Weight stable but diet changed
Pain controlled by topical agents
Narcotics initiated
G-tube placed ...

Pain and Suffering on Concurrent Chemotherapy with RT
Pain and Suffering on Concurrent Chemotherapy with RT

Weeks After Start of Radiation Therapy

Radiation Therapy

Recovery

Pain and Suffering

0 1 2 3 4 5 6 7 8 9 10

Radiation Therapy Recovery

I can’t take it !!!

I can take it!

Worse than imagined!

G-tube used...

Severe pain

Excess secretions

Aspiration risk, ~100%

Narcotics and g-tube use gradually decline

(2 months): Slight improvement in week... depression common

RECOVERY
## Opportunities for Medical Intervention

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A role for induction therapy before chemo.RT?

- PARADIGM trial (DFCI): A phase III study comparing sequential therapy to concurrent chemoradiotherapy in locally advanced SCCHN (Haddad, Lancet Oncol, 2013)
  - Protocol Design:
    - TPF → Carbo.RT  vs  Cisplatin.RT
    - Designed to prove superiority of TPF, N = 300
      - N = 145, study terminated “early” when no difference in DFS / OS noted
    - Patients: Oropharynx 80 / 145 = 55%
    - Three year outcomes:
      - OS  TPF / C.RT 73%  C.RT 78%
      - PFS  TPF / C.RT 67%  C.RT 73%
## Opportunities for Medical Intervention

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Palliative Chemotherapy for Recurrent / Metastatic SCCHN

- Effective standard medications exist
  - “Platins”, “Taxanes”, 5-Fluorouracil, Cetuximab
    - All approved for use in HNCA
  - Duration control depends on p16 / HPV status
    - HPV-: RR 20-30%, survival: “few months to 2 yrs”
    - HPV+: RR 30-50%, survival: “many months to 4 yrs”
    - Solitary metastatic lesions potentially “curable”, esp. if HPV+
- Forthcoming therapy!
  - Anti-PD1 monoclonal antibodies under active investigation
    - Approved for use in melanoma, squamous lung cancer
Tumor Tolerance by T-cells mediated by…
T-Cell PD-1 activation by Tumor PD-L1

• PD 1 is expressed in antigen stimulated T-cells
  – When activated, induces downstream signaling that inhibits T-cell proliferation, cytokine release, and cytotoxicity

• Many tumors suppress T-cell activity by expressing PD-L1 ligand

• Anti-PD 1 Antibodies have potential to disrupt T-cell / tumor tolerance and induce long-lasting anti-tumor responses
Anti-PD-1 Therapy in SCCHN

- Individual responses can be dramatic

- 96 y.o. female, HPV negative, PD-L1 positive, disease
  - Progressed on previous cetuximab
  - Treatment ongoing
  - Neil Howard Segal, MD, PhD ASCO 2014
Anti-PD 1 Antibodies in HNCA: Phase 2 experience

- Pembrolizumab (MK-3475) in KEYNOTE-012 Study
  - N = 117 pts, Objective Response Rate = 24.8%
    - Shrinkage = 56%, Shrinkage + Stable = 81%
    - HPV+: ORR = 20.6%
    - HPV-: ORR = 27.2%
  - N = 104 pts, RR 20% in both HPV+ and HPV negative patients
    - Chow, Annals of Oncology 2014
    - Disease control > 1 yr in some patients
    - Median duration of control not defined in these early studies
    - Toxicity quite limited: fatigue (20%), pruritus (10%), no deaths
- Efforts to define who will respond prior to therapy in progress
- FDA approval expected
Anti-PD 1 Antibodies in HNCA: Phase 3 trials

Nivolumab (BMS): CheckMate-141 Trial

• Initiated May 2014

• N = 361 pts with incurable SCCHN of oral cavity, pharynx, larynx and progression on a platinum-based therapy

• Randomized 2:1 ratio to Nivolumab 3mg/kg q2wks vs physician choice
  – MTX 40-60mg/m2/wk  Standard of care in 1960-70s
  – Docetaxel 30-40 mg/m2/wk  Standard of care in 1990s
  – Cetuximab 400, then 250 mg/m2/wk  Standard of care in 2000s

• Trial terminated early owing to improved primary endpoint, OS!

• Final results expected ASCO 2016

• FDA approval expected
“Lines” of Standard Agents

<table>
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<tr>
<th>Pt Status</th>
<th>First Line</th>
<th>Second Line</th>
<th>Third Line</th>
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<td>Robust / “Needs” Response</td>
<td>Carboplatin / FU / Erbitux</td>
<td>Nivolumab or Pembrolizumab?</td>
<td>Weekly Taxane</td>
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<tr>
<td>Average</td>
<td>Carboplatin / Taxol</td>
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<td>FU / Erbitux</td>
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<td>Poor PS</td>
<td>Weekly Taxane</td>
<td>Nivolumab or Pembrolizumab?</td>
<td>Cetuximab?</td>
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Returning to HPV-associated Head and Neck Cancer…
The Obvious and Positive

- HPV-related oropharyngeal cancers are….
  - Increasingly common
  - Commonly advanced at presentation, but if:
    - Small volume: potentially amenable to single-modality surgical resection (TORS)
    - For Stage 3-4 disease, prognosis “excellent” ~75-80% with standard regimens of concurrent chemotherapy and radiation
    - Treatment via clinical trial is possible
    - Majority of trials recognize excellent prognosis
    - Generally attempt to define an alternative treatments of equal cancer control but lesser toxicity
What Patients Hear…

• I have cancer… advanced…..life threatening
• I may die
• Treatment is horrible
• I won’t be able to swallow
  – I will need a feeding tube to survive
What Patients Think…

• My life as I knew it is over
• I did not do anything wrong to deserve this, and

• I have a sexually transmitted disease and it’s a cancer !!!
FAQs for the Medical Oncologist

• Answers are influenced by the roles that we play …
  – Classical Roles for the Medical Oncologist
    • “Chemist”
    • “Psychologist”
    • “Priest”
  – Roles in the era of HPV+
    • Marriage Counselor
    • Sex Therapist
    • Family Practitioner offering care as if:
      – Pediatrician / Gynecologist / School Nurse
FAQs for the Marriage Counselor

• Is this really a sexually transmitted disease?
  – Yes!
  – Clear association with age of menarche and first intercourse, number sexual partners, oral-genital contact
  – Data support a “dose effect” to acquisition
    • Higher dose exposure to HPV, higher risk of HPV-related CA
  – Risk of HPV-related HNCA greater in spouses of those with cervical dysplasia
FAQs for the Marriage Counselor

• How did I get this cancer?
  – For individual, date / time / method of exposure unknown
  – Clearly a “sexually-transmitted disease” best linked to oro-genital contact, HOWEVER:
    • Oral–oral transmission a possible source of infection
      – Oral HPV prevalence linked to open-mouth kissing linked in absence of oral sex in 3 studies
  – HPV-infection of oral cavity likely adheres to standard ID principles of “risk” related to dose-time exposure
    • Risk likely amplified in immune deficient patients
FAQs for the Marriage Counselor

- When was I infected? By whom?
  - Time and source of original infection is unknown
    - Primary infection years to decades earlier
    - Perhaps not by spouse, even if past or active cervical dysplasia
  - Frequency of infection is quite high
    - Oral or genital HPV infection in past
      - ~80% of sexually active at some time in their lives
    - Prevalence of oral HPV infection (at any one time)
      - HIV (-) adults: Any HPV 2.6-9.2%
        HPV (16,18) 1.5-4.5%
      - HIV (+) adults: HPV (16,18) 14-25%
Oral HPV Infection: Prevalence

Data: National Health and Nutrition Examination Survey, 2009-2010
Gillison et al. JAMA. 2012;307(7):693-703

- Methods: HPV detection via PCR & ISH after 30sec oral rinse in ~5600
- Results: Men and women aged 14 to 69 years
  - Any HPV+ 6.9% (M:F = 10.1 : 3.6)
  - HPV16+: ~1% (yet single most common HPV subtype)
- Risk associated with: age, sex, # sexual partners, current tobacco use
  - > 20 lifetime sexual partners, 20% risk of active HPV infection
FAQs for the Marriage Counselor

• When was I infected? By whom?
  – HPV oral exposure and transient infection remarkably common
  – Frequency of HPV episomal integration into DNA and initiation of carcinogenic process is fortunately rare
    • HPV oral cavity infections / yr: > 6 Million
    • HPV-related cancers / yr (all sites) ~20K
    • HPV-related HNCA / yr: ~10K
  – For all patients, the issue is less why, when or how infected, but rather why so unfortunate to have cancer as an outcome
    • Reason for individual is unknown
    • Risk based on dose-exposure, smoking history, immune competence
FAQs for the Sex Therapist

• Am I infectious?
  – Probably not! Transmission of HPV unlikely at time of cancer
  – Type specific immunity usually occurs after prolonged infection
    • Limits transmission and prevents re-infection
  – Duration of infectivity at an earlier time unknown
    • Recent data from pt’s with cervical infection suggests “shedding” for up to 12-18 months
Can I get infected again?

- Re-infection with same HPV-subtype possible but not common as majority of patients have type-specific immunity
- Infection with another HPV-subtype is possible
  - “Second primary” HPV-related HNCA not yet reported
    - Certainly possible, but must be rare
FAQs for the Sex Therapist

• How significant is the “epidemic”?  
  – In young males, a ~4% annual ↑ HPV-related HNCA  
    • Tonsil: 4% annual increase  
    • Base of tongue: 2% annual increase  
  – By year 2020:  
    • Males with HPV-related HNCA > women with cervical cancer  

• What caused the epidemic?  
  – Change in sexual practices played a role  
  – Complete answer is unknown
Cases of Genital Warts by Gender: 1971 - 2004

- Increase in viral STDs in the era of increased condom use due to:
  - Increased sexual partners
  - Increased oral sex
  - Improper condom use

Fig. 1. Number of diagnoses of genital warts (first, recurrent and re-registered episodes) by sex, STD clinics: England and Wales 1971–2004. Source: Health Protection Agency, 2006.
## Opportunities for Medical Intervention

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Vaccines: Gardasil®

- “Virus-like Particles”, IM q2m x 3
  - ~$600 / treatment course
  - 4 VLPs included
    - HPV - 16/18: 70% cervical ca
    - HPV - 6/11: 90% of genital warts
- FDA approved for girls in June 2006
  - Routine vaccination, ages 11-12 targeted
    - Age range: 9-26 years old
    - Value greatest prior to onset sexual activity
- FDA approved in 2009 for boys / men
- FDA approved Gardasil-9 in 12/14
  - HPV-31,-33,-45,-52, and -58 (20% cervical CA)
- Toxicity: No serious toxicities known
- Duration of Immunity: 5+ yrs
- Compliance with vaccination suboptimal
Objectives and Conclusions

- To relate the changing epidemiology and presentation of head and neck cancer in the US
  - Alcohol and tobacco based HNCA remains most common
    - Decreasing in prevalence, prognosis mixed
  - HPV-related HNCA in young males increasing 4% annually
    - Prognosis excellent, ~80%

- To relate the standard and emerging treatments of head and neck cancer, one of the curable of adult malignancies
  - Surgery and radiation therapy remain the curative modalities
    - Improved reconstructive techniques, and enhanced RT technologies offer hope for improved outcomes and better QOL
  - Chemotherapy enhances the curative effects of RT, although with marked increased in acute toxicities, esp mucositis, and possible G-tube dependence
Objectives and Conclusions

• To relate the acute and chronic consequences of treatment experienced by all cured patients
  – Acute toxicities generally manageable
  – Late toxicities impacting speech, swallowing, cosmesis occasionally disabling

• To relate avenues of investigation into new treatments and prevention strategies for patients with this disease
  – Newest curative treatment modality: IMRT with concurrent radiation sensitizers
  – Newest treatment: Anti-PD1 therapy forthcoming
  – Best prevention therapy: Anti-HPV vaccines, Gardasil® or Cervarix®
MGH Center for Head and Neck Cancers

- Head and Neck Surgery
  - Daniel Deschler, MD
  - Kevin Emerick, MD
  - Derrick Lin, MD
  - Mark Varvares, MD

- Oral Surgery
  - Meredith August, DMD, MD
  - Thomas Dodson, DMD, MD

- Radiation Oncology
  - Paul Busse, MD
  - Annie Chan, MD
  - Jen Powers, NP

- Radiology (MEEI)
  - Hugh Curtin, MD
  - Mary Beth Cunnane, MD

- Medical Oncology
  - John Clark, MD
  - Lori Wirth, MD

- Pathology
  - William Faquin, MD
  - Peter Sadow, MD

- Nurse Practitioners
  - Lisa Arcikowski, NP
  - Karen Quinn, NP

- Speech and Swallow
  - Tessa Goldsmith
  - Allison Holman