# Head and Neck Cancer: An Overview

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## 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

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

## 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
Physical Exam

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

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

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

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

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

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

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

Advances in Reconstruction Makes Primary Surgery Feasible
## 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
Distant Metastases

<table>
<thead>
<tr>
<th>YEARS FROM RANDOMIZATION</th>
<th>% FAILED</th>
<th>Induction CT</th>
<th>Concurrent CT (p=0.97 vs. Induction)</th>
<th>RT alone (p=0.044 vs. Induction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
<td>92.1%</td>
<td>91.8%</td>
<td>84.6%</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>85.5%</td>
<td>75.8%</td>
</tr>
<tr>
<td>2</td>
<td></td>
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<td></td>
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<tr>
<td>3</td>
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<td>5</td>
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</table>

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

- 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

Survival – Cancer of BOT

<table>
<thead>
<tr>
<th>Rx</th>
<th>Trials</th>
<th>#</th>
<th>T4</th>
<th>Stage IV</th>
<th>LC</th>
<th>5-Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>S +/- XRT</td>
<td>8</td>
<td>390</td>
<td>13</td>
<td></td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>500</td>
<td>11</td>
<td></td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>XRT +/- N.D.</td>
<td>9</td>
<td>806</td>
<td>13</td>
<td></td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>473</td>
<td>14</td>
<td></td>
<td>52%</td>
<td></td>
</tr>
</tbody>
</table>
### Survival in Cancer of the Tonsil
*Parsons, 2002*

<table>
<thead>
<tr>
<th>Treatment Approach</th>
<th>No. Studies</th>
<th>N</th>
<th>T4 (%)</th>
<th>Stage IV (%)</th>
<th>Local Control</th>
<th>5-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery with pos-op XRT</td>
<td>5</td>
<td>406</td>
<td>12</td>
<td>70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XRT +/- N.D.</td>
<td>7</td>
<td>321</td>
<td>44</td>
<td>47%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XRT +/- N.D.</td>
<td>12</td>
<td>1833</td>
<td>14</td>
<td>68%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XRT +/- N.D.</td>
<td>14</td>
<td>2276</td>
<td>49</td>
<td>43%</td>
<td></td>
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</tr>
</tbody>
</table>

*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 metanalysis)
- 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)

Registration
Tumor Staging
Molecular Markers
Imaging QOL

Induction (DDP / 5FU or Carboplatin/5FU)

Endoscopic Biopsy

PR → XRT Chemotherapy (DDP or Carboplatin days 1,22,43)

<PR → Salvage Surgery → XRT

→ 8 weeks

Adjuvant Chemotherapy (2 cycles-Taxol)

* Salvage Surgery

→ Follow Up

→ ND alone

* 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

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

Who are the HPV + Patients

Disease-specific survival of patients according to p16 stain proportion

Disease-specific survival of patients according to epidermal growth factor receptor intensity
Survival Based on HPV and Smoking

Response rates by tumor HPV status

<table>
<thead>
<tr>
<th></th>
<th>HPV-pos</th>
<th>HPV-neg</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete or Partial</td>
<td>82%</td>
<td>55%</td>
<td>0.01</td>
</tr>
<tr>
<td>Protocol therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete or Partial</td>
<td>84%</td>
<td>57%</td>
<td>0.007</td>
</tr>
</tbody>
</table>

ECOG 2399 Study Design

Tumor HPV status and survival

Fakhry C et al. JNCI 2008
Survival outcomes by tumor HPV status

<table>
<thead>
<tr>
<th></th>
<th>HR**</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>0.36</td>
<td>0.15-0.85</td>
</tr>
<tr>
<td>HPV-positive tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression-free</td>
<td>0.27</td>
<td>0.10-0.75</td>
</tr>
<tr>
<td>HPV-positive tumor</td>
<td></td>
<td></td>
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</tbody>
</table>

** 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

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

<table>
<thead>
<tr>
<th>HPV-tumor association</th>
<th>Cervical Cancer</th>
<th>Oropharynx Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk DNA present</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Tumor specificity</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>E6/E7 expression</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Clonality-Copy number</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Clonality-Variant analysis</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Clonality-Integration</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Malignant phenotype</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

Expected associations for HPV-caused tumors

- Sexual behaviors
- HPV infection
- HPV in tumor
- Head and neck cancer

Two different risk-factor profiles

- Tobacco
- Alcohol
- Dentition
- Oral Sex
- Marijuana

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Two distinct head and neck cancers

<table>
<thead>
<tr>
<th>Anatomic site</th>
<th>HPV-positive</th>
<th>HPV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsil / BOT</td>
<td>All sites</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>HPV-positive</th>
<th>HPV-negative</th>
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<tbody>
<tr>
<td>Basaloid</td>
<td>Keratinized</td>
<td></td>
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<table>
<thead>
<tr>
<th>Age</th>
<th>HPV-positive</th>
<th>HPV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger</td>
<td>Older</td>
<td></td>
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<table>
<thead>
<tr>
<th>SE status</th>
<th>HPV-positive</th>
<th>HPV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low</td>
<td></td>
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<table>
<thead>
<tr>
<th>Risk factors</th>
<th>HPV-positive</th>
<th>HPV-negative</th>
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</thead>
<tbody>
<tr>
<td>Sexual behavior</td>
<td>Alcohol / tobacco</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cofactors</th>
<th>HPV-positive</th>
<th>HPV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>Diet, hygiene</td>
<td></td>
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<table>
<thead>
<tr>
<th>Survival</th>
<th>HPV-positive</th>
<th>HPV-negative</th>
</tr>
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<tbody>
<tr>
<td>Improved</td>
<td>Worse</td>
<td></td>
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<table>
<thead>
<tr>
<th>Incidence</th>
<th>HPV-positive</th>
<th>HPV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing</td>
<td>Decreasing</td>
<td></td>
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</tbody>
</table>

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

- 45,769 oral (oral cavity and oropharynx) squamous cell cases
- 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

Increasing incidence of oropharynx cancers in the US

Chaturvedi et al. JCD, 2008
Proportion of all HNSCC that are oropharynx, U.S. 1973-2005

Actuarial life-table estimates of survival

<table>
<thead>
<tr>
<th>Period</th>
<th>Two-year survival</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973-1982</td>
<td>46.6 vs. 47.2%</td>
<td>0.71</td>
</tr>
<tr>
<td>1983-1992</td>
<td>56.0 vs. 49.6%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>1993-2004</td>
<td>69.7 vs. 50.3%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Tonsillar cancer HPV prevalence by calendar period, Swedish Cancer Registry

<table>
<thead>
<tr>
<th>Period</th>
<th>HPV prevalence</th>
<th>Chi square</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970-1979</td>
<td>7 of 30, 23%</td>
<td>Ref</td>
</tr>
<tr>
<td>1980-1989</td>
<td>12 of 42, 28%</td>
<td>0.79</td>
</tr>
<tr>
<td>1990-1999</td>
<td>48 of 84, 57%</td>
<td>0.0025</td>
</tr>
<tr>
<td>2000-2002</td>
<td>32 of 47, 68%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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 515 pts
  - 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)

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

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