Patterns of Distant Metastases in HPV-positive Head and Neck Squamous Cell Carcinoma
I do not intend to discuss an off-label use of a product during this activity.
Financial Disclosure(s)

I have not had any relevant financial relations during the past 12 months to disclose.
Introduction

- Oral human papillomavirus (HPV) involved in the pathogenesis of a subset of head and neck squamous cell carcinomas (HNSCC)

- Overall incidence of HNSCC decreasing in the United States
  - Incidence of HPV+ HNSCC increasing
  - Estimated by 2020 → incidence of HPV+HNSCC > HPV-related cervical cancer in the United States

- HPV+HNSCC → unique clinical characteristics compared to HPV-negative HNSCC

• HPV positivity associated with overall survival advantage
  ○ Retrospective review of patients enrolled in RTOG 0129
  ○ 3 year overall survival → 82.4% (HPV+) versus 57.1% (HPV-)
  ○ HPV+HNSCC → 58% reduction in the risk of death

• HPV+HNSCC → responds better to platinum based induction regimens and to radiation therapy compared to HPV-HNSCC

• De-intensification treatment approaches currently being examined in HPV+HNSCC patients

Introduction

- Rate of distant metastases (DM) appears similar between HPV+HNSCC and HPV-HNSCC

- Observational studies suggest a unique pattern of DM in HPV+HNSCC
  - Unusual sites of DM
  - Prolonged time to DM

- HPV status → independent predictor of overall survival after disease progression

Introduction

- Concurrent tobacco use appears to negate protective effects of positive HPV status in HNSCC patients

- HPV+HNSCC patients with concurrent tobacco use → over five times more likely to develop recurrence
  - 35% of HPV+HNSCC patients who ever used tobacco → recurred
  - 6% of HPV+HNSCC patients who never used tobacco

Methods

• Examined the pattern of distant metastases among HNSCC patients treated at UTSW from 2006-2012

• Outcome data collected for three patient groups:
  ○ Group 1 → all patients with documented HPV+HNSCC
  ○ Group 2 → HPV-/unknown primary disease of the hypopharynx, larynx, glottis (“high risk”)
  ○ Group 3 → HPV-/unknown primary disease of the oral cavity, oropharynx, hard palate, or tonsil (“intermediate risk”)

• HPV status not consistently collected prior to 2010 at our institution
## Results

<table>
<thead>
<tr>
<th>Groups</th>
<th>Distant metastases at any site (patients)</th>
<th>Lung metastases only (patients)</th>
<th>Median time to metastases (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=109) HPV+HNSCC</td>
<td>7/109 (6.4%)</td>
<td>6/109 (5.5%)</td>
<td>11</td>
</tr>
<tr>
<td>Group 2 (n=546) High risk HPV-/unk</td>
<td>25/546 (4.6%)</td>
<td>10/546 (1.8%)</td>
<td>15</td>
</tr>
<tr>
<td>Group 3 (n=839) Intermediate risk HPV-/unk</td>
<td>34/839 (4.1%)</td>
<td>12/839 (1.4%)</td>
<td>9</td>
</tr>
</tbody>
</table>
Results

Sites of distant metastases

- Lung
- Liver
- Bone
- CNS

Percentage of patients

- HPV+ head and neck squamous cell carcinoma
- Hypopharynx, larynx, glottis (HPV-/unk)
- Oral cavity, oropharynx, hard palate, or tonsil (HPV-/unk)
Results

- No difference in the overall rate of distant metastases between HPV+HNSCC and HPV-/unknown HNSCC at all primary disease sites.

- Statistically significant difference in the rate of metastases to the lung in HPV+HNSCC compared to HPV-/unknown HNSCC at all sites (p=0.002).
Results

- Statistically significant difference in rate of metastases to the lung in HPV+HNSCC compared individually to HPV-/unk cancers of the:
  - Hypopharynx, larynx, glottis (p=0.012)
  - Oral cavity, oropharynx, hard palate, or tonsil (p=0.002)
## Results

<table>
<thead>
<tr>
<th>Groups</th>
<th>Smoking frequency in patients with distant recurrence</th>
<th>Smoking frequency in patients without distant recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=109)</td>
<td>5/7 (71.4%)</td>
<td>60/102 (58.8%)</td>
</tr>
<tr>
<td>HPV+HNSCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2 (n=546)</td>
<td>25/25 (100%)</td>
<td>459/521 (88.1%)</td>
</tr>
<tr>
<td>High risk HPV-/unk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3 (n=839)</td>
<td>22/34 (64.7%)</td>
<td>544/805 (67.6%)</td>
</tr>
<tr>
<td>Intermediate risk HPV-/unk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

- Trend towards improved overall survival for HPV+HNSCC
- Median follow up from diagnosis for HPV+HNSCC → 18 months
Conclusions

- Statistically significant increase in the rate of lung metastases in HPV+HNSCC compared to HPV-/unknown HNSCC

- HPV+HNSCC demonstrated a shorter interval to development of distant metastases compared to “high risk” HPV-/unknown disease

- Effect of increased lung metastases in HPV+HNSCC on overall survival compared to HPV-HNSCC tumors remains unclear
Clinical Implications

- Increased rate of distant metastases to the lung in HPV+HNSCC → role for heightened radiographic surveillance following treatment completion

- Studies regarding various de-intensification strategies currently underway
  - Phase III RTOG 1016 → cisplatin or cetuximab administered with concurrent standard dose radiotherapy
  - Phase II ECOG 1308 → induction chemotherapy used to select patients for dose reduction of radiotherapy
Clinical Implications

- ECOG 1308
  - HPV+ patients receiving reduced dose radiotherapy → high rates of tumor control
  - Minimal late toxicities
  - Need confirmatory phase III data

- Further study needed to better characterize the patterns of distant metastases in HPV+HNSCC → identifying candidate patients for treatment de-intensification