Young Patients with Oral Cancer: Etiology and Prognosis

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Disclosures:

Nothing to disclose

Learning Objectives:

- Understand the challenges of treating young patients with head and neck oral cavity carcinoma.
- Review the data on prognosis for this population.
- Know the most recent data on the etiology of carcinoma of the oral cavity in young non-smokers, non-drinkers.

Case study:

- 24 year old female with a left lateral tongue lesion.
  - No PMH
  - NS, ND
- Resection (partial glossectomy) with selective neck dissection.
- Adjuvant chemoradiation given due to perineural invasion, multiple nodes present.
- After 6 months, recurrence present.
- In time it takes to see have her see reconstructive surgeon (6 days), it has rapidly progressed.
- Becomes unresectable within days.
- Parents lost their only child.
How does that happen?

- Is SCCA of the oral cavity different in young versus old patients?
  - Is Disease Free Survival worse?
  - Are there more recurrences?
- Could it be virally mediated?
- Does HPV play a role?
- Should we treat it differently in young patients than we do for older patients?
  - Undertreat?
  - Overtreat?
  - Sequelae of treatments, especially adjuvant therapies

Clinicopathological and prognostic characteristics:

- Pts under 40 account for less than 4% of all oral malignancies.
- Seems to represent a distinct biological entity but underlying genetic causes remain unknown.
- Incidence of oral SCCA has been rising, especially in young white women, age 18 - 44

Oral SCCA rising in young white people, esp. females

Pts under 45:

- Tend to be non-smokers (NS)
- Lower F:M ratio than older cohort
- Fewer second primaries
- At this age, could have been a smoker or drinker so traditional risk factors might be a factor….


Majchrzak et al; Radiol Oncol 2014; 48(1):1-10
Pts under 40:

- 176 pts
- Divided into two groups
- Prognosis did not differ but recurrence patterns did.
- Young pts:
  - Five year RFS: 30%
  - Five year DSS: 63%
- Older pts:
  - Five year RFS: 47%
  - Five year DSS: 62%
- BUT young pts had different failure pattern
- Recurrences occurred at the primary site

Fang et al; Oncol lett 2014 7(6): 2099-2102.

Pts under 30:

- Patients under 30:
  - 113 pts: only 16 (14%) were under 30
- Higher rates of regional metastases and distant failure
  - Half recurrences were distant vs none in the over 60 group
  - Recurrence was more aggressive, with a fatality rate of 100%
- BUT Kaplan-Meier analysis yielded no differences in disease-free or overall survival.


Pts under 20:

- Meta analysis: 186 cases
- Mean age of 14
- SCCA occurs most frequently in tongue (70%), then gingiva (20%) and lips (2%)
- Rarely in the floor of mouth
- Two groups:
  - Healthy (156)
  - Systemic condition (30)
  - 7% occurred on buccal mucosa

Bodner et al; 2014: Oral Oncol 50:84-89

Treatment

- Trying to avoid adjuvant therapy if possible
- Trying to not over or under treat
- Understanding that recurrences are often deadly
QOL seems to be very good for treated patients

- 62 pts treated for oral SCCA when they were less than 40 yrs old
- 26 responded
- Radiation therapy significantly affected their QOL but overall scores were quite good.

Thomas et al; 2012; Ann Otol Rhinol Laryngol 121(6):395-401

Etiology:

- Due to young age and lack of traditional risk factors:
  - Genetic factors
  - Genetic instability:
    - Increased c’some fragility following mutagen exposure
    - Alterations in DNA repair genes
    - Higher frequency of microsatellite instability
    - Young cohort does not have same genetic alterations as older pts
    - Increased RR of SCCA if first degree family members had HNSCC
  - Chronic immunodeficiency states:
    - Bloom syndrome
    - Wiskott-Aldrich syndrome
    - Immunosuppression
    - Organ transplantation
    - Fanconi Anemia
    - Autosomal dominant
    - 14% have HNSCC by age 40

Majchrzak et al; Radiol Oncol 2014; 48(1):1-10

Tumor suppressor genes:

Gatekeepers:
- Inhibit cell proliferation or promote apoptosis
- Mutations do not predispose to oral cancer except Li Fraumeni Syndrome
- Increased second primaries including Oral SCCA

Caretakers:
- Maintain the integrity of the genome by DNA repair
- Fanconi’s anemia
  - 21 cases of FA - 50% were on tongue and 29% cases were on gingiva

Bodner et al; Oral Oncol 2014

Etiology (con’t):

- Viral infections
  - HPV
  - ?
- Behavioral risk factors
  - No association with marijuana and oral SCCA (Rosenblatt)

Majchrzak et al; Radiol Oncol 2014; 48(1):1-10
Oral SCCA:

**ADULT**
- Site:
  - Tongue: 40%
  - FOM: 28%
- Gender:
  - Strong male predominance
- Risk factors:
  - Tobacco
  - Alcohol
  - Betel quid use

**YOUNG**
- Site:
  - Tongue: 70%
  - FOM: 2%
- Gender:
  - More female
- Risk factors:
  - Genetic
  - Viral???

Does HPV play a role?

**HPV:**
- 78 pts with lateral tongue
- P16 IHC and RNA in situ hybridization for E6/E7 mRNA
- HPV mRNA found in only one case
- Found in no patient under 40 (n=11)
- P16 overexpression found in 9 (12%) cases
- No role in young Oral SCCA
- P16 not a reliable surrogate for transcriptionally active HPV

**HPV and young pts in Japan:**
- Defined as <40 yrs old
- 40 pts
- HPV DNA detected with PCR
- 2 (5%) young pts were positive for HPV DNA
- HPV unlikely to cause Oral SCCA in young pts
- P16 expression not accurate surrogate for HPV DNA


Further evidence – no viral etiology…

- Analyzed 7 oral tongue carcinomas from young patients for viral mRNA
- Used short-read massively-parallel sequencing
- No cancer had viral transcripts
  - But controls had some viral material

Bragelman et al; Oral Oncol 2013 49(6)525-33.

What about p53?

- Exomic sequencing of tumor DNA from 6 nonsmokers compared to other sequenced cases.
- RNA from 20 tumors evaluated by massively parallel sequencing to search for potentially oncogenic viruses.

FOUND:

- NS (53 of 89 pts) were younger than smokers
- NS more likely to be female
- NS had fewer TP53 mutations than smokers (p= 0.02)
- Young age and fewer TP53 mutations suggested viral role
- No tumor-associated viruses detected

Li et al, Head Neck 2014 Jun 21

| TABLE 1. Clinical comparison of nonsmokers and smokers with oral tongue cancer. |
|-----------------------------------------------|-------------|-------------|-----------------|
| Age                                           | Nonsmokers, % | Smokers, %  | p-value        |
| <50 y                                         | 50.9         | 19.4        | .003           |
| >50 y                                         | 49.1         | 80.6        |               |
| Sex                                           |              |             | .069           |
| Male                                          | 41.5         | 61.1        |               |
| Female                                        | 58.5         | 38.9        |               |
| Tumor histologic grade                       |              |             | .053           |
| Well-differentiated                           | 13.6         | 32.3        |               |
| Moderately to poorly differentiated           | 86.4         | 67.7        |               |
| Pathologic stage                              |              |             | .999           |
| Early                                         | 65.3         | 72.2        |               |
| Advanced                                      | 34.7         | 27.8        | .543           |
| Treatment                                     |              |             |               |
| Surgery                                       | 65.2         | 75          |               |
| Surgery + RT                                  | 26.4         | 19.4        |               |
| Surgery + CRT                                 | 9.4          | 5.6         |               |
| Recurrence                                   |              |             | .026           |
| Yes                                           | 43.1         | 20          |               |
| No                                            | 56.9         | 80          |               |

Abbreviations: RT, radiotherapy; CRT, chemoradiotherapy.
p53 and CDKN2a mutations in Nonsmoker Oral SCCA:

- 51 tumors
- Mutations associated with poorer survival outcomes
- TP53 mutations in 20% tumors
  - Worse DFS and overall survival
- CDKN2a mutations in 8% tumors
  - Worse DFS and overall survival
  - Earlier recurrence
  - More often died from their disease

Heaton et al; Laryngoscope 2014;124(7)

p53 mutations common in Oral SCCA in young adults:

- Younger than 45 yrs
- 31 pts
- Found p53 mutations in 14 (45%) of tumors
- No HPV


Could Stromal Myofibroblasts be Different?

- Stromal myofibroblasts are frequently associated with more aggressive behavior
- Compared 29 young pts (<40) with older patients
- Found less myofibroblasts in lesions from younger patients
  - Controlled for staining with smooth muscle actin expression
  - No significant difference

Dysplasia at the margins:

- T1-2N0 oral tongue cancer
- 126 pts

Findings:
- Dysplasia present at final margins 37% of time
- Five year local control (LC) and DFS significantly worse for pts with moderate or severe dysplasia at margins
- Mild dysplasia did not impair LC or DFS

Conclusions:
- May wish to consider adjuvant therapy, despite added morbidity.

Sopka et al, 2013 Oral Oncol 49(11)

DFS:

Figure 2: Disease-free survival as a function of dysplasia at the final surgical margin.

Locoregional control:

Table 2: 5-Year actuarial outcomes.

<table>
<thead>
<tr>
<th></th>
<th>LC (%)</th>
<th>DFS (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>73</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>No dysplasia at the margin</td>
<td>80</td>
<td>78</td>
<td>72</td>
</tr>
<tr>
<td>Any dysplasia at the margin</td>
<td>60</td>
<td>60</td>
<td>77</td>
</tr>
<tr>
<td>Severe dysplasia at the margin</td>
<td>54</td>
<td>54</td>
<td>74</td>
</tr>
<tr>
<td>Moderate dysplasia at the margin</td>
<td>49</td>
<td>49</td>
<td>77</td>
</tr>
<tr>
<td>Mild dysplasia at the margin</td>
<td>81</td>
<td>81</td>
<td>76</td>
</tr>
</tbody>
</table>
Margins:

- Divided 126 cases into groups:
  - Margins from glossectomy specimen
  - Margins from revision
  - Margins from tumor bed


Margins (con’t):

- Average distance from carcinoma to closest margin:
  - 4.5 mm
  - 2.4 mm
  - 3 mm

- Local progression-free survival at 3 years:
  - 0.90
  - 0.76
  - 0.73


Margins (con’t):

- Reliance on tumor bed margins appears to be associated with worse local control

- May be due to the narrower distance from carcinoma to closest margin

Is oral SCCA a distinct entity in patients under 40?

- Attempt to determine whether clinical outcomes are different
- 176 pts
- Divided into two (2) groups:
  - 15 pts – young
  - 161 pts - old

Fang et al 2014; Oncol Lett 7(6):2099-2102

DSS:

Differences in clinical course:

- 360 pts and only 13 were young (< age 40)
- Prognosis for both groups were the same
- BUT rapid progression and early recurrences in young patients

Pabiszczak et al; 2013; 17(3):286-90
**International Cancer Survival Standards (ICSS)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Overall</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>5-year RS SE</td>
<td>N</td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-44</td>
<td>1307</td>
<td>60.6</td>
<td>1.9 1025</td>
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<td>45-54</td>
<td>3754</td>
<td>52.9</td>
<td>2.1 3017</td>
</tr>
<tr>
<td>55-64</td>
<td>5054</td>
<td>52.0</td>
<td>1.1 3938</td>
</tr>
<tr>
<td>65-74</td>
<td>3697</td>
<td>51.0</td>
<td>1.3 2674</td>
</tr>
<tr>
<td>75+</td>
<td>1980</td>
<td>59.3</td>
<td>2.5 983</td>
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<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Local</td>
<td>3971</td>
<td>70.9</td>
<td>1.9 2797</td>
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<tr>
<td>Regional</td>
<td>4714</td>
<td>37.2</td>
<td>1.5 3654</td>
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<td>Distant</td>
<td>373</td>
<td>64.4</td>
<td>1.7 292</td>
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<tr>
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<td>5832</td>
<td>57.7</td>
<td>1.2 4892</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
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<td></td>
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<tr>
<td>1</td>
<td>1677</td>
<td>75.6</td>
<td>2.3 1095</td>
</tr>
</tbody>
</table>

Listl et al; PLoS One 2013;8(1)

**Distinct entity?**

- Soudry et al: young adults with oral SCCA had worse N stage at diagnosis and more evidence of perineural invasion (1992 – 2007 tertiary center database)
- But no difference in other parameters

**Research:**

- UM-SCC-103 cell line
  - Derived from highly aggressive Oral SCCA dx’d in a 26 year old woman
  - Stem cells (CD44(high)) are able to be transplanted and form tumors that have same heterogeneity as primary tumor.


**Tumor : specimen index (TSI)**

- T1-2 oral tongue cancer
- N = 433
- TSI = the percentage of specimen that is occupied by the tumor in relation to the entire specimen
- Margins were negative in 84% of pts with TSI < 45 and were 63% in pts with TSI > 45
- Better locoregional recurrence-free probability and DSS with lower TSI

Conclusions:
- Prognosis may be the same over 3 – 5 years
- BUT failures are dire and deadly and different
- May benefit from standardizing how we define ‘young’ because there are few patients
- May not be able to lump 20 year old patients with 40 year old patients for studies
- Genetic testing
- Tumors will be on oral tongue in majority of cases in young oral cancer patients

Conclusions:
- HPV does not play a role
- Still looking for other viral etiologies
- Consider taking margins from glossectomy specimen to truly provide best chance for complete resection

Thank you!