High Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck

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Virginia Tech Carilion School of Medicine

Disclosures

• I have no financial relationships to disclose
Objectives

• Discuss clinical and histological features that define high risk cSCC
• Review staging systems used to risk satisfy high risk cSCC
• Outline workup and treatment of patients with high risk cSCC

Epidemiology of skin cancer in the US

1 in 5 Americans will be diagnosed with skin cancer in their lifetime.

**Lifetime risk of SCC 1:10**
**BCC 1:3, Melanoma 1:50**
Men: 9-14%
Women: 4-9%

**SCC**
1 million cases/year
4-8,000 deaths/year

**Annual cost of treating keratinocyte carcinoma**
4.8 billion dollars

Photo: [http://www.cancer.org](http://www.cancer.org) The American Cancer Society 2018
**Estimated incidence of keratinocyte carcinoma in US**
(Peer-reviewed national incidence estimate)

- National incidence estimates reported in 2006 and 2012 are based on the review of claims databases.
  - National Ambulatory Medical Care Survey database
  - Centers for Medicare & Medicaid Services Physicians Claims databases
  - BCC to SCC ratio traditionally reported as 4:1
  - Medicare fee-for-service population study
    - Ratio 1:1


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**Cutaneous SCC (cSCC)**
- 2-8% local recurrence
- 5% chance of nodal mets
- 1.5% disease specific death

**High risk cSCC: subset of SCCs that have predictable aggressive behavior**
- 15% local recurrence
- 45% metastatic risk

What features define this tumor as high risk and predict probability of local and regional recurrence based on the NCCN guidelines?

- 72 year old female, hx of CLL
- Present for treatment of recurrent moderately differentiated SCC
- Original tumor excised 1 year prior to presentation
- Tumor measured 3.0 X 2.5 cm
- Complained of symptoms of numbness, tingling and pain on the rt forehead
- Excised with 4 stages of Mohs
- Intraoperatively, tumor was present in the muscle, extensive PNI of large caliber nerves and within muscle, and vascular invasion was noted

![Image of histological sections of a tumor with annotations]

**NCCN Guidelines Version 1.2020 Squamous Cell Skin Cancer**

<table>
<thead>
<tr>
<th>Risk Factors for Local Recurrence or Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;P</td>
</tr>
<tr>
<td>Location/size†</td>
</tr>
<tr>
<td>Borders</td>
</tr>
<tr>
<td>Primary vs. recurrent</td>
</tr>
<tr>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Site of prior RT or chronic inflammatory process</td>
</tr>
<tr>
<td>Rapidly growing tumor</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
</tr>
<tr>
<td>Pathology (See SCC-A)</td>
</tr>
<tr>
<td>Degree of differentiation</td>
</tr>
<tr>
<td>Acantholytic (adenoid), adenosquamous (showing mucin production), desmoplastic, or metaplastic (carcinosarcomatous) subtypes</td>
</tr>
<tr>
<td>Depth‡</td>
</tr>
<tr>
<td>Perineural, lymphatic, or vascular involvement</td>
</tr>
</tbody>
</table>

**RISK FACTORS FOR LOCAL RECURRENCE OR METASTASES**

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area L&lt;20 mm</td>
<td>Area L≥20 mm</td>
</tr>
<tr>
<td>Area M&lt;10 mm²</td>
<td>Area M≥20 mm²</td>
</tr>
<tr>
<td>Well-defined Primary</td>
<td>Poorly defined Recurrent</td>
</tr>
<tr>
<td>(-)</td>
<td>(†)</td>
</tr>
<tr>
<td>(-)</td>
<td>(†)</td>
</tr>
<tr>
<td>(-)</td>
<td>(†)</td>
</tr>
</tbody>
</table>
High risk cSCC: Location

- High (H), Medium (M), and Low (L) risk areas identified

High risk cSCC: Size

Tumor diameter >2 cm is the risk factor most highly associated with disease specific death.

<table>
<thead>
<tr>
<th>Size</th>
<th>Local recurrence</th>
<th>Nodal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 cm</td>
<td>7.4%</td>
<td>9.1%</td>
</tr>
<tr>
<td>&gt; 2 cm</td>
<td>15.2%</td>
<td>30.3%</td>
</tr>
</tbody>
</table>

Must include peripheral rim of erythema in size measurement per NCCN guidelines (2020).

High risk cSCC: Depth

- Tumors invading beyond subcutaneous structures have an 11-fold higher risk of locoregional recurrence.

<table>
<thead>
<tr>
<th>Depth</th>
<th>Nodal failure¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.0 mm</td>
<td>None</td>
</tr>
<tr>
<td>2.1-6.0 mm</td>
<td>4 %</td>
</tr>
<tr>
<td>&gt; 6.0 mm</td>
<td>16%</td>
</tr>
</tbody>
</table>

- Depth measured from the granular layer of adjacent normal epidermis to the base of the tumor
- NCCN (2020) identifies tumor as >6 mm or invasion beyond subcutaneous fat as high risk


High risk cSCC: Differentiation

- Division of SCC has been reduced into 2 groups based on differentiation
  - Well or Moderately differentiated
  - Poorly differentiated

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Local recurrence</th>
<th>Nodal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well, moderate</td>
<td>13.6%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Poor</td>
<td>28.6%</td>
<td>32.8%</td>
</tr>
</tbody>
</table>

- Heterogeneous nature of SCC with “within tumor” variation

High risk cSCC: Histology

Desmoplasic SCC

- Architectural similarity to sclerosing BCC
  - Tumors in small nests and strands
  - Pronounced stromal reaction
- Represents 7% of all SCCs
- Sun-exposed sites
- Pattern compromises > 30%
- Frequent perineural invasion

High Risk variant of SCC
- Local recurrence 10X
- Metastasis 6X

75 year old man present for Mohs of moderately differentiated SCC. History: rapidly enlarging nodule. Pre-op size 2.0 cm. Intraoperatively, tumor was noted to be in galea and large caliber PNI was noted.

Cutaneous adenosquamous carcinoma

- 1985, uncommon
- Presents as a keratotic plaque on the head and neck of elderly
- Histology: Well-differentiated islands of squamous cells containing areas of glandular differentiation
  - Keratocysts, stromal desmoplasia
  - Lumens +CEA, epithelial component P63+, K 5/6+
- **High Risk: >50% risk of locoregional recurrence**
- Distant metastasis rare
- Immunosuppressed
- WHO classification: overlap with squamoid eccrine ductal carcinoma

Carcinosarcomatous SCC

- Biphasic tumor with malignant epithelial and mesenchymal components
- The mesenchymal part can be composed of osteosarcoma, neurogenic sarcoma, rhabdomyosarcoma, chondrosarcoma, and malignant fibrous histiocytoma


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High Risk cSCC and Immunosuppression

<table>
<thead>
<tr>
<th>Associations</th>
<th>Incidence vs general population</th>
<th>Local recurrence</th>
<th>Regional metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solid organ transplant recipients</strong></td>
<td>Age at transplant</td>
<td>65-250X</td>
<td>13-39%</td>
</tr>
<tr>
<td></td>
<td>Duration and intensity of immunosuppression</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic lymphocytic leukemia</strong></td>
<td>Rai Stage</td>
<td>8-10 X</td>
<td>15-25%</td>
</tr>
<tr>
<td><strong>HIV</strong></td>
<td>CD4 nadir</td>
<td>2-5X</td>
<td></td>
</tr>
</tbody>
</table>


Perineural invasion (PNI)

- Perineural tumor is the direct spread of tumor in, around, and through nerves
- PNI occurs in 5-14% of SCCs
- PNI associations
  - Large tumor diameter
  - Recurrent tumor
  - Poor differentiation
- Independent predictor of lymph node metastasis and recurrence
  - Local recurrence 7-15%
- Skip lesions- artifact of processing
- Most vulnerable nerve is CN V
  - Asymptomatic vs symptomatic
  - Sensory (CN V) vs Motor (CN VII)

Clinical vs. microscopic perineural invasion

- Clinical perineural invasion
  - Evidence of clinical neuropathy
  - Radiographic evidence of PNI
- Worse prognosis with clinical PNI

<table>
<thead>
<tr>
<th>PNI</th>
<th>Local failure (5 yrs post XRT)</th>
<th>Regional failure (5 yrs post XRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic</td>
<td>10-15%</td>
<td>20-30%</td>
</tr>
<tr>
<td>Clinical</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

- Elective treatment of nodal basin (surgery and/ or XRT) mainstay of therapy in patients with clinical PNI


Large caliber nerve > 0.1 mm.
Perineural invasion misdiagnosis

- Malignancy accounts for 5% of all facial paralysis
- Slowly progressive facial paralysis over months vs. Bell’s palsy
- Consider malignancy
  - Episodes of “recurrent” paralysis
  - Persistent paralysis (>6 month)
  - Paralysis associated with pain
- In patients with normal imaging studies, and history of cutaneous carcinoma, consider surgical exploration and nerve biopsy.


Lymphovascular invasion

- Independent predictor of lymph node metastasis (OR 7.54, p<.0001)
- Recurrent tumors are more likely to exhibit lymphovascular invasion than primary tumors (17 vs 8%)
- Lymphovascular invasion has been significantly associated with disease specific death and all cause death

Podophyllin stain

• 79 yo man with poorly-differentiated SCC, 3.0 x 1.7 cm, located on the right temple presented for Mohs

• **Recurrent:** History of numerous EDCs over the past 3 years by a non-dermatologist

• During MMS, perineural invasion was noted, nerve diameter of 1.3 mm

• Tumor cleared with 2 Mohs stages

• Intraoperatively, tumor and was noted in the **temporalis fascia**

• Final defect 5.5 x 4.5 cm, FTSG

**What are the features that define this tumor as a high risk SCC?**

**Post-op adjuvant XRT to tumor bed and draining lymph node basin in the neck and parotid**

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• 18 months completing XRT, patient developed retro-bulbar pressure

• Pain became refractory and accompanied by right facial numbness

• Imaging CT soft tissue of the head, neck, and orbit was performed
  • CT reveals tumor infiltrating right orbit and right cerebral hemisphere
  • Biopsy confirmed recurrent poorly-differentiated SCC with PNI

Patient died from complications of locoregional disease and intracranial invasion 2 months after imaging studies.
Could we have predicted this patient’s risk of locoregional recurrence and death within 3 years after initial treatment?

Staging high risk cSCC

- **Purpose of staging:** Accurate predictions in patient outcomes guide decisions regarding nodal staging and adjuvant therapy

- **Staging systems**
  - American Joint Commission on Cancer (AJCC-8)
  - Brigham-Women’s Hospital Staging System (BWH)
  - International Union Against Cancer (UICC)
  - Breuninger system
In all staging systems, bone involvement, orbital involvement, and skull base invasion place patients in the highest stages.
Brigham and Women’s T-Staging System for SCC

**Advantages vs AJCC-7**
- BWH T2b includes only 5% of the cohort.

**Shortcomings**
- Only 20% of T2b tumors have an adverse outcome. The majority of patients do well.
- 40% of local recurrences and 16% of nodal mets occur in BMW stage T1 and T2a. These are missed in the high risk groupings.

**Table 2. Alternative Tumor Staging System for cSCC**

<table>
<thead>
<tr>
<th>Primary Tumor</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>In situ squamous cell carcinoma</td>
</tr>
<tr>
<td>T1</td>
<td>0 Risk factors</td>
</tr>
<tr>
<td>T2a</td>
<td>1 Risk factor</td>
</tr>
<tr>
<td>T2b</td>
<td>2-3 Risk factors</td>
</tr>
<tr>
<td>T3</td>
<td>4 Risk factors or bone invasion</td>
</tr>
</tbody>
</table>

- Outcomes:
  - Local recurrence, nodal mets, DSD, all cause death
  - Multivariate analysis to determine independent prognostic predictors for each outcome of interest
  - Four factors were found to predict more than one outcome

**How would this tumor be staged with BWH?**

- 79 yo man with poorly-differentiated
- 3.0 x 1.7 cm, located on the right temple
- Recurrent: History of numerous EDCs over the past 3 years by a non-dermatologist
- During MMS, perineural invasion was noted, nerve diameter of 1.3 mm
- Tumor cleared with 2 Mohs stages and tumor was noted in the temporalis fascia

**1. Poor differentiation**
**2. Perineural invasion**
**3. Tumor diameter > 2 cm**
**4. Invasion beyond subcut fat**

AJCC-8 squamous cell carcinoma T-staging (2017)

<table>
<thead>
<tr>
<th>T-Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor &lt;2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;2 cm but &lt;4 cm</td>
</tr>
</tbody>
</table>
| T3      | • Tumor >4 cm OR  
           • Minor bone erosion OR  
           • PNI >0.1 mm caliber or nerve deeper than dermis OR  
           • Deep invasion: beyond subcutaneous tissue or ≥6 mm deep |
| T4      | Bone invasion or skull base involvement |

Management of patients with high risk cSCC

- Surgery
- Imaging
- Nodal biopsy
- Adjuvant treatment

Treatment: Surgery

Clinical outcomes in high-risk squamous cell carcinoma patients treated with Mohs micrographic surgery alone

Geraardo Marion, MD,1 John A. Zidek, MD,1 and David Brodland, MD2
Hines, North Carolina, and Pittsburgh, Pennsylvania

Background: There is little evidence to predict patient outcomes after the treatment of high-risk cutaneous SCC (cSCC) using Mohs micrographic surgery (MMS).

Objectives: We sought to report the rates of poor outcomes in patients with hrSCC treated by MMS alone and to determine if any specific clinical factors may be more predictive of these outcomes.

Methods: We conducted a retrospective chart review of all patients with hrSCC who were treated in our clinic between October 2011 and December 2015.

Results: We identified 677 hrSCC lesions that met the inclusion criteria. During the follow-up period, there were 83 local recurrences (2.5%), 34 nodal metastases (4.1%), 25 distant metastases (3.0%), and 7 disease-specific deaths (0.7%). Two factors, poor differentiation, and invasion beyond the subcutaneous fat, were positively associated with local recurrence, nodal metastasis, and disease-specific death through multivariate analysis.

Conclusions: Invasion beyond the subcutaneous fat and poor differentiation may carry a particular risk of poor outcome than other factors in hrSCC. MMS alone provides excellent marginal control with low rates of local recurrence, nodal metastasis, and disease-specific death. (J Am Acad Dermatol 2019;90:535-8.)

Key words: extirpative oncology, cutaneous squamous cell carcinoma, dermatologic surgery, high-risk squamous cell carcinoma, Mohs micrographic surgery.

- Cohort of T2b/T3 lesions had a LR rate of 10.3%, a NM rate of 16.5%, and a DSD rate of 4.8.
- This cohort experienced the lowest rates of LR, NM, and DSD published thus far for hrSCC using the BWH staging system.
- Study supports that patients with hrSCC may have better outcomes when treated with Mohs Surgery.
- In multivariate analysis, invasion beyond subcutaneous tissue and poor differentiation had the greatest correlation with poor outcomes.
Imaging

Sentinel lymph node biopsy

- Stepwise progression of cSCC to regional node followed by distant metastasis
- 7% of patient with negative PET CT scans are found to have +SLNB
  - Sensitivity 77%
  - Specificity 100%
  - False negative rate of 4.6%

**Table 4. SLN+ by T Stage in Patients With Nonanogential cSCC in 2 Staging Systems**

<table>
<thead>
<tr>
<th>T Stage</th>
<th>No. of SLN+ Tumors/Total No. of Tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Not included</td>
</tr>
<tr>
<td>T1</td>
<td>0/9</td>
</tr>
<tr>
<td>T2a</td>
<td>6/85 (7.1)</td>
</tr>
<tr>
<td>T2b</td>
<td>5/17 (29.4)</td>
</tr>
<tr>
<td>T3</td>
<td>3/6 (50.0)</td>
</tr>
</tbody>
</table>


Adjuvant therapy

- Radiation
- Chemotherapy

87 yo man presented with 1.7 x 1.5 cm SCC on the rt post ear
- Poorly differentiated
- Mohs stage 1: Heavy inflammation
- Cleared with 2 stages Mohs (performed 18 days after the initial biopsy)
• Presented 1 year after initial Mohs procedure with enlarging subcutaneous nodule
• Excisional biopsy: poorly differentiated SCC in subcutaneous tissue
• Treated with 3 stages of Mohs
• PET-CT scan negative
• Referred for adjuvant XRT to tumor bed, parotid, and ipsilateral neck nodes

NCCN panel recommends consideration of adjuvant XRT for any SCC that sows evidence of extensive perineural or large nerve involvement.
Indications for post-operative XRT

- Size >2 cm or >6mm deep
- Close or positive margins
- Large caliber PNI
- Node positive disease
- Multiply recurrent disease
- Poorly differentiated (spindle cell variant, desmoplastic)
- Rapidly growing
- Satellite dermal metastasis
- Lymphovascular invasion
- Immunosuppressed

Utility of Adjuvant XRT

Outcomes of Adjuvant Radiotherapy Following Negative Surgical Margins for Cutaneous Squamous Cell Carcinoma

Jonathan Miller, MD,* Timothy Chang, MD,* David Schwartz, MD,* Markot Peters, MD,** and Christian Baum, MD***

BACKGROUND The role of adjuvant radiotherapy (ART) for cutaneous squamous cell carcinoma (cSCC) following negative surgical margins is unclear.

OBJECTIVE To retrospectively examine the clinical outcomes in a cohort of patients with cSCC who completed ART after Mohs micrographic surgery or wide local excision with negative margins.

METHODS AND MATERIALS After the institutional review board approval, a retrospective review was conducted of all patients with cSCC treated in the Mayo Clinic Department of Radiation Oncology from March 10, 1998, through April 28, 2013. Inclusion criteria were age >18 years, resection with negative histologic surgical margins, and completion of ART.

RESULTS Thirty-two patients met the inclusion criteria: 15 patients died, 12 without evidence of disease related to cSCC. Three patients developed recurrent disease, all with poorly differentiated cSCC, >2 cm in clinical diameter, perineural invasion, and Bingham and Wright’s (BW) stage T2N0T; 2 of 3 patients were immunosuppressed; and 2 of 3 patients died from cSCC-related causes.

CONCLUSION These data suggest that combination of surgical resection and ART is a reasonable option for Bingham and Wright’s T2N0T tumors. The authors have indicated no significant interest with commercial supporters.


Utility of Adjuvant XRT

Evaluation of the utility of localized adjuvant radiation for node-negative primary cutaneous squamous cell carcinoma with clear histologic margins

Emily Starnell Bjorn, MD, MPH*, Shiloo A. Rovsing, MD*, Cyril Keena T. Ong, MD, MPH, Jason Keas, MD, PhD*, Chrystyne D. Schmidt, MD, MSCE**

Table 1: Clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>Surgical microsurgery (&lt;2cm)</th>
<th>Surgery + ART (n=30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence, n (%)</td>
<td>2 (10)</td>
<td>9 (60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Node metastasis, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Distant metastasis, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Disease-specific death, n (%)</td>
<td>0 (0)</td>
<td>1 (6.7)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Table 2: Clinical outcomes

<table>
<thead>
<tr>
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<tr>
<td>Distant metastasis, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Disease-specific death, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Abbreviations: ART, adjuvant radiation therapy; PN, perineural invasion.*p-value determined using Fisher’s Exact Test.
Adjuvant systemic therapy for metastatic or locally advanced, unresectable cSCC

- Cisplatin / carboplatin as single agent or combination therapy (5-FU)
- Epidermal growth factor receptor (EGFR) antagonist: Cetuximab
- Immunotherapy with PD-1 inhibitors: Cemiplimab

Conclusions

- Subset of high risk cSCC that displays a tendency for local and regional recurrence
- Various staging systems help risk stratify patients with high risk cSCC
- Surgery is the mainstay of treatment
- Emerging role for peri-operative imaging and SLNB
- Systemic therapy may play an important role for inoperable tumors
- PD-1 inhibitors present a new treatment option