High-Risk Cutaneous Squamous Cell Carcinoma

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www.MSKCC.org
DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Christopher A. Barker, MD
S026 Tumor Board

DISCLOSURES

Memorial Sloan Kettering Cancer Center: Employment
Elekta, Amgen, Merck, UCSF: Investigator – Grants
Elsevier, Charlotte AHEC, Weill Cornell Medical Center, Driver Group: Advisory Board – Honoraria
Outline

• What is high-risk cutaneous squamous cell carcinoma (SCC)?
• Staging systems and risk-grouping systems
• Assessment: Clinical and Pathologic
• Treatment: Definitive and Adjuvant
High-Risk Squamous Cell Carcinoma

• What makes it “high-risk”?
  – High-risk for recurrence
  – High-risk for regional node metastasis
  – High-risk for distant metastasis
  – High-risk for death from disease
What Defines “High-Risk” Cutaneous Squamous Cell Carcinoma?

• No consensus (several definitions)
• Staging systems use similar criteria
• Depends on perspective!
  – Dermatologist
  – Dermatologic Surgeon
  – Surgical Oncologist
  – Radiation Oncologist
  – Medical Oncologist

<table>
<thead>
<tr>
<th>Clinical Criteria</th>
<th>Low-Risk</th>
<th>High-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td>Primary</td>
<td>Recurrence</td>
</tr>
<tr>
<td><strong>Site of RT/inflammation</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Growth</strong></td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td><strong>Neurologic symptoms</strong></td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Immunosuppression</strong></td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>
| **Location, Size** | -Trunk/extremities*, <2 cm  
-Face†/scalp/neck/pretibia, <1 cm | -Trunk/extremities*, ≥2 cm  
-Face†/scalp/neck/pretibia, ≥1 cm  
-Face‡/genitalia/hands/feet | |
| **Borders**       | Well-defined | Poorly-defined | |

*excluding pretibia, hands, feet, nails, ankles  
†excludes “mask area” (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular, postauricular, temple, ear)  
‡includes the areas above

<table>
<thead>
<tr>
<th>Pathologic Criteria</th>
<th>Low-Risk</th>
<th>High-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiation</td>
<td>Well or moderate</td>
<td>Poor</td>
</tr>
<tr>
<td>Subtype</td>
<td>Not adenoid (acantholytic), adenosquamous (mucin-producing), desmoplastic</td>
<td>Adenoid (acantholytic), adenosquamous (mucin-producing), desmoplastic</td>
</tr>
<tr>
<td>Thickness</td>
<td>&lt;2 mm</td>
<td>≥2 mm</td>
</tr>
<tr>
<td>Clark level</td>
<td>I-III</td>
<td>IV-V</td>
</tr>
<tr>
<td>Perineural involvement</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lymphatic involvement</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Vascular involvement</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
**Primary Tumor Criteria** | **Stage**
--- | ---
Primary tumor cannot be assessed | Tx
No evidence of primary tumor | T0
Carcinoma in situ | Tis
Tumor ≤2 cm AND <2 high risk features* | T1
Tumor >2 cm OR ≥2 high risk features* | T2
Tumor invades maxilla, orbit, or temporal bone | T3
Tumor invades skeletal bones or perineural invasion of skull base | T4

*high risk features: >2mm thick, Clark level IV-V, perineural invasion, primary tumor on ear or hair-bearing lip, undifferentiated or poorly differentiated tumor

### Regional Lymph Node Metastasis Criteria

<table>
<thead>
<tr>
<th>Description</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional nodes cannot be assessed</td>
<td>Nx</td>
</tr>
<tr>
<td>No regional node metastases</td>
<td>N0</td>
</tr>
<tr>
<td>Metastasis in 1 ipsilateral lymph node, ≤3 cm in greatest diameter</td>
<td>N1</td>
</tr>
<tr>
<td>Metastasis in 1 ipsilateral lymph node, &gt;3 cm in greatest diameter</td>
<td>N2a</td>
</tr>
<tr>
<td>Metastasis in &gt;1 ipsilateral lymph nodes, ≤6 cm in greatest diameter</td>
<td>N2b</td>
</tr>
<tr>
<td>Metastasis in &gt;1 contralateral lymph nodes, ≤6 cm in greatest diameter</td>
<td>N2c</td>
</tr>
<tr>
<td>Metastasis in a lymph node &gt;6 cm in greatest diameter</td>
<td>N3</td>
</tr>
</tbody>
</table>

### Distant Metastasis Criteria

<table>
<thead>
<tr>
<th>Description</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No distant metastasis</td>
<td>M0</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>M1</td>
</tr>
<tr>
<td>Primary Tumor Criteria</td>
<td>T-stage</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Primary tumor cannot be identified</td>
<td>TX</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>Tis</td>
</tr>
<tr>
<td>Tumor ≤2 cm</td>
<td>T1</td>
</tr>
<tr>
<td>Tumor &gt;2 cm AND ≤4 cm</td>
<td>T2</td>
</tr>
<tr>
<td>Tumor &gt;4 cm OR minor bone erosion OR perineural invasion* OR deep invasion†</td>
<td>T3</td>
</tr>
<tr>
<td>Tumor with gross cortical bone/marrow invasion OR skull base foramen invasion</td>
<td>T4</td>
</tr>
<tr>
<td>Tumor with gross cortical bone/marrow invasion OR skull base foramen involvement</td>
<td>T4a</td>
</tr>
<tr>
<td>Tumor with skull base involvement OR skull base foramen involvement</td>
<td>T4b</td>
</tr>
</tbody>
</table>

*perineural invasion=tumor cells within the nerve sheath of a nerve lying deeper than dermis or measuring ≥0.1 mm in caliber, or with clinical or radiographic involvement of named nerves without skull base invasion or transgression
†deep invasion=invasion beyond the subcutaneous fat or >6mm (measured from granular layer of adjacent normal epidermis to the base of the tumor)
Alternative Risk and Staging Systems

• Risk systems
  – Immunosuppression, Treatment, Extranodal spread, and Margin status (ITEM) score (Cancer 2009)

• Staging systems
  – Union Internationale Contre le Cancer (UICC), Tübingen (JDDG 2012), Arkansas (Derm Surg 2006), Sydney (Cancer 2009), Brigham and Women’s (JAMA Derm 2013)
Factors Used in Risk and Staging Systems

• Primary tumor
  – Clinical: site, diameter, invasion of tissues beyond subcutaneous fat, perineural spread
  – Pathologic: differentiation, depth of invasion, invasion of tissues beyond subcutaneous fat, perineural invasion, desmoplasia

• Regional metastasis
  – Clinical: number, size, and location
  – Pathologic: number, size and location
  – Lymph node vs in-transit metastases

• Host immunocompetency
What Must Be Done To Assess Risk?

• Clinical staging procedures
  – Clinical assessment
  – Primary tumor biopsy
  – Imaging (optional)
  – Lymph node biopsy (optional)

• Pathologic staging procedures
  – Complete, margin-negative excision
  – Complete regional lymphadenectomy
Clinical Assessment

• History and symptom assessment
  – Presentation: is this *recurrent* SCC?
  – Site: *high-risk? Irradiated* or *inflamed*?
  – Growth rate: *fast* or *slow*?
  – Neurologic symptoms: *pain, paresthesias, pruritus, formications, weakness*

• Comorbidity assessment
  – Immune function (*medications, medical problems*)

• Physical examination
  – Primary tumor *diameter, fixation, border definition*
  – Regional neurologic (*strength, sensation, reflexes*)
  – *Regional lymph nodes* and *in-transit lymphatics*
Primary Tumor Biopsy

- Shave vs punch
- Dermatopathology review and clinical correlation
  - Subtype
  - Depth of invasion
  - Vascular invasion
  - Lymphatic invasion
  - Perineural invasion
Cutaneous Squamous Cell Carcinoma with Perineural *Invasion* vs *Spread*

- Perineural *invasion* (PNI) describes pathologic findings (pPNI)
  - Limited vs extensive
  - Small caliber nerve (<0.1 mm) vs large caliber nerve (≥0.1 mm)
- Perineural *spread* (PNS) describes clinical or radiologic condition
  - Also called “clinical perineural invasion” (cPNI)
  - Worse prognosis than pPNI
Lymph Node Biopsy

• Fine needle aspiration of palpable lymph nodes
  – Not excisional or core biopsy
• Ultrasound-guided fine needle aspiration of radiographically detected but non-palpable lymph nodes
  – Ultrasound guidance may improve accuracy
• Sentinel lymph node biopsy
  – Consider for clinically node negative patients at highest risk for regional metastases
Imaging: Primary Tumor

- Evaluate depth of invasion
  - Fixed to underlying bone?
    - CT superior for evaluating bone invasion
  - Fixed to underlying soft tissues?
    - MRI superior for evaluating soft tissue invasion
- Evaluate perineural spread with MRI
  - Gadolinium contrast will increase sensitivity
Imaging: Regional Lymph Nodes

• CT: rapid, large field of view
  – Iodinated contrast will increase sensitivity
• MRI: slower, better soft tissue resolution
  – Gadolinium contrast will increase sensitivity
• US: no radiation, operator dependent
• PET: costly, also evaluates distant metastasis, good if concurrent lymphoid malignancy
• Get to know your local diagnostic radiologist, and communicate!
Imaging: Distant Metastasis

- Chest x-ray: lowest sensitivity
- CT neck, chest, abdomen and pelvis: rapid
  - Iodinated contrast will increase sensitivity
- PET: highest sensitivity
Treatment of High-Risk Tumor: Surgery

• Goal: complete, margin-negative excision that is not functionally or cosmetic debilitating to patient
• Preferred first-line therapy in most patients
• Options include:
  – Local excision (margin width depends on risk)
  – Mohs
  – Resection with complete margin assessment
Treatment of High-Risk Tumor: Radiotherapy

• Goal: complete and durable response that is not functionally or cosmetically debilitating

• Second-line therapy in patients
  – With unresectable tumors
  – With medical problems precluding surgery
  – That decline surgery

• Options include:
  – Megavoltage electrons or photons
  – Orthovoltage photons
# Radiation for Advanced (T4) Cutaneous Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>University of Southern California</th>
<th>University of Florida</th>
<th>University of Oklahoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number patients</strong></td>
<td>23</td>
<td>85</td>
<td>21</td>
</tr>
<tr>
<td><strong>Mean/median age</strong></td>
<td>64 years</td>
<td>n/r</td>
<td>63 years</td>
</tr>
<tr>
<td><strong>Basal cell carcinoma</strong></td>
<td>61%</td>
<td>60%</td>
<td>48%</td>
</tr>
<tr>
<td><strong>Recurrent</strong></td>
<td>39%</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Average radiation dose</strong></td>
<td>55 Gy</td>
<td>65-75 Gy</td>
<td>67 Gy</td>
</tr>
<tr>
<td><strong>5-year local control</strong></td>
<td>80%</td>
<td>53%*</td>
<td>57%**</td>
</tr>
<tr>
<td><strong>BCC 5-year local control</strong></td>
<td>100%</td>
<td>n/r***</td>
<td>80%</td>
</tr>
<tr>
<td><strong>SCC 5-year local control</strong></td>
<td>66%</td>
<td>n/r***</td>
<td>36%</td>
</tr>
<tr>
<td><strong>5-year cause-specific survival</strong></td>
<td>n/r</td>
<td>76%</td>
<td>n/r</td>
</tr>
</tbody>
</table>

*49% at 10 years

**crude local control with 12 month median follow-up

***no significant difference between BCC and SCC

Treatment of Lymph Node or In-transit Metastases: Surgery

• Goal: complete, margin-negative regional lymphadenectomy that is not functionally or cosmetically debilitating to the patient
• Preferred first-line therapy in most patients
Treatment of Lymph Node or In-transit Metastases: Radiotherapy

• Goal: complete and durable response that is not functionally or cosmetically debilitating

• Second-line therapy in patients
  – With unresectable tumors
  – With medical problems precluding surgery
  – That decline surgery
Adjuvant Therapy: When Should We Do More?

• Adjuvant therapy = adjunctive therapy given before (neoadjuvant), during (concurrent) or after (adjuvant) definitive therapy (surgery or radiotherapy) to improve disease control/outcomes
  – Not expected to produce cure if given alone
  – Radiotherapy (lower dose than definitive)
  – Systemic therapy (chemo or immunotherapy)
• In high-risk cSCC, no prospective data proving benefit
Adjuvant Radiation for Primary Cutaneous Squamous Cell Carcinoma

• No randomized or prospective trials
• Considered for patients with highest risk of local recurrence
  • Tumors >6 mm thick
  • Desmoplastic growth pattern
  • Lymphovascular space invasion
  • Perineural invasion or spread
  • Incompletely resected tumor
Risk of Local Recurrence After Excision to Negative Margins

- 615 patients with cSCC excised to negative margins studied in prospective trial
- Multivariate models revealed 2 factors associated with local recurrence:
  - Tumor thickness
    - 12% risk if >6 mm thick
  - Desmoplastic growth (including perineural or lymphovascular invasion)
    - 24% if desmoplastic

Adjuvant Radiation After Excision with Close/Positive Margins

- Retrospective analysis of 68 patients with cutaneous squamous cell carcinoma of lip

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone (n=51)</th>
<th>Surgery and adjuvant RT (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>37 (73%)</td>
<td>11 (65%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>25 (49%)</td>
<td>10 (59%)</td>
</tr>
<tr>
<td>Lower lip</td>
<td>46 (90%)</td>
<td>15 (88%)</td>
</tr>
<tr>
<td>Margins close/positive</td>
<td>14 (27%)</td>
<td>16 (94%)</td>
</tr>
<tr>
<td>Moderate/poorly differentiated</td>
<td>18 (35%)</td>
<td>9 (53%)</td>
</tr>
<tr>
<td>T1</td>
<td>44 (86%)</td>
<td>15 (88%)</td>
</tr>
<tr>
<td>T2-T3</td>
<td>7 (14%)</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>9 (18%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Lymph node recurrence</td>
<td>19 (37%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Adjuvant Radiation After Excision to Negative Margins

• 315 patients with head and neck cSCC excised to negative margins analyzed retrospectively

• In multivariate model, patients selected for adjuvant RT had 92% reduction in recurrence risk (compared to local excision alone)
  – T and N stage, perineural invasion and inflammation also associated with risk of recurrence

Skull Base or Subcranial Resection for cSCC with Perineural Spread

- 21 patients with head and neck cSCC with PNS 1996-2006
- 86% underwent adjuvant radiation
- 5-year disease specific survival 64.3%

Adjuvant Radiation For Regional Lymphatic Metastases from cSCC

• No prospective or randomized trials
• Considered for patients with highest risk of regional recurrence
  • Tumors >6 mm thick
  • Tumors >5 cm
  • Multiple nodes involved
    • 1 parotid node
    • >1 cervical or axillary nodes
    • >2 groin nodes
  • Large involved nodes
    • Cervical or axillary nodes >3 cm
    • Groin nodes >4 cm
  • In-transit metastases
  • Extranodal extension
  • Incompletely resected metastases
Risk of Regional Nodal Recurrence After Excision to Negative Margins

- 615 patients with cSCC excised to negative margins studied in prospective trial
- Multivariate models revealed 4 factors associated with lymph node recurrence:
  - Tumor thickness
    - 4% risk if 2-6 mm thick
    - 16% risk if >6 mm thick
  - Tumor size
    - 2% if ≤2 cm
    - 8% if 2-5 cm
    - 20% if >5 cm
  - Immunosuppression (16%)
  - Primary tumor on ear (10%)

Adjuvant Radiation After Lymph Node Dissection

• 167 patients with head and neck cSCC underwent lymph node dissection

• In multivariate model, patients selected for adjuvant RT had 76% reduction in recurrence risk (compared to surgery alone)
  – Number of nodes also associated with risk of recurrence

Combining Chemotherapy/Systemic Therapy with Radiation

• For other locally advanced (T3-T4, N+) cancers, has improved outcomes (locoregional control and overall survival)
  – As *definitive* or *adjuvant* therapy
• Typically uses platinum or fluorouracil based regimens
• Recent investigations of molecularly targeted therapy
High-Risk Nodal Disease
- 1 parotid node
- >1 cervical node
- >3 cm cervical node
- Extrannodal extension

Advanced Primary Disease
- Cartilage, bone, muscle invasion
- >4 cm tumor
- In-transit metastases

Accural (n=320) complete, first analysis in June 2015
Definitive Chemoradiation for Unresectable or Inoperable cSCC

- Phase II single-arm study of 14 patients
  - Platinum chemotherapy and radiation
  - Planned enrollment of 30 patients
  - Median age 66
- Grade 3-4 adverse events 28%
- Complete response in 57%
- Partial response in 43%
- 3-year survival 54%

Nottage MK et al. ASCO 2012.
• Retrospective analysis of 12 patients
  – Median age 78 years
  – 75% with moderate or severe comorbidities
  – 42% with immune dysfunction
• Grade 3 adverse events 16-25%
• Complete response in 36%
• Partial response in 27%
• 4-year recurrence-free survival 40%

• Phase I single-arm study in 15 patients
  – Median age 68 years
  – 93% with T4
• Grade 3 adverse events 13-47%
• 2-year disease-free survival 60%

Case

- 80 year old man presented with rapidly growing tumor of left cheek
- Biopsy demonstrated poorly-differentiated cSCC in dermis and focally in lymphatic channel
- Wide local excision revealed poorly differentiated cSCC, invasive 9 mm, invading subcutis, with perineural invasion (0.1 mm nerve), deep margin positive
Case: Question 1

• What additional evaluations could be helpful?
  – A. PET scan to evaluate for distant metastasis
  – B. CT scan of the neck to evaluate for regional metastasis and residual primary tumor
  – C. MRI of the parotid area to evaluate for perineural spread and residual primary tumor
  – D. Chest xray to evaluate for distant metastasis
  – E. No additional evaluations would be helpful
Case: Question 2

- What is your next step in management?
  - A. Punch biopsy of suspicious lymph node
  - B. Excisional biopsy of suspicious lymph node
  - C. Fine needle aspiration of suspicious lymph node
  - D. Lymphadectomy
  - E. Observation of suspicious lymph node
Ultrasound guided FNA shows cSCC
Case: Question 3

• What is your next step in management?
  – A. Adjuvant radiotherapy
  – B. Adjuvant chemotherapy and radiotherapy
  – C. Parotidectomy and lymphadenectomy
  – D. Mohs surgery
  – E. Observation
Parotidectomy and lymphadenectomy
Case: Question 4

• What is your next step in management?
  – A. Adjuvant radiotherapy
  – B. Adjuvant chemotherapy and radiotherapy
  – C. Adjuvant programmed death-1 (PD1) blockade
  – D. Mohs surgery
  – E. Observation
Adjuvant radiotherapy (protons)

-Cytotoxic chemotherapy (platinum, fluorouracil), contraindicated because of comorbidities
-Cetuximab offered, but patient declined
-Completed 66 Gy/33 fractions with expected dermatitis, which resolved
Alive without recurrence 2 years later
Conclusions

• High-risk cutaneous SCC is variably defined
• Careful clinical and pathologic assessment can identify patients at high-risk for recurrence, nodal metastasis, distant metastasis and death
• Further study of adjuvant therapy for high-risk SCC is needed to improve outcomes
  – Prospective trials needed
  – Refine approach through genomic analyses
Thanks!

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