High Risk Cutaneous Squamous Cell Carcinoma: Recognition and Management

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Disclosures

• Advisory Board, Regeneron-Sanofi
• Speaker Bureau, Genentech
Objectives

• Following this session, attendees should be able to:
• 1) identify lesions suspicious for cutaneous squamous cell carcinoma (cSCC)
• 2) understand the clinical and histologic features of high risk cSCC
• 3) understand the management options for low risk and high risk cSCC, including new treatment approaches for advanced disease
Epidemiology of cSCC

- More than 1 million new cases diagnosed in US each year with annual increase of 2%-4%
- Significant risk of metastasis (4%)
- Case-fatality rate approx. 1.5% at 15,000 cases/year
cSCC - Classification

• Low risk tumors
• High risk tumors
Low risk cSCC

• 5-year recurrence rate is 5-8%
• 5-year rate of metastasis is 5%
High Risk cSCC

• SCC at greater risk for recurrence and metastasis than low risk cSCC
cSCC - Risk Factors

• Ultraviolet radiation
• Ionizing radiation
• Genodermatoses
• Human papillomavirus (HPV)
• Chemical carcinogens
• Immunosuppression
• Chronically injured/diseased skin
cSCC - Ionizing radiation

- Used commonly in 1940's-50's to treat benign dermatoses
- SCC risk directly related to total accumulated dose
- Latent period before tumor development varies inversely with total dose
- Tumor development typically related to x-radiation, but gamma and grenz rays further augment risk
cSCC - Genodermatoses

- Oculocutaneous albinism
- Xeroderma pigmentosum
- Dystrophic epidermolysis bullosa
- Epidermodyplasia verruciformis
cSCC - Human papillomavirus (HPV)

• HPV types 6 and 11 common in genital tumors
• HPV type 16 common in periungual tumors
cSCC - Chemical agents

• Arsenic
  • Patent medicines- Fowler's solution, Asiatic pills
  • Tainted wine and unprocessed well water in developing countries
  • Metal ore workers and insecticide handlers
cSCC - Chemical agents

• Arsenic
  • Produces invasive and in situ tumors on exposed and covered skin
  • Arsenical keratoses and/or pits on palms and soles
  • Circular areas of hypopigmentation on trunk
  • Carcinogenicity is dose-dependent, with an associated risk of internal malignancy
cSCC - Immunosuppression

- Organ transplant patients at increased risk
- Higher SCC:BCC ratio
- Transplant patients 65x more likely to develop cSCC
  - Lesions appear 2-4 years after transplant
  - Lesions increase in number over time
  - Lesions more aggressive than in normal hosts
- Tumor formation may be potentiated by immunosuppressive medications, leukemia, lymphoma
cSCC – Injured or chronically diseased skin

Longstanding ulcers
Sinus tracts
Osteomyelitis
Radiation Dermatitis
Vaccination scars

Discoid lupus erythematousus
Lichen sclerosus et atrophicus
Lichen planus
Dystrophic epidermolysis bullosa
Lupus vulgaris
cSCC - Classification

- Low risk tumors
- High risk tumors
Low risk cSCC

• Size <1 cm
• Well defined
• Primary
• Located on neck, trunk, extremities
Low risk cSCC- Treatment

• Electrodesiccation and curettage (ED&C)
• Excision
• Cryosurgery
• Radiation therapy
• Photodynamic therapy
## Low risk cSCC – post-treatment recurrence

<table>
<thead>
<tr>
<th>Procedure</th>
<th>&lt; 5 yr follow-up</th>
<th>&gt; 5 yr follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryotherapy</td>
<td>3.2%</td>
<td>N/A</td>
</tr>
<tr>
<td>ED+C</td>
<td>1.3%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Excision</td>
<td>5.7%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Radiation</td>
<td>6.7%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Non-Mohs modalities</td>
<td>4.0%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Mohs surgery</td>
<td>N/A</td>
<td>3.1%</td>
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</table>
Keratoacanthoma (KA)

• Low-grade keratinocyte malignancy originating in pilosebaceous units
• Rapid growth over weeks to months, followed by resolution over 4-6 months in most cases
• Infrequently presents as multiple tumors or giant lesions (5-15 cm)
• Rarely progresses to invasive or metastatic disease
Keratoacanthoma

• May have invasive growth pattern on deep margin
• Histologic and clinical differentiation from cSCC can be difficult
• Can be distinguished histologically in 85% of cases
• Should be treated as cSCC if not readily classifiable
Verrucous carcinoma

• May resemble large warts
• Locally aggressive but rarely metastasizes
• Adequate excision generally results in complete cure
• Reports of malignant transformation after XRT
Clinical Profile of the High Risk cSCC

• Size (>2 cm diameter)
• Anatomic site (ear, lip, central face)
• Rapid growth
• Recurrence
• Immunosuppression
• Arising within scar, sinus tract, radiated site
Histologic Profile of the High Risk cSCC

- Depth of invasion to or below deep dermis
- Poorly differentiated
- Perineural invasion
- Recurrence
- Immunosuppression
High risk cSCC - Size > 2 cm

• Recur in 15% of cases
  • twice the rate of lesions < 2 cm
• Metastasize in 30% of cases
  • three times the rate of lesions < 2 cm
• Five year cure rate is 70% with standard treatments
High risk cSCC - Anatomic site

• Rates of recurrence and metastasis range from 10-25% for cSCCs of lip and ear
• Other high risk sites include:
  • Scalp, forehead, temple
  • Eyelids, nose, mucous membranes
  • Dorsal hands
  • Genitalia, perianal region
High risk cSCC - Clinical features

• Rapid growth
  • Tumors may metastasize in up to 33% of cases
• Tumors arising in injured or chronically diseased skin
  • Risk of metastasis approaches 40%
High risk cSCC - Clinical features

• Immunosuppression
  • Risk of metastasis >12%

• History of previous treatment
  • Risk of metastasis 25% for most cutaneous lesions
  • Risk of metastasis 30-45% for ear and lip tumors

• History of irradiation
High risk cSCC - Histologic features

• Well differentiated cSCC
  • Local recurrence rate 13.6%
  • Metastatic rate 9.2%
  • 5 year cure rate 94.6%

• Poorly differentiated cSCC
  • Local recurrence rate 28.6%
  • Metastatic rate 32.8%
  • 5 year cure rate 61.5%
High risk cSCC - Histologic features

- Depth > 4 mm or extension into reticular dermis or subcutaneous fat
  - Local recurrence rate 17.2%
  - Metastatic rate 45.7%
High risk cSCC - Perineural invasion

• Occurs in only 5% of cSCCs
• Contiguous movement of tumor cells along nerve fibers (neurotropic spread)
• Not clinically or histologically apparent until significant tumor extension has occurred
• Local recurrence rate: 47.2%
• Metastatic rate: 47.3%
• Most patients with perineural invasion die within 5 years of presentation
High risk cSCC - Treatment

• Mohs micrographic surgery
• Excision with 6-10 mm margins to appropriate anatomic depth
• Consideration of adjunctive treatment for very high risk lesions
cSCC - Prognosis

• Patients with primary cSCC have excellent prognosis
  • Mohs surgery cure rates: 95-97%

• Patients with metastatic disease have dismal prognosis
  • Regional LN involved in ≈ 80% of cases; 10 year survival rate < 20%
  • Distant metastases present in ≈15% of cases; 10 year survival rate < 10%
BWH cSCC staging system

• 4 tumor risk factors predicted poor outcomes:
  • Poorly differentiated histology
  • Diameter of 2 cm or greater
  • Perineural invasion of any caliber
  • Invasion beyond SQ fat (excluding bone invasion)

Evaluation of AJCC Tumor Staging for cSCC and a proposed alternative staging system. A Jambusaria-Pahlajani et al. JAMA Dermatol 2013 (149): 402-10
## BWH T staging system

<table>
<thead>
<tr>
<th>Alternative T stage</th>
<th>Definition</th>
<th>Risk of poor outcome</th>
</tr>
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<tbody>
<tr>
<td>T0</td>
<td>In situ SCC</td>
<td>N/A</td>
</tr>
<tr>
<td>T1</td>
<td>0 risk factors</td>
<td>1.8%</td>
</tr>
<tr>
<td>T2a</td>
<td>1 risk factor</td>
<td>9.9%</td>
</tr>
<tr>
<td>T2b</td>
<td>2-3 risk factors</td>
<td>33.3%</td>
</tr>
<tr>
<td>T3</td>
<td>4 risk factors or bone invasion</td>
<td>100%</td>
</tr>
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</table>
BWH T2b and T3 patients

• Subset of high risk cSCC patients
• Tumors with greater propensity for local invasion and regional and distant metastasis
• Not well controlled with conservative treatment
• Require more aggressive management
• High rates of morbidity and mortality
BWH T2b and T3 = Very High Risk cSCC

- Multidisciplinary management
- Dermatologists
- Surgical oncologists
- Medical oncologists
- Pathologists
- Transplant physicians
- Radiation oncologists
- ENT, plastics, oculoplastics
Systemic agents for cSCC

• Cis-platin based combination chemotherapy most commonly used
  • Response rates high
• Toxic effects common: myelosuppression (25%-30%), dose-cumulative peripheral neuropathy (30%-100%), severe emesis (100%)
• Targeted molecular therapy (EGFR inhibitors)
• Immunotherapy/checkpoint inhibition (pembrolizumab, cemiplimab)
EGFR inhibitor: Cetuximab

• Recombinant human-mouse chimeric Ab which competitively inhibits EGFR
• Works well in head and neck SCC, even in cis-platin or XRT-refractory disease
• <18% response rate for locally advanced/metastastic cSCC
Cetuximab for VHSCC

• Recommended by medical oncology over cis-platinum because of its relative lack of side effects and ease of administration

• Pt started on 4 week cycle of 400 mg/m$^2$ on day 1, followed by 250 mg/m$^2$ weekly for 3 weeks
PD-1 and PD-L1 inhibitors
Programmed cell death protein 1 (PD-1) inhibitor
First-in-class drug approved by FDA for unresectable melanoma
Cancer cells upregulate PD-L1 on tumor cells and TILS to escape immune system
Checkpoint blockade of immune inhibitory pathways using antibodies (PD-1) to PD-L1
Advanced cSCC

• 79 y/o man with myeloproliferative disorder who underwent Mohs surgery for SCC on left cheek
cSCC in-transit mets pre- and post pembrolizumab

One year later  Two years later  Three years post initiation of PD-1 inhibitor
Cemiplimab

• Anti PD-1 human monoclonal antibody
• FDA approved for metastatic or locally advanced cSCC not suitable for curative treatment with surgery or radiation on 9/28/18
• Administered IV, 350 mg over 30 minutes, q2 weeks until disease progression or unacceptable toxicity
FDA approval of cemiplimab

• Based on analysis of data from open label, multicenter, nonrandomized phase 2 trial (EMPOWER-CS CC-1) and two advanced cSCC expansion cohorts from a multicenter open label non-randomized phase 1 trial
• Largest prospective data set in advanced cSCC

## Cemiplimab for cSCC

<table>
<thead>
<tr>
<th>Efficacy endpoints</th>
<th>Metastatic (n=75)</th>
<th>Locally advanced (n=26)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Phase 1 and 2</td>
<td>Phase 1 expansion cohort</td>
</tr>
<tr>
<td>Confirmed ORR</td>
<td>47% (35/75)</td>
<td>50% (13/26)</td>
</tr>
<tr>
<td>Complete RR</td>
<td>5% (4/75)</td>
<td>0%</td>
</tr>
<tr>
<td>Partial RR</td>
<td>41% (31/75)</td>
<td>50% (13/26)</td>
</tr>
<tr>
<td>Median time to response</td>
<td>1.9 months</td>
<td>2.3 months</td>
</tr>
<tr>
<td>Durable disease control (&gt;6 months)</td>
<td>61.3%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Safety of cemiplimab

• Most common adverse reactions
  • Fatigue (29%)
  • Rash (25%)
  • Diarrhea (22%)
• Serious adverse events (28%)
  • Cellulitis, sepsis, pneumonia, hypercalcemia
Pre- and post 6 weeks of cemiplimab
Pre- and post 8 weeks of cemiplimab

B Patient in Phase 2 Study

Baseline

Week 8
Metastatic disease patients: best response

A Best Tumor Response for 45 Patients in the Phase 2 Study

- Complete or partial response
- Could not be evaluated
- Progressive disease
- Stable disease

Patients

Best Percentage Change from Baseline in the Diameter of Target Lesions

Progression-free survival in metastatic disease treated with cemiplimab
New and emerging cSCC treatments

• Targeted agents and immune checkpoint inhibitors
• Mostly well tolerated with few treatment-limiting side effects
• Have potential to revolutionize management of patients with locally advanced or metastatic cSCC
Importance of Multidisciplinary Care

• Emerging multidisciplinary care models across the country.

• Association of Community Cancer Centers education project on *Multidisciplinary Advanced Cutaneous Squamous Cell Carcinoma Care.*

Publication available in print and online!
George Washington Cancer Center

• Academic Comprehensive Cancer Program accredited by American College of Surgeons Commission on Cancer (CoC).

• Newly developed cutaneous oncology program.

• Multidisciplinary team led by dermatologic surgeons.

• Focus on personalized care.

• Ongoing clinical trials in adjuvant therapy.
Oregon Health Services University
Knight Cancer Institute

• NCI-designated Comprehensive Cancer Center.
• Academic Comprehensive Cancer Program accredited by American College of Surgeons Commission on Cancer (CoC).
• Sees a large volume of high-risk cSCC patients.
• cSCC program modeled after well-established melanoma program.
• Expanding provider access via virtual tumor boards.
• Goal to increase access to clinical trials.
University of Missouri-Ellis Fischel Cancer Center

- Certified member of MD Anderson Cancer Care Network.

- Academic Comprehensive Cancer Program accredited by American College of Surgeons Commission on Cancer (CoC).

- **Emerging multidisciplinary cutaneous oncology team** with a dedicated cutaneous oncology tumor board and board-certified dermatopathologists.

- Team involves social work, pharmacy, patient, and nurse navigators.

- **Teledermatology** and the **ECHO platform**.

- **Ongoing clinical trials** in biomarker assessment.
References

• Jambusaria-Pahlajani et al. Evaluation of AJCC Tumor Staging for cSCC and a proposed alternative staging system. JAMA Dermatol 2013 (149): 402-10
• O’Bryan K et al. An evolving paradigm for the work-up and management of high-risk cSCC. JAAD 2013; 69: 595-602
Questions?
Thank You

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This lecture will be made available as an on-demand webinar.

For more information about this project:

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