Cutaneous Squamous Cell Carcinoma: Are You Following the Latest Guidelines of Care?

Jerry Brewer, MD
Cutaneous Squamous Cell Carcinoma
Are You Following the Latest Guidelines of Care?

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Disclosure Statement
I, Jerry D. Brewer, MD, do not have any relevant financial interest or other relationships with a commercial entity producing health-care related product and or services.

Objectives
• Discuss and describe the latest NCCN guidelines for squamous cell carcinoma
• Describe the new staging criteria for squamous cell carcinoma
• Identify how these updated guidelines may affect patient care and clinical practice

Ice Breakers

Keystone Habits
• Charles Duhigg

Exercising Regularly
As infrequently as once per week
• Start eating better
• More productive at work
• Smoke less
• Show more patience with colleagues and family
• Use credit cards less
• Say they feel less stressed
• “Triggers wide spread change!! There is something about it that makes other good habits easier”
Cutaneous Squamous Cell Carcinoma
Are you following the latest guidelines?

Objectives

• Gain a deeper understanding of the latest NCCN guidelines for squamous cell carcinoma
• Understand the new staging criteria for squamous cell carcinoma
• Understand how these updated guidelines may affect patient care and clinical practice

Who is the NCCN

• Consortium of multiple institutions
• Dedicated to excellence in cancer therapy and research
• Guidelines for many human malignancies
  • 1997 – breast, colon, and prostate
  • 1998 – melanoma
  • 1999 – nonmelanoma skin cancer (NMSC)

How are guidelines developed

• Not strictly “evidence-based”
• Developed through consensus when evidence lacking
• Statement of consensus of it’s authors
• No guarantees or warrantees
• NCCN
  • Disclaims any responsibility for the application or use of their guidelines in any way
Use of guidelines
• Any clinician
  • Expected to use independent medical judgment
  • Consider individual clinical circumstances

Outline
• Overview
• Staging criteria
  • Biopsy technique
  • Perineural invasion
• NCCN guidelines
• SLNB

Overview
• Incidence of NMSC
  • Thought to be on the rise
  • 3% to 8% per year since 1960
• Most frequent cancer worldwide
• More than 2-3 million new cases in US/year
• Annual cost
  • > $400 million

Overview
• Rising incidence
  • Expanding elderly population
  • Incidence 30 times higher in pts > 70 yrs
  • 3 fold higher in pts > 85 yrs vs 70-75 yrs
• Improved medical treatments
  • Organ transplant recipients
  • Longer post-transplant survivals
  • 65 fold increased incidence of SCC

Overview
• Cutaneous squamous cell carcinoma (cSCC)
  • Vast majority early stage
  • Some metastasize
  • 20% of all skin cancer-related death
  • 2500 deaths in US annually
• Proper data collection
  • Prohibitive to date
  • Few prognostic factors are well understood

Overview

- Prognosis and survival outcomes
- Studied > 25 years for MM
- SCC – little is known
  - Prognostic variables that affect survival

AJCC staging efforts

- 2006 committee established
  - Dr. Arthur Sober
- Available published studies and prognostic factors
  - Reviewed and analyzed over 3 years
  - When large data sets or multivariate analyses were missing
    - Univariate data or consensus of expert opinion

Changes from 6th to 7th Edition of AJCC

- Previous edition “Carcinoma of the Skin”
  - Eliminated
- Two chapters created
  - Merkel Cell Carcinoma
  - Cutaneous Squamous Cell Carcinoma and Other Cutaneous Carcinomas
- 1st time
  - Mechanism for staging NMSC
  - Evidence-based medicine

Changes from 6th to 7th Edition of AJCC

- Previous edition didn’t include the sites
  - Eyelid, nonglabrous lip, vulva, and penis
- Eyelid, vulva and penis
  - Continue as excluded
  - Eyelid staged by the ophthalmic task force
  - Vulva and penis already staged
- Nonglabrous lip and ear
  - Included
Metastatic potential
- 5% of cSCC metastasize
- Usually to regional lymph nodes
- Increases to 10% to 20%
- High risk tumors

High risk factors
- Size
  - > 2 cm
- Breslow thickness
  - > 2 mm
- Clark level IV or greater
- Perineural invasion

**Many of these factors not included in 6th edition**
Prevents accurate stratification of high risk patients


Tumor diameter

Kaplan E. Novanetanum skin cancer (including cutaneous squamous cell carcinoma) staging system in 6th edition of American Joint Committee on Cancer.

Primary tumor (T):  
T1: Primary tumor cannot be assessed  
T2: Tumor ≤ 1 cm, but not ≤ 0.2 cm, in greatest dimension  
T3: Tumor > 1 cm, but not > 2 cm, in greatest dimension  
T4: Tumor > 2 cm, or metastatic tumor

Regional lymph nodes (N):  
N0: No regional lymph node metastasis  
N1: Regional lymph node metastasis

Tumor diameter

Several studies
- 2 cm as threshold
- 3.8-fold increased risk
- Metastasis to lymph nodes


Tumor diameter

Among tumors exceeding 2 cm
- Local recurrence rates
  - Doubled (15% vs 7%)
- Metastatic rates
  - Tripled (30% vs 9%)


Tumor diameter

Small tumors can also metastasize
- 266 pts with metastatic SCC to lymph nodes
  - Majority were < 2 cm

Tumor diameter

- Breakpoints beyond 2 cm difficult to establish
- Some studies
  - 3 cm and 4 cm as significant thresholds
- Other studies
  - 2 cm vs 5 cm no difference
- Little evidence to support a 5 cm breakpoint
- Removed from 7th edition


Tumor depth

- Does depth matter?
- Many studies
  - Diameter and depth important


Tumor depth

- 673 SCCs of lower lip
  - No metastases in tumors < 2 mm in depth
  - 15% metastatic rate
    - > 6 mm in depth
  - Metastatic rate with tumor invasion
    - Adipose tissue – 4.1%
    - Muscle – 12.5%
    - Bone – 12.5%
- Many studies confirm…depth matters


Tumor depth
- 6th edition
  - Extradermal structures
- 7th edition
  - T3 – cranial bone
  - T4 – skull base


Tumor depth
- If tumor depth really matters
  - Should we change the way we biopsy SCC
  - Punch biopsy more often?
  - Transecting the base of an SCC
  - Dogma similar to MM?

Other high-risk tumor features
- Prognostic validity
  - Insufficient to place into stage-specific locations
- Group of high-risk features approved
- Combined with diameter determine T1 vs T2


Area “H”
- Central face
- Eyelids
- Eyebrows
- Periorbital skin
- Nose
- Lips (cutaneous and vermilion)
- Chin
- Mandible
- Pre and postauricular skin
- Temple
- Ear
- Genitalia
- Hands and Feet

Anatomic site
- Specific locations
  - Nonglabrous lip
  - Ear
- Increased local recurrence
- Metastatic potential

**Staging SCC**

Example Case

- 2.2 mm depth
- Nonglabrous lip
- Perineural invasion

Stage II: T2N0M0

**Immunosuppression**

- Correlates with worse prognosis
- Strong consideration to include
- Strict TNM criteria
  - Preclude including clinical risk factors
- AJCC recommendation
  - Collect immunosuppression
  - Additional factor by registries
  - Designated as an “I” after staging

**Immunosuppression**

- Incidence of local recurrence
  - 4% SCCIS at 5 yrs
  - 19% Stage I at 5 yrs
  - 54% Stage II at 3 yrs
  - 10 fold greater risk than stage I

**Case – bad outcome**

- 70 year old man
- 8 year history of CLL
- Prior treatment with chlorambucil, cyclophosphamide, fludarabine
- SCC dorsal nose
- Mohs surgery
Perineural invasion

• 5.95% of SCCs
  • Males – 77.1%
  • Recurrent SCC – 4.7% vs 6.9%
• Other associations
  • Face
  • Lower degrees of differentiation
    • 54.3% - moderately differentiated
    • 28.6% - poorly differentiated


SCC with Perineural Invasion

• Occurs – 2 to 14% cases
• Associated with a marked poor prognosis
• Significantly higher risk of
  • Local recurrence (18%)
  • Regional metastasis (14%)
  • Distant metastasis (12%)
  • Disease specific death (16%)

SCC with Perineural Invasion

• Subsequent metastatic rates
  • As high as 47%
• Overall survival rates
  • Less than 30%

Squamous Cell Carcinoma with PNI

• Poor prognostic factors
  • Tumor diameter ≥ 2 cm
  • “H” Zone
  • Recurrent tumors
  • Depth ≥ 2 mm
  • Immune compromised host
  • Poorly differentiated tumor
  • Perineural invasion

How Important is PNI

<table>
<thead>
<tr>
<th>High Risk SCC</th>
<th>SCC with PNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Recurrence</td>
<td>7%</td>
</tr>
<tr>
<td>Regional Mets</td>
<td>10%</td>
</tr>
<tr>
<td>Distant Mets</td>
<td>4%</td>
</tr>
<tr>
<td>Disease-Specific Death</td>
<td>4%</td>
</tr>
</tbody>
</table>

Clinical vs Pathologically Discovered PNI SCCs and BCCs with PNI

<table>
<thead>
<tr>
<th>PNI discovered pathologically</th>
<th>PNI discovered clinically</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year local control</td>
<td>5 year local control</td>
</tr>
<tr>
<td>90% (84% for SCC)</td>
<td>57%</td>
</tr>
<tr>
<td>Relapse free survival</td>
<td>76%</td>
</tr>
<tr>
<td>Disease specific survival</td>
<td>76%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>90%</td>
</tr>
</tbody>
</table>

Case

• 62 yo Caucasian male
• Liver transplant – 1998
  • No other significant past medical problems
• July 20, 2009
  • Invasive moderately differentiated SCC of right temple
• August 20, 2009
  • Mohs surgery

Original Biopsy
**Mohs Pathology**

**Surgery**

- Final defect size
  - 8.1x5.5cm

**Post-op**

**Imaging**

- MRI
  - Abnormal enhancement from right lateral canthus to superficial aspect of right parotid
  - Lateral canthus – post-operative changes
  - Right cheek – concerning for perineural involvement of facial nerve
  - No evidence of invasion of right orbital structures
  - No evidence of invasion into parotid gland

**Lessons Learned**

- Don’t ever judge an SCC by its size
- Immunosuppressed patients
  - Can have rapidly growing unpredictable SCCs
- Moderately and poorly differentiated SCCs
  - Can become aggressive very quickly
Perineurally invasive SCC

- 91 yo male
- Diagnosed with CLL April 2002
  - Rai stage 0
  - Gradually progressive over the years
    - WBC count from 22 K to 40 K

Perineurally invasive SCC

- Skin cancer history
  - Feb 94 – 1 BCC
  - Aug 99 – 1 BCC
  - April 02 – 1 SCCIS
  - December 09 – 1 SCC
Lessons Learned

- Aggressive SCC in setting of CLL
  - Could slow progression of CLL be a factor
  - Could elderly age be a factor
- Be suspicious of even subtle erythematous patches in elderly CLL patients

Diameter of Involved Nerves

- 48 patients with SCC and PNI
- Small caliber nerve involvement (<0.1mm)
  - No increased risk of metastasis or death due to disease
  - Local recurrence 9%
- Large caliber nerve involvement (0.1mm or larger)
  - Local recurrence 50%
  - Nodal metastasis – 38%
  - Distant mets and disease specific death – 32%
  - All-cause death – 48%

### Histopathologic grade

- Dr. Mohs (1978)
  - Significant differences in cure rates
  - Well differentiation – 99.24%
  - Poor differentiation – 42.1%
- Other studies have confirmed

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**AJCC Staging Criteria**

Table 1. No normal/ Table II. Definition of cutaneous squamous cell carcinoma tumor (T) staging in 7th edition of American Joint Committee on Cancer

#### N and M staging

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
</tbody>
</table>

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N and M staging


M Classification
- unchanged

Table IV. Seventh edition American Joint Committee on Cancer definition of cutaneous squamous cell carcinoma distant metastasis (M) staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>M0</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No distant metastasis</td>
<td>Present distant metastasis</td>
</tr>
</tbody>
</table>

Compared with 6th edition of American Joint Committee on Cancer, there were no changes in M classification. Presence and absence of distant metastases defines M stage grouping.

Final TNM staging


<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>In situ</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0 or N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>N0 or N1</td>
<td>M0</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N</td>
<td>M0</td>
<td></td>
</tr>
</tbody>
</table>

Table V. Final 7th edition American Joint Committee on Cancer stage grouping for cutaneous squamous cell carcinoma

NCCN Guideline Highlights

Goal: “expand on AJCC staging to develop more comprehensive stratification system”

High risk patients
- Organ transplant recipients
- Immunosuppression
- Lymphoma
- Drug induced
- HIV
- Xeroderma pigmentosum
### High risk features
- Location
- Size
- Primary vs recurrent
- Immunosuppression
- Previously radiated sites
- Perineural involvement
- Degree of differentiation
- Young age
- Not a clinical risk factor

### Location and size
- “H” zone
- > 2 cm in diameter

### Immunosuppression
- Prior PUVA
- Organ transplantation
  - “Because organ transplant recipients have collectively worse outcomes, these patients and their neoplasms are designated as high risk.”

### Perineural involvement
- If large nerve
  - MRI should be considered
  - Extent and skull involvement

### Excluded parameters
- Infiltrative component
- Correlates well with degree of differentiation
- Spindle cell SCC
  - Associated with PNI
  - Indirect association – no need for listing

### Post-operative radiation
- Reduces recurrence in high risk patients
- Consider if the following
  - Substantial PNI
  - Tissue margins positive after Mohs
  - Regional disease of the trunk/extremities
  - Nodal involvement of head and neck
- Observation reasonable
  - One small node and no extracapsular spread
Additional clinical risk factors

- Site of chronic inflammatory process
- Chronic scarring – increased metastasis
- Rapidly growing tumor
- Increased metastasis and death
- Neurologic symptoms
  - Occur with PNI 40% of time
- Other histologic parameters
  - Adenoid or adenosquamous SCC
  - Desmoplasia

Other risk factors

- 615 patients
  - 4% metastases
  - 3% local recurrence
- Tumor thickness
  - < 2 mm – no metastases
  - > 6 mm – 16% metastatic rate

Risk of local recurrence

- Increased tumor thickness (> 6 mm)
  - HR 6.03 (95% CI 2.71-13.43; p<0.0001)
- Desmoplasia
  - HR 16.11 (95% CI 6.57-39.49; p<0.0001)

Desmoplasia

- Greek
  - Desmos – fetter or bond
  - Plasia – to form
- A fibrous or connective tissue formation response
  - From invasion of tumor into healthy tissue

Other risk factors

- Multivariate analysis – metastases
  - Tumor thickness
    - HR 4.79 (95% CI 2.22-10.36; p<0.0001)
  - Tumor diameter
    - HR 2.22 (95% CI 1.18-4.15; p=0.0128)
  - Ear
    - HR 3.61 (95% CI 1.51-8.67; p=0.0040)
  - Immunosuppression
    - HR 4.32 (95% CI 1.62-11.52; p=0.0035)
Take Home Messages

- Breslow thickness can be key in SCC
- SCC > 6 mm
- 16% risk of metastasis
- Increased risk of metastasis
- Immunosuppression
- Ear site
- Large diameter
- Think about lymph nodes if > 6 mm
- SLN biopsy
- Imaging
- Frequent follow up
- Pathology reports
- Should begin to report SCC thickness?

Sentinel lymph node biopsy

- “For certain high-risk squamous cell lesions, sentinel lymph node mapping may be considered, although the benefit of this technique has yet to be proven.”

Sentinel Lymph Node Biopsy

Introduction

- Rising incidence of CSCC
  
- Metastatic rate of CSCC: 4-5%
  
- DSS with nodal involvement: 60-70%
  
- Predictable metastatic pattern (regional→distant)
  
- SLNB for CSCC is a relatively safe procedure

Factors in favor of SLNB for SCC

- Rising incidence of SCC
- Metastatic rate of 4-5%
- Predictable metastatic pattern
  
- Commonly spreads to regional LN first
  
- Regional to distant
- SLNB for SCC
- Relatively safe and effective
- Neck dissection and radiation combined
- Lower relapse rate
- Better disease free survival
Questions

• Which patients with cutaneous SCC should have a SLNB?

• Does SLNB for cutaneous SCC predict outcome?

Case

• 64 yo man with history of multiple NMSC
• PMH
  • RA, Colon CA (resected), COPD, Atrial fib
• Social History
  • Retired, lifetime non-smoker, no chewing tobacco, no alcohol
• Medications
  • ASA, Advair, Digoxin, Diltiazem, Hydroxychloroquine, Metoprolol, Mirtazapine, Prednisone, Tiotropium, Warfarin

Pathology Report

**DIAGNOSIS:**
A. Left lower lip vermillion border, Skin punch biopsy: Invasive, moderately-differentiated (G2) squamous cell carcinoma, tumor thickness 2.2 mm, T classification pT2

**Comment:**
The tumor involves the lateral margins of the specimen. Tumor invades to the level of the muscle. Perineural spread is present (diameter of largest involved nerve: 0.07 mm). Desmoplasia is present.

7th Edition AJCC Staging System

**Example Case:**
- 2.2 mm depth
- Nonglabrous lip
- Perineural invasion

Stage II: T2N0M0

Case 2

• 65 yo judge from California
• SCC on left year
  • Mohs surgery early to mid 2011
  • 3 layers for clear margins
• Around February 2012
  • New lesion
  • Biopsy
  • Read descriptively
  • Possible AK
History

- Imiquimod
  - Used for 10 days
- Pain tenderness
- Increased redness
  - Inferior to original surgery site
- Treated as chondritis
- Cephalosporin
- Doxycycline
- Bactrim
- Medrol dose pack

Punch biopsy 4-17-12

Course

- Mohs surgery
  - Clear margins
- Superficial parotidectomy
  - Negative
- Sentinel lymph node biopsy
  - Negative

Biopsy 6-27-12

Course

- July 2012
  - Recurrent pain in remaining helix
- Biopsy
  - Recurrent moderately differentiated SCC
- MRI
  - No evidence of disease
  - Slightly large level IIb lymph node
**Course**
- Fine needle aspirate of LN
  - Positive for SCC
- PET scan
  - No evidence of distant metastasis

**Plan**
- Total auriclectomy
- Neck dissection
- Post-operative radiation
  - Primary tumor bed
  - Left neck

**Lessons**
- SCC on high risk site with high risk features
  - Ear
  - Greater than 2mm in thickness
  - Greater than 2cm in length
  - Invasive to cartilage
  - Recurrent
  - Moderately differentiated
- Post-operative radiation after 1st surgery
- Confirmatory margin

**Biopsy 7-9-12**

**REFERENCES**

Conclusions

• Positive SLNB
  • 24% of anogenital patients
  • 21% of non-anogenital patients

A timeline of knowledge for CSCC and SLNB

Application of 7th Edition AJCC Staging System for CSCC and SLNB

• 85 non-anogenital SCC
  • 21% with positive SLNB
  • 71 with sufficient data to stage with AJCC
  • 14 with insufficient data to stage with AJCC
  • 6/14 (42.9%) with positive SLNB

Report since 2006...

• 42 cases with sufficient data to stage according to AJCC
Application of 7th Edition AJCC Staging System for cSCC and SLNB

- 113 patients with cSCC and SLNB
  - T1: n = 7
  - T2: n = 102
  - T3: n = 0
  - T4: n = 4

- 0 positive SLNB

- T2 and < 2 cm: n = 8
  - 0 positive SLNB

- T2 and ≥ 2 cm: n = 94
  - 12 positive SLNB (12.7%)

- 3 (75%) with positive SLNB

Summary

- 113 patients with cSCC and SLNB
  - 13.2% with (+) SLNB
  - No T1 lesions with SLNB (+)
  - ≥ T2 lesions (n=106)
    - 14% with SLNB (+)
    - 0% SLNB (+) if T2 and < 2 cm
    - 12.7% SLNB (+) in T2 and > 2 cm
    - 75% SLNB (+) in T4 lesions

- Univariate risk factor for metastasis: depth > 2 mm
- Multivariate risk factors for metastasis: depth, immunosuppression, ear, horizontal size

- PNI > 0.1 mm diameter: 38% developed nodal metastasis
Summary
• Data – SLNB for cSCC
  • Limited
• SLNB for cSCC
  • Appears to be accurate
  • Relatively well-tolerated
• Optimal tumor/patient characteristics for SLNB
  • Evolving
• New AJCC staging criteria
  • Starting point for future studies

Conclusions

Squamous cell carcinoma
Am I following the latest guidelines of care
• Tumor thickness
  • Required on pathology report
  • Change in biopsy behavior
• Optimal treatment
  • Immunosuppressed patients
  • PNI
  • When to use adjuvant radiation therapy
• SLNB
  • Should we be using this more often

What We Don’t Know

How to Unlock the Puzzle?...
• Which tumors behave badly
• Other molecular factors
• Things that affects the behavior of carcinogenesis in general
Cutaneous Squamous Cell Carcinoma
Are You Following the Latest Guidelines of Care?

Thank You!

Questions