Non-Melanoma Skin Cancer

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I have no relevant conflicts of interest
Overview

- Basal Cell Carcinoma (BCC)
- Squamous Cell Carcinoma (SCC)
  - Incidence
  - Risk Factors
  - Clinical Presentation
  - Treatment

Non-melanoma skin cancer
BCC/SCC and “Other” Tumors (Non-inclusive list)

- Atypical fibroxanthoma
- Dermatofibrosarcoma protuberans
- Microcystic adnexal carcinoma
  - Merkel cell carcinoma
  - Extramammary Paget’s Disease
- Superficial cutaneous leiomyosarcoma
- Other apocrine and eccrine neoplasms

Basal Cell Carcinoma (BCC)
Basal Cell Carcinoma:
Background

• Derived from non-keratinizing cells of the basal layer of the epidermis
• Is the most common skin cancer (4:1 SCC; 20:1 melanoma)
• Generally grows slowly
• If allowed to remain on the skin can become locally destructive
• Rarely metastasize

Basal Cell Carcinoma:
Epidemiology

• The most common malignancy
• Rogers HW et al. Arch Dermatol, 2010
  • Estimated that 3.5 million non-melanoma skin cancers (NMSC) occurred in 2.5 million individuals in the United States in 2006
  • 75-80% of NMSC are BCC (≈2.8 million)
  • 20-25% of NMSC are SCC (≈0.7 million)
• Estimated lifetime risk of BCC in the white population is 33–39% for men and 23–28% for women.
**Basal Cell Carcinoma: Risk Factors**

- Ultraviolet light (UVL) exposure
- Male sex
- Light hair and eye color
- Northern European ancestry
- Inability to tan

**Basal Cell Carcinoma: Pathogenesis**

- Sun exposure
- Personal history of non-melanoma skin cancer
- Family history of non-melanoma skin cancer
- Skin type
- Gene Mutations
- Exposure to artificial UV light
- Immunosuppression
- Ionizing radiation
- Arsenic
- Genetic syndromes (Nevoid basal cell carcinoma syndrome, Bazex syndrome, etc.)

After initial skin cancer diagnosis, the risk of developing another BCC

- At 3 years is 30%
- At 5 years is 50%
BCC: Pathogenesis – Sun exposure

- Key etiologic agent
- Particularly UVB spectrum (290nm-320nm)
  - Induces mutations in tumor suppressor genes
  - Some studies suggest intense periods of light exposure can be particularly damaging
- Increased rates seen in tanning bed users and those who receive iatrogenic light therapy (PUVA)

Basal Cell Carcinoma: Clinical Presentation

- Lesion that bleeds easily
- Lesion that does not heal
- Oozing or crusting spots in a lesion
- Scar-like lesion without having injured the area
- Irregular blood vessels in or around the lesion
Basal Cell Carcinoma: Nodular Type

- Approximately 50% of all BCC
- Primarily on the head and neck
- Key to clinical diagnosis:
  - Arborizing telangiectasias
  - Pearly luminescence
  - Ulcerate when larger
  - Bleed easily
- May have brown, blue, purple color (pigmented BCC)
## Basal Cell Carcinoma: Superficial Type

- More frequently on the trunk and extremities
- Often confused with eczema, psoriasis, or tinea in its early stages
- Keys to clinical diagnosis:
  - Pink plaque non-responsive to standard interventions
  - Thread like border that has characteristic clinical finding of BCC
10

Basal Cell Carcinoma: Morpheaform and Micronodular Type

• Morpheaform BCC
  • Often presents as a pink to ivory plaque
  • A more difficult clinical diagnosis
• Micronodular BCC
  • May present as macules, papules or slightly elevated plaques
  • May be difficult to differentiate from nodular BCC

• **Main issue with both subtypes is subclinical spread**
Basal Cell Carcinoma: Biological Behavior

- Local Invasion
  - Generally a slow growing tumor
  - Rate of doubling estimated between 6 and 12 months
- Metastasis
  - Occurs only rarely; rates varying from 0.0028% to 0.55%
  - Lymph nodes and lung were the most common sites involved

Basal Cell Carcinoma: Treatment
BCC: Current Treatment Options

- Standard Excision
- Curettage with electrocautery
- Curettage alone
- Curettage with topical therapy
- Cryosurgery
- Photodynamic therapy
- Ablative laser (continuous CO2)
- Imiquimod
- Intralesional interferon-α-2b
- Mohs Micrographic Surgery
- Vismodegib

BCC: Risk Factors for Recurrence

<table>
<thead>
<tr>
<th>H&amp;P</th>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location/Size</td>
<td>Area L &lt; 20mm</td>
<td>Area L &gt; 20mm</td>
</tr>
<tr>
<td></td>
<td>Area M &lt; 10mm</td>
<td>Area M &gt; 10mm</td>
</tr>
<tr>
<td></td>
<td>Area H &lt; 6mm</td>
<td>Area H &gt; 6mm</td>
</tr>
<tr>
<td>Borders</td>
<td>Well defined</td>
<td>Poorly defined</td>
</tr>
<tr>
<td>Primary vs Recurrent</td>
<td>Primary</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Site of prior RT</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtype</td>
<td>Nodular, superficial</td>
<td>Aggressive growth pattern*</td>
</tr>
<tr>
<td>Perineural involvement</td>
<td>(-)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

Area H = Mask areas of the face (central face, eyelids, eyebrows, periorbital, nose, lips (cutaneous and vermilion), chin, mandible, preauricular, and postauricular skin/sulci, temple, ear), genitalia, hands, and feet
Area M = cheeks, forehead, scalp, and neck
Area L = trunk and extremities
* Morpheaform, sclerosing, or micronodular features in any portion of the tumor
BCC: Current Treatment Options

• The goal of primary treatment of basal cell skin cancer:
  ① Cure of the tumor
  ② Maximal preservation of function
  ③ Maximal preservation of cosmesis
  ④ Cost

Surgical Excision for BCC

• The most common treatment modality for BCC
• Reported 5-year recurrence rates of 3.2 – 10% for primary BCC, and 17% for recurrent BCC
• Rowe et al, J Dermatol Surg Oncol, 1989
  • Reviewed all studies on BCC treatment from 1947 to 1989 (included 106 studies)
• General margin is 4mm
  • For non-high risk BCC; for larger BCC (>2cm) the appropriate margin is so variable it is difficult to make a margin recommendation
Basal Cell Carcinoma: Electrodessication and Curettage

• Good for:
  • Well defined BCC
  • Areas with low risk for recurrence
• Advantages
  • High clearance rate in appropriate BCCs
  • Fast, no suture removal
• Disadvantages
  • If extends to subcutaneous tissue, must perform excisional procedure
  • Potentially more apparent scar
  • No margin assessment

BCC: 5-year cure rates for primary BCC, Meta-analysis

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>5-year cure rate* ^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical excision</td>
<td>90%</td>
</tr>
<tr>
<td>Electrodessication and curettage</td>
<td>92%</td>
</tr>
<tr>
<td>Radiation</td>
<td>91%</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>92%</td>
</tr>
<tr>
<td>All non-MMS</td>
<td>91%</td>
</tr>
<tr>
<td>MMS</td>
<td>99%</td>
</tr>
</tbody>
</table>


^The 5-year cure rates for recurrent BCC was 90-92% with MMS, and 80% with all non-MMS modalities.
Basal Cell Carcinoma: Mohs Surgery
Pivotal BCC Treatment Papers

• “Basal Cell Carcinoma Treated with Mohs Surgery”
  • Prospective multicenter interventional case series
  • 3370 patients completed the 5 year follow-up
  • Primary outcome measure: Recurrence @ 5 years
  • Recurrence, Primary tumors: 1.4%
  • Recurrence, Recurrent tumors: 4%

There are several large or prospective studies that have looked at MMS for BCC

<table>
<thead>
<tr>
<th>Study years</th>
<th>Mohs 25,26</th>
<th>Robins 27</th>
<th>Julian and Bowers 28</th>
<th>Current Study 1993-2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor location</td>
<td>Head</td>
<td>Head</td>
<td>Head</td>
<td>Mainly head and neck</td>
</tr>
<tr>
<td>Overall No. of tumors with 5-y follow-up (primary/secondary)</td>
<td>8643 (7257/1386)</td>
<td>2960 (NA)</td>
<td>228 (NA)</td>
<td>3370 (1886/ 1484)</td>
</tr>
<tr>
<td>Overall 5-y recurrence (primary/secondary)</td>
<td>1.0% (0.7%/3.2%)</td>
<td>2.6% (1.8%/3.4%)</td>
<td>3.8% (1.7%/4.8%)</td>
<td>2.6% (1.4%/ 4.0%)</td>
</tr>
</tbody>
</table>

NA, Not available
BCC: Treatment

• The higher cure rates associated with MMS could likely be applied to all BCCs; however, from a practical standpoint, low-risk BCCs are generally well managed with non-MMS modalities

FROM THE ACADEMY


BCC: Key Points

• The most common malignancy in humans
• Multifactorial in origin
• If left without treatment, can be very destructive
• Many treatment modalities available, and appropriate patient selection will deliver most effective care
Cutaneous Squamous Cell Carcinoma (cSCC)

**cSCC: Background**

- Malignancy arising from epithelial keratinocytes
- Second most common cutaneous malignancy behind BCC
- Incidence is increasing
cSCC: Epidemiology

- The second most common cutaneous malignancy
- Rogers HW et al. Arch Dermatol, 2010
  - Estimated that 3.5 million non-melanoma skin cancers (NMSC) occurred in 2.5 million individuals in the United States in 2006
- 75-80% of NMSC are BCC (≈2.8 million)
- 20-25% of NMSC are SCC (≈0.7 million)

- Incidence is increasing
  - 1976 to 1989: incidence was 39 per 100,000 in women and 63 per 100,000 in men in the United States
  - 1990 to 1992: incidence was 100 per 100,000 for women and 191 per 100,000 for men in the United States
  - Possible factors:
    - increased UV exposure, ozone depletion
    - increased prevalence of human papillomavirus (HPV)
    - ionizing radiation
    - genetics
    - immunosuppression
### cSCC: Pathogenesis, UV exposure

- Cumulative sun exposure is believed to be the most important factor contributing to the development of SCC  
  - Majority of SCCs occurring on sun-exposed skin  
  - Incidence doubles with every 8-10 degree decline in latitude in high-risk populations  
- UVB (290–320 nm) is more carcinogenic in SCC development than is UVA (320–400 nm)  
  - Majority of UVB-induced damage to DNA is repaired  
  - Xeroderma pigmentosa patients have defective excision repair mechanisms of thymidine dimer base pairs and therefore display greater photosensitivity and higher incidence of SCC development.

### cSCC: Pathogenesis, Other factors

- Myriad of other risk factors  
  - Chronic dermatoses, chronic scars, and exogenous chemicals  
  - Personal and family history of SCC  
  - Human Papillomavirus  
    - Inhibits p53 tumor suppressor gene  
    - May also inhibit cell apoptosis  
    - Estimated to be involved in the pathogenesis of up to 90% of NMSCs in immunocompromised individuals and up to 50% of NMSCs in immunocompetent individuals
cSCC: Pathogenesis, Immunosuppression

- Many forms of immunosuppression lead to increased rates of NMSC, particularly SCC
- Of particular concern are solid organ transplant (SOT) patients
  - SCC:BCC ratio in normal population is 1:4
  - SCC:BCC ratio in SOT is 4:1
  - Amount of immunosuppression is important
    - Highest rates in heart transplant patients
  - Type of immunosuppression is important
    - Higher rates with azathioprine than cyclosporine

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**cSCC: Clinical Presentation**

- Presents with a variety of clinical features
  - Can range from indolent to very aggressive
- Progression from actinic keratosis to squamous cell carcinoma in situ (SCCIS) to invasive squamous cell carcinoma (SCC)
  - Many invasive SCC are believed to evolve de novo
cSCC: Actinic Keratoses

- Atypical proliferation of keratinocytes at the basal layer (lowest layer) of the epidermis
### cSCC: Actinic Keratoses

- More acceptance that these can be precursor lesion to SCCIS and SCC
- Controversy about rate of transformation
  - Difficult to assess in a controlled trial
  - One study show a per year transformation rate of 0.075% to 0.096% per lesion per year
  - Thus, patient with 7.7 AKs, average number for an affected person, invasive SCC would develop at a rate of 10.2% over 10 years if left untreated*

cSCC: Squamous Cell Carcinoma In-Situ (SCCIS)

- Also known as Bowen’s Disease
- Proliferation of atypical keratinocytes throughout the epidermis
- May arise from an AK or de novo
- Rate of transformation estimated to be between 3-8%*

cSCC: Invasive Squamous cell carcinoma (SCC)

- Malignant proliferation of keratinocytes that involves the dermis
- May develop from AK, SCCIS or de-novo

Particular sites carry certain risks
- Higher metastasis rate of SCC on the lip, ear, and temple
- Periungual SCC have higher local recurrence rates, but low metastatic rates
- Marjolin’s Ulcer (SCC in a chronic wound) have higher metastasis rates

A few of the subtypes
- Keratoacanthoma
  - Characterized by rapid growth, and involution in some instances
- Verrucous Carcinoma
  - Buschke–Löwenstein tumor, epithelioma cuniculatum, Ackerman tumor
  - Related to HPV types 6 and 11
  - Considered a low grade SCC; anaplastic change has been seen with radiation
cSCC: Invasive Squamous cell carcinoma (SCC)

- Clinical findings:
  - Can present as keratotic, non-healing papules, plaques or nodules
  - Most commonly on sun exposed skin
  - SCC-Keratoacanthoma type presents as a nodule with a central keratotic core
cSCC: Staging

- For SCC, the rate of Local Recurrence and Metastasis must be considered
- Most patients have a low risk for lymph node or distant metastasis
- If at a high-risk for these, consideration for further work-up considered
  - Lymph node evaluation
  - Imaging

Risk Factors for Cutaneous Squamous Cell Carcinoma Recurrence, Metastasis, and Disease-Specific Death
A Systematic Review and Meta-analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Factor</th>
<th>No. of Studies</th>
<th>Risk Ratio</th>
<th>(95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis</td>
<td>Invasion beyond subcutaneous fat</td>
<td>5</td>
<td>11.21</td>
<td>3.59-34.97</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Breslow thickness &gt;2 mm</td>
<td>3</td>
<td>10.76</td>
<td>2.55-45.31</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Breslow thickness &gt;6 mm</td>
<td>2</td>
<td>6.93</td>
<td>4.02-11.94</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Diameter &gt;20 mm</td>
<td>8</td>
<td>6.15</td>
<td>3.56-10.65</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Poor differentiation</td>
<td>18</td>
<td>4.98</td>
<td>3.30-7.49</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>PNI</td>
<td>12</td>
<td>2.95</td>
<td>2.31-3.75</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Temple</td>
<td>7</td>
<td>2.82</td>
<td>1.72-4.63</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Ear</td>
<td>13</td>
<td>2.33</td>
<td>1.67-3.23</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Lip</td>
<td>13</td>
<td>2.28</td>
<td>1.54-3.37</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression</td>
<td>6</td>
<td>1.59</td>
<td>1.07-2.37</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Cheek</td>
<td>5</td>
<td>1.30</td>
<td>0.61-2.77</td>
<td>.49</td>
</tr>
</tbody>
</table>

### Table 3: Summary of the AJCC, UICC, and BWH Tumor Staging Systems

<table>
<thead>
<tr>
<th>Tumor Staging System</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AJCC</strong></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤2 cm in greatest dimension, with &lt;2 high-risk factors&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;2 cm in greatest dimension or with ≥2 high-risk factors&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor with invasion of orbit, maxilla, mandible, or temporal bones</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with invasion of other bones or direct perineural invasion of skull base</td>
</tr>
<tr>
<td><strong>UICC</strong></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;2 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor with invasion of deep structures (eg, muscle, cartilage, bone [excluding axial skeleton], orbit)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with invasion of axial skeleton or direct perineural invasion of skull base</td>
</tr>
<tr>
<td><strong>BWH</strong></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>0 High-risk factor&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>T2a</td>
<td>1 High-risk factor</td>
</tr>
<tr>
<td>T2b</td>
<td>≥2 High-risk factors</td>
</tr>
<tr>
<td>T3</td>
<td>≥4 High-risk factors or bone invasion</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC, American Joint Committee on Cancer; BWH, Brigham and Women’s Hospital; T, tumor stage from TNM staging system; UICC, Union for International Cancer Control.

SCC: Current Treatment Options

- Standard Excision
- Curettage with electrodessication
- Curettage alone
- Curettage with topical therapy
- Cryosurgery
- Photodynamic therapy
- Radiation therapy
- Imiquimod/topical chemotherapeutics
- Intralesional fluorouracil or methotrexate (KA subtype)
- Mohs Micrographic Surgery
- Oral chemotherapy

SCC: Current Treatment Options

- The goal of primary treatment of squamous cell skin cancer:
  ① Cure of the tumor
  ② Maximal preservation of function
  ③ Maximal preservation of cosmesis
  ④ Cost
Surgical Excision for SCC

- One of the most common treatment modality for SCC
- Reported 5-year recurrence rates of around 7% for primary SCC, and 23% for recurrent SCC
- General margin is 4mm

Squamous Cell Carcinoma: Electrodeposition and Curettage

- Good for:
  - SCCIS, very minimally invasive SCC*
  - Areas with low risk for recurrence
- Advantages
  - High clearance rate in appropriate SCCs
  - Fast, no suture removal
- Disadvantages
  - If there is perifollicular involvement, higher rate of recurrence
  - No margin assessment
  - Potentially more apparent scar
## SCC: Risk Factors for Recurrence

<table>
<thead>
<tr>
<th>H&amp;P</th>
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<th>High Risk</th>
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<tr>
<td>Borders</td>
<td>Well defined</td>
<td>Poorly defined</td>
</tr>
<tr>
<td>Primary vs Recurrent</td>
<td>Primary</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Site of prior RT</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Rapidly Growing Tumor</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Neurologic Symptoms</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree of Differentiation</td>
<td>Well differentiated</td>
<td>Moderately or poorly differentiated</td>
</tr>
<tr>
<td>Depth: Thickness or Clark Level</td>
<td>&lt;2mm or I, II, III</td>
<td>≥2mm or IV, V</td>
</tr>
<tr>
<td>Adenoid (acantholytic), adenosquamous, or desmoplastic</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Perineural involvement</td>
<td>(-)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

## SCC: 5-year cure rates for primary SCC, Meta-analysis

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>5-year cure rate*^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical excision</td>
<td>92%</td>
</tr>
<tr>
<td>Electrodessication and curettage</td>
<td>96%</td>
</tr>
<tr>
<td>Radiation</td>
<td>90%</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>N/A%</td>
</tr>
<tr>
<td>All non-MMS</td>
<td>92%</td>
</tr>
<tr>
<td>MMS</td>
<td>97%</td>
</tr>
</tbody>
</table>

SCC: Treatment: When to Consider MOHS

- One or more risk factors
- Tumors of any size in certain high-risk sites
  - Lip SCC
  - Ear SCC
  - Nail Unit SCC

SCC: Key Points

- The second most common skin cancer in humans
- Multifactorial in origin
- If left without treatment, can be locally destructive and progress to regional and distant metastasis
- Many treatment modalities available, and appropriate patient selection will deliver most effective care