Field Cancer and Multiple SCC: Molecular Insights and Clinical Management

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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DISCLOSURES
Novartis: Investigator — Research Funding

I will discuss off-label treatments not approved by the FDA
The Problem: Multiple lesions in the field

Only 1 SCC, but numerous AK pose significant risk of subsequent cancer

AK in a sun damaged “field” of skin are analogous to weeds in a garden or field

SCC in situ (1st skin cancer)

The Problem: Multiple SCC

SCC 1 year ago

SCC 1 year ago

SCC and SCC in situ
Recurrent after Mohs surgery

Many SCC and AK
Multiple SCC Associated with Poor Prognosis

1. **Increased risk of subsequent SCC**  
   - After first SCC, 42% subsequent SCC within 5 years  
   - After second or later SCC, 72% subsequent SCC within 5 years  
   (Wehner, M.R, et al. *JAMA Dermatology* 2015; v151:p382)

2. **Increased risk of SCC progression**  
   - Patients with 2-9 SCC: 2X risk of recurrence, 2.5X risk of nodal metastasis  
   - Patients with >10 SCC: 12X risk of recurrence, 11X risk of nodal metastasis  

The Problem: Progressive Disease

Man in late 80s, >10 prior SCC/BCC

12 month period:  
8 new SCC  
7 new BCC

Rapidly enlarging neck mass  
Metastatic SCC  
Treated with surgery and radiation  
Died 18 months later
• Review of 783 cases of oral SCC
• 11% of cases had multiple primary lesions (grossly)
• In all cases, adjacent clinically benign mucosa was microscopically abnormal
  • Dyskeratosis and separate islands of SCC in situ or invasive SCC

• Proposed the concept of “field cancerization”
  • An area of epithelium is altered by a regional carcinogenic effect, leading to irreversible changes that eventually manifest in cancer

Proof of concept in cutaneous SCC
• 57% of normal skin adjacent to SCC had pathologically diagnosed AK
  Lanoue, Chen, and Goldenberg, Cutis 97:415, 2016
• 79% of normal skin biopsies in field of AK harbor AK or SCC

Key implications
• Oral (and cutaneous) SCC arises from multifocal areas of precancerous change
• “Recurrence” after excision may represent new primary cancer development
Working Definition of Field Cancer

>3 AK or presence of “AK patch” (AK >1 cm) associated with 6-18x increased risk of SCC


Field Cancer: 3 features
- defined region of skin
- multiple AK (or AK patch)
- at least 1 SCC

Multi-step Tumorigenesis

Hypotheses:
1. Burden of precursor lesions determines risk of carcinoma ✅ YES
2. Treatment of precursor lesions decreases incidence of carcinoma ✅ YES

Genetic Drivers of Cutaneous SCC

- Genome-wide sequencing has identified recurrent driver mutations in SCC
- >85% of mutations are UV signature mutations

<table>
<thead>
<tr>
<th>SCC tumors sequenced</th>
<th>Gene Mutation Frequency</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td><strong>TP53</strong> 95% 59% 51%</td>
<td>Pickering, et al., <em>Clin Cancer Res</em> 2014</td>
</tr>
<tr>
<td>11</td>
<td>91% 75% 42%</td>
<td>Wang, et al., <em>PNAS</em> 2011</td>
</tr>
<tr>
<td>20</td>
<td>65% 40% 50%</td>
<td>South, et al., <em>J Invest Dermatol</em> 2014</td>
</tr>
<tr>
<td>100</td>
<td>42% 54% 34%</td>
<td>Lee, et al., <em>Nat Genet</em> 2014</td>
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</tbody>
</table>

- **TP53** is the gene encoding the p53 tumor suppressor protein, often called the “guardian of the genome”
- Majority of actinic keratoses (>60%) also harbor **TP53** mutations

TP53 Mutant Clones Expand with UVB Exposure

- Mutant **TP53** cells can be identified by antibody staining as clusters or clones
- Number of clusters correlates with skin cancer risk

- Mice exposed to daily UVB develop **TP53** mutant clones
- Clones increase in number and size only during UVB exposure

Stopping UVB exposure decreased the number of pre-malignant lesions


High Burden of Carcinogenic Mutations in Normal Skin

- DNA sequencing of normal eyelid skin
- Up to 32% of skin cells had carcinogenic mutations (UV signature)
- Mutation burden in normal skin was comparable to breast cancer
- Sun-exposed skin is “a patchwork of thousands of evolving clones”

Sunblock Use Decreases AK (and Field Damage)

- Australian trial, 588 patients with 1-30 AK
  - randomized to SPF 17 sunblock vs vehicle, instructed to apply 4.5 ml daily
  - 7 month follow up over summer months
- Sunscreen = 28% reduction in new AK
  - and 39% increased regression of old AK
- Patients using greatest amount of sunblock had greatest protection
  - recommended amount: 950g (33 ounces)

For actinic field damage, regular sunblock use is effective even in patients with established disease.
### Sunblock Use Decreases SCC

- Australian population-based trial of 1621 patients
  - low risk population, only 27% had history of skin cancer
  - randomized to SPF 16 broad-spectrum sunscreen daily vs “discretionary use”
  - follow up every 3 months for 4 years

- **Sunscreen = 39% reduction in new SCC** (28 vs. 48 SCC, $p < 0.05$)
  - sunscreen had no effect on BCC
  

- Additional 8 year follow up of same patients
  - sunscreen use was discretionary in follow up period
  - **Sunscreen = 41% reduction in new SCC** (81 vs 142 SCC, $p < 0.05$)


### Sun Protection Basics

- Don’t forget the ears
- Combine with physical protection:
  - Hat
  - Sunglasses
  - Clothing
Summary: Field Cancer Paradigm

1. SCC is caused by the accumulation of genetic mutations induced by UV radiation
2. Visible (actinic keratosis) and invisible (mutant clone) lesions precede SCC development
3. A sun-damaged field has thousands of mutant clones with malignant potential
4. Patients with multiple AK and SCC are at increased risk of adverse outcomes
5. Lesion-directed therapy alone does not address invisible precursors (TP53 clones) in high risk patients

Field-Directed Therapy

This (not just this)

1. Sun protection
2. Topical therapy
   - 5-fluorouracil
   - Imiquimod
   - Ingenol mebutate
3. Photodynamic therapy
4. Systemic therapy
   - Acitretin
   - Nicotinamide
5. Special considerations in transplant recipients
• 954 moderate risk patients: >2 SCC or BCC in prior 5 years (>1 on face)
• Randomized to 5-FU 5% cream twice daily (face and ears) for 2-4 weeks OR vehicle control
• 2.8 year median follow up

Any SCC at 1 year:
4% of 5-FU group 1% of control
p = 0.002

5-Fluorouracil: Titrate to Effect
Various preparations and dosing regimens available

• 207 low risk patients (>5 AK) randomized to 0.5% 5-FU cream once daily for 1, 2 or 4 weeks, or vehicle control
• Increasing efficacy (and local irritation) with longer duration of treatment

5-Fluorouracil Combination with Calcipotriol?

Calcipotriol is a topical vitamin D derivative used as immunomodulatory treatment for psoriasis
Calcipotriol shown to promote T cell activation and anti-tumor response in animal models

- Clinical trial of topical 5-FU combined with calcipotriol
- 132 low risk patients (>5 AK) randomized to twice daily treatment x4 days:
  - 5-FU plus calcipotriol
  - OR
  - 5-FU plus Vaseline vehicle
- Clinical assessment of visible lesions at 8 weeks

Repeating PDT Is Required for Suppression

1. Prospective study of 12 transplant patients treated with cyclic PDT to arms (or legs) every 4-8 weeks for 2 years

<table>
<thead>
<tr>
<th></th>
<th>12 months before PDT</th>
<th>1st year of PDT</th>
<th>2nd year of PDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of SCC</td>
<td>20</td>
<td>4 (79% reduction)</td>
<td>1 (95% reduction)</td>
</tr>
</tbody>
</table>


2. Trial of 40 transplant patients randomized to receive PDT one arm only: over 2 year follow up, 15 SCC in PDT arm and 10 SCC in control arm
Repeated PDT Is Required for Suppression

- PDT decreases, but does not eliminate, TP53 mutant clones (Bagazgoitia, et al., Br J Dermatol 165:144, 2011)

![pre PDT](image1) ![post PDT](image2)

- Current field treatments are only suppressive, and must be repeated or continuous to maintain SCC prevention

Unique Features of Lower Extremity SCC

- Retrospective review of patients with >4 lower extremity SCC
  - 18 female, 4 male
  - Age 62-92 years
- Over 4.5 years:
  - 360 SCC (average 16 SCC/patient)
  - 74 SCC in situ
  - 54 BCC
- All SCC treated with local surgery, no metastasis or local progression

Case Example: Field Cancer on Legs and Acitretin

- Pooled data from 2 patients treated with acitretin, 10 – 25 mg/day
- Largest lesions were treated surgically
- Both patients without further SCC after 6 months on acitretin
- Both patients discontinued acitretin after 12-18 months, no rebound

Field Cancer on Legs Treated with Chemowraps
5-Fluorouracil 5% cream under occlusion with zinc oxide compression wraps: apply once weekly

References:
### Field Cancer Risk Management

<table>
<thead>
<tr>
<th>Field Cancer Risk</th>
<th>Clinical Features</th>
<th>General Management</th>
<th>Primary Field Treatment</th>
<th>Secondary Treatment</th>
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<tbody>
<tr>
<td><strong>LOW</strong></td>
<td>Multiple AK in field AND ≥ 1 SCC</td>
<td>UV protection and lesion-directed therapy as indicated</td>
<td>Topical or PDT field therapy as needed</td>
<td>Consider nicotinamide</td>
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<td><strong>MODERATE</strong></td>
<td>Multiple AK AND 2-3 SCC/year</td>
<td></td>
<td>Repeated topical or PDT field therapy</td>
<td>Consider acitretin</td>
</tr>
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<td><strong>HIGH</strong></td>
<td>Multiple AK AND &gt;3 SCC/year OR &gt;10 lifetime SCC</td>
<td></td>
<td>Acitretin</td>
<td>Repeated field therapy, consider additional systemic agent</td>
</tr>
</tbody>
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### Case Example

- Man in mid 70s
- 10-15 grade 1-2 AK on scalp
- Several hypertrophic lesions and AK patches
- 2cm keratotic plaque
- 5 SCC in prior 2 year period
- Previous 5-FU and PDT treatment (over 1 year ago)
Case Example: Moderate Risk Field Cancer

Requires Combination Therapy
1. Biopsy of 2 lesions
   a. SCC in situ
   b. Hypertrophic AK
2. Mohs surgery for 2cm SCC in situ
3. Lesion-directed therapy: cryotherapy or shave or curettage of hypertrophic AK
4. PDT field therapy to scalp 1-3 months after Mohs (may repeat)
5. Nicotinamide therapy
6. Consider acitretin if persistent 2-3 SCC/year

Summary: Field Directed Therapy

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<th>Advantages</th>
<th>Drawbacks</th>
<th>FDA Approved?</th>
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<td>5-fluorouracil</td>
<td>Predictable response, proven reduction in SCC</td>
<td>4 week treatment</td>
<td>Only for AK</td>
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<tr>
<td>Imiquimod</td>
<td>Unpredictable, &gt;4 week treatment</td>
<td>Only for AK</td>
<td></td>
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<tr>
<td>Ingenol mebutate</td>
<td>Short 2-3 day treatment</td>
<td>Unpredictable, may be costly</td>
<td>Only for AK</td>
</tr>
<tr>
<td>PDT</td>
<td>Single day treatment, ensured compliance</td>
<td>Specialized equipment, time-intensive (for MD)</td>
<td>Only for AK</td>
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<tr>
<td>Acitretin</td>
<td>Potent reduction in SCC</td>
<td>Laboratory monitoring, side effects, potential rebound phenomenon</td>
<td>NO</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>Well-tolerated OTC supplement</td>
<td>Minimal SCC reduction, minimal clinical experience</td>
<td>NO</td>
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**Thank You**

Questions or comments:

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The Dermatology Foundation

has supported & advanced my career.