POST-TRANSPLANT NON-MELANOMA SKIN CANCER

An Overview
Skin cancer incidence/risks

- 1/5 Americans will get skin cancer
- Most common cancer: 1.2 million cases of non-melanoma skin cancer (NMSC) – including squamous and basal cell carcinomas – diagnosed annually in US
- **Fair** skin, cumulative **UVB** exposure, and **age** are the main risk factors
Organ Transplantation: Overview

- In 2008, there were **200,000** living with transplanted organs with **100,000** on waiting lists

- Almost **30,000** transplants were performed

- Many cancers more common post-transplant: B, T, NK-cell cell lymphomas, Kaposi’s sarcoma, angiosarcoma, malignant fibrous histiocytoma, others

- Ref: Athar, et al., 2011
Post-transplant skin cancer

- 95% of post-transplant cancers are skin cancers
- Post-transplant risk of SCC is 65-250 X increased, risk of BCC is 10 X increased
  - Normal population BCC:SCC ratio is 3:1. Reversed in immunosuppressed 1:4
- Post-transplant risk of skin cancer >1/3 at 10 years post-op
  - At 10 year mark, 45% in Australia, 10% in England
- Post-transplant SCC is by definition high risk and more likely to metastasize
  - TNM system insufficient. High risk features: depth >4mm, recurrent, perineural/lymphovascular invasion, parotid proximity, positive margins, nodes with ECE

Why do the immune-suppressed get cancer?

1. Virus-associated tumors
   - EBV-associated B-cell lymphoma common
   - HHV-8-associated Kaposi’s sarcoma
   - HPV: found in 90% of post-transplant skin SCC (gen. pop. = < 30%)
     - The HPV E6 protein degrades BAK (anti-apoptosis), interferes with thymine dimer repair.

2. Decreased immune surveillance
   - Cell lines of the innate immune system (natural killer cells, macrophages, dendrites) suppressed.

3. Direct effects of immunosuppressants
   - Cyclosporine A (CsA)

Ref: Nindl, Gottschling, Stockfleth (2007)
Cyclosporine

- Calcineurin inhibitor: prevents secretion of **IL-2** from TH cells
- Multivaiable analysis of immunosuppressant regimens has shown cyclosporine to be an **independent risk** factor for NMSC
- Cells cultured with cyclosporine prone to developing **mutations** associated with poor-outcomes
- **Switching** from CsA to M-TOR inhibitors (Sirolimus) associated with decreased risk of NMSC

References: Kessler, et al., 2006 and Tang et al., 2007
NMSC – what can be done?

- Role for prevention in post-transplant patients
  - Sun avoidance, sunblock (possibly)
  - Retinoids (topical, systemic)
  - Capecitabine, low dose
When is radiation warranted?

- NCCN guidelines – could use RT in average risk pts.

- “The role of RT was probably the single largest source of disagreement among the NCCN Panel of experts. The panel was divided into two groups on the issue: the radiation oncologists wanted to use this therapy for almost all tumors, whereas the surgeons did not want to use RT.”

- General consensus: normal-risk situations, surgery is preferential monotherapy, RT acceptable for cosmesis reasons in older patients.
Radiotherapy – High Risk Disease

- **Consider** RT for trunk/arms disease with positive nodes, especially if ECE or multiple nodes.

- **High risk:** Treatment is primarily surgical, adjuvant radiotherapy “widely accepted” (NCCN)
  - Head and neck (mask distribution), recurrent disease, immunosuppression, prior radiotherapy, perineural invasion, poor differentiation, neurological symptoms
    - Other authors include: size >2cm, lymphovascular invasion, parotid proximity

- Head and neck with positive nodes: RT **always** recommended
Post-transplant radiotherapy

- No available large studies on radiation in post-transplant NMSC

- International transplant skin cancer collaborative (ITSCC) which publishes recommendations
  - Radiation: Use recommended if positive margins or extensive perineural invasion

Ref: Stasko, et al., 2004
Radiotherapy – High Risk Disease (Head and Neck)

- Positive margins
  - Adjuvant local RT: 50-55 Gy via electrons or orthovoltage photons

- Dermal metastases
  - 50-60 Gy, wide field

- Known nodal/extranodal spread
  - Adjuvant nodal RT: 55-60 Gy w/ megavoltage photons
Indications for radiotherapy, cont.

- Multiple high-risk features/prox. to parotid
  - Elective nodal RT: 50 Gy

- Perineural invasion (peri-orbital, parotid)
  - Target neural pathway 50-55 Gy, hyperfractionated

Ref: Veness, 2007
Outcomes

- Efficacy of radiotherapy for NMSC post-transplant...?

- High-risk (perineural invasion) NMSC:
  - Surgery alone control rates 38-87%
  - Surgery + RT control rates 92-100%

- Head and neck (locally advanced) patients: after resection + RT (per NCCN)
  - Local recurrence: 30% at 5 years
  - Distant metastasis: 25% at 5 years
  - 5 year survival: 40%

NCCN guidelines:

**PRINCIPLES OF RADIATION THERAPY FOR SQUAMOUS CELL SKIN CANCER**

<table>
<thead>
<tr>
<th>Primary Tumor&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Dose Time Fractionation Schedule</th>
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</thead>
<tbody>
<tr>
<td><strong>Tumor Diameter</strong></td>
<td>Dose Fractionation and Treatment Duration</td>
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<tr>
<td>&lt; 2 cm</td>
<td>64 Gy in 32 fractions over 6-6.4 weeks</td>
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<tr>
<td></td>
<td>55 Gy in 20 fractions over 4 weeks</td>
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<tr>
<td></td>
<td>50 Gy in 15 fractions over 3 weeks</td>
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<tr>
<td></td>
<td>35 Gy in 5 fractions over 5 days</td>
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<tr>
<td>≥ 2 cm</td>
<td>66 Gy in 33 fractions over 6 - 6.6 weeks</td>
</tr>
<tr>
<td></td>
<td>55 Gy in 20 fractions over 4 weeks</td>
</tr>
<tr>
<td>Postoperative adjuvant</td>
<td>50 Gy in 20 fractions over 4 weeks</td>
</tr>
<tr>
<td></td>
<td>60 Gy in 30 fractions over 6 weeks</td>
</tr>
</tbody>
</table>

**Regional Disease**—all doses at 2 Gy per fraction using shrinking field technique

- **After Lymph node dissection**
  - Head and neck; with ECE: 60-66 Gy over 6 - 6.6 weeks
  - Head and neck; without ECE: 56 Gy over 5.6 weeks
  - Axilla, groin; with ECE: 60 Gy over 6 weeks
  - Axilla, groin; without ECE: 54 Gy over 5.4 weeks
- **No lymph node dissection**
  - Clinically (-) but at risk for subclinical disease: 50 Gy over 5 weeks
  - Clinically evident adenopathy: head and neck: 66-70 Gy over 6.6 - 7 weeks
  - Clinically evident adenopathy: axilla, groin: 66 Gy over 6.6 weeks

- Protracted fractionation is associated with improved cosmetic results.
- Radiation therapy is contraindicated in genetic conditions predisposing to skin cancer (e.g., basal cell nevus syndrome, xeroderma pigmentosum) and connective tissue diseases (e.g., scleroderma).
Canoe trip


