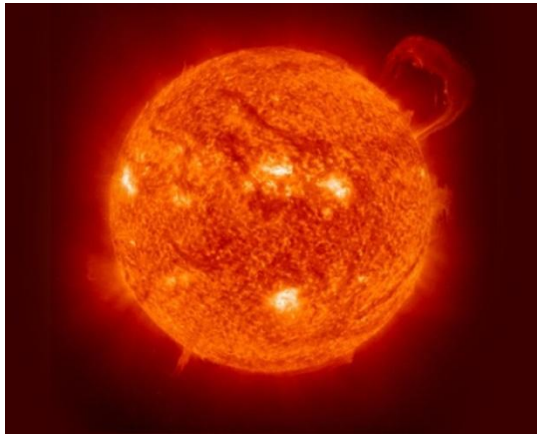


# POST-TRANSPLANT NON- MELANOMA SKIN CANCER

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 **histiocyoma**, others

# Post-transplant skin cancer

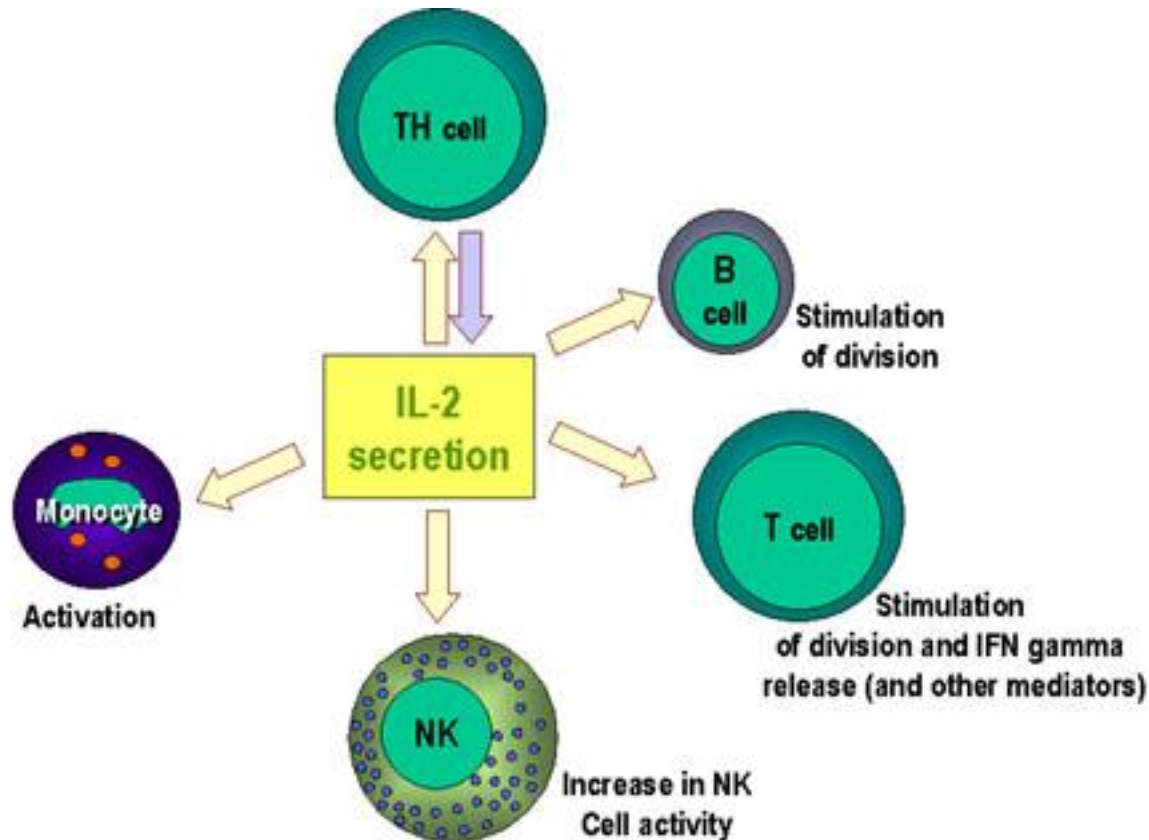
- **95%** of post-transplant cancers are *skin* cancers
- Post-transplant risk of SCC is **65-250 X** increased, risk of BCC is **10 X** increased
  - ▣ Normal population BCC:SCC ratio is 3:1. Reversed in immunosuppressed 1:4
- Post-transplant risk of skin cancer **>1/3** at 10 years post-op
  - ▣ At 10 year mark, 45% in Australia, 10% in England
- Post-transplant SCC is by definition **high risk** and **more likely to metastasize**
  - ▣ Veness, et al. 1999: **26 post-transplant SCC patients, 13 died of systemic disease.**
  - ▣ 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)

# 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



- Image: <http://pathmicro.med.sc.edu/bowers/imm-reg-ver2.htm>

# 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 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**

# 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

# 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

<u>Primary Tumor<sup>1</sup></u>	<u>Dose Time Fractionation Schedule</u>
<u>Tumor Diameter</u>	<u>Dose Fractionation and Treatment Duration</u>
< 2 cm	64 Gy in 32 fractions over 6-6.4 weeks 55 Gy in 20 fractions over 4 weeks 50 Gy in 15 fractions over 3 weeks 35 Gy in 5 fractions over 5 days
≥ 2 cm	66 Gy in 33 fractions over 6 - 6.6 weeks 55 Gy in 20 fractions over 4 weeks
Postoperative adjuvant	50 Gy in 20 fractions over 4 weeks 60 Gy in 30 fractions over 6 weeks
<u>Regional Disease--all doses at 2 Gy per fraction using shrinking field technique</u>	
• 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

ECE= Extracapsular extension

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

# Canoe trip



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