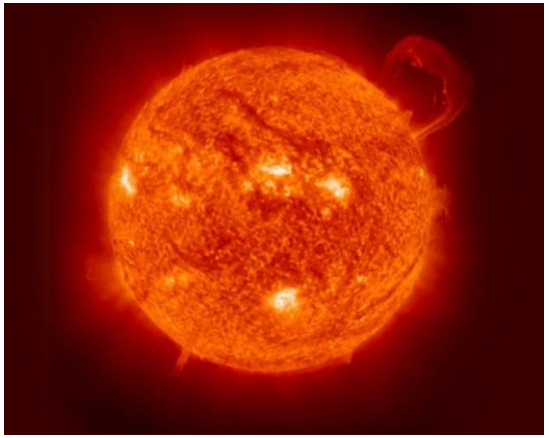
POST-TRANSPLANT NON-MELANOMA SKIN CANCER

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 immunosupressed 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

- Ref: Euvrard, Kanitakis, Claudy (2003) Cherpelis, Marcusen, and Lang (2002). Veness, et al. 1999

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.

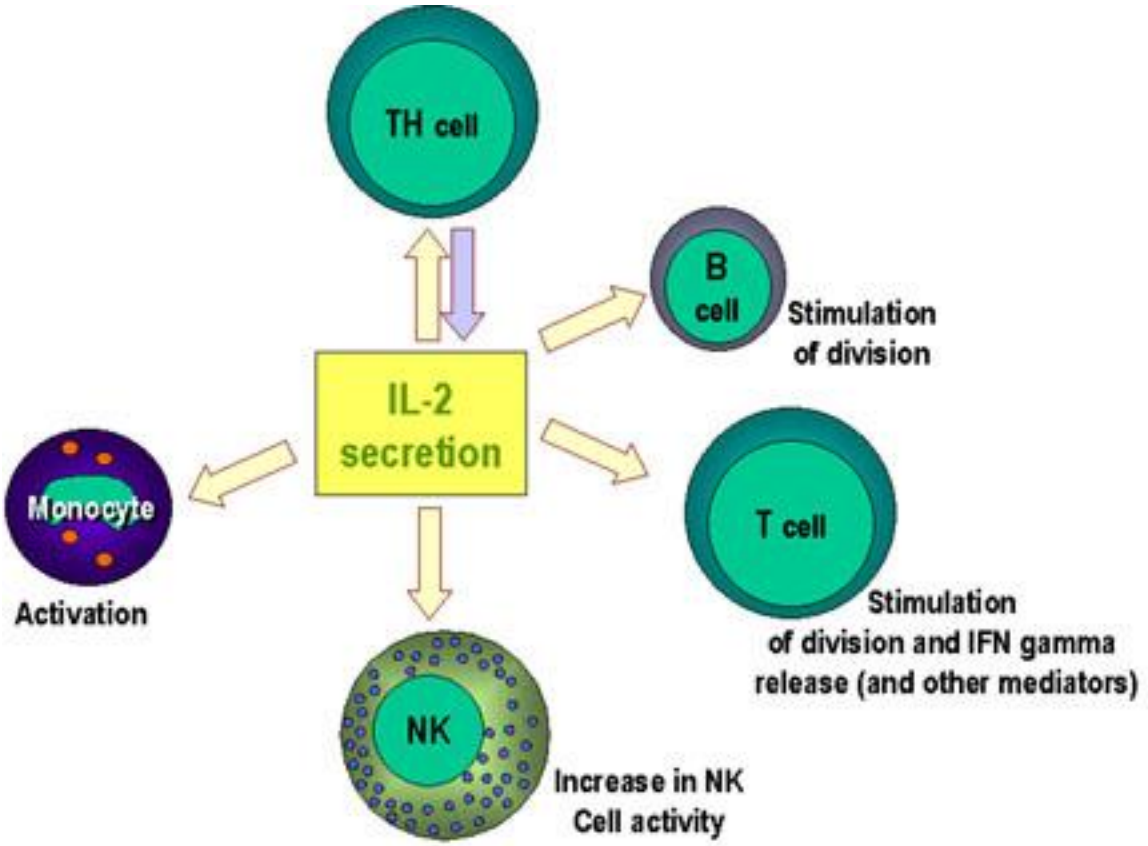
- 2. Decreased immune surveillance
  - Cell lines of the innate immune system (natural killer cells, macrophages, dendrites) suppressed.

- 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



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

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 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%**

Ref: Laramore G, et al., 1992 Han and Ratner, 2006

NCCN guidelines:

PRINCIPLES OF RADIATION THERAPY FOR SQUAMOUS CELL SKIN CANCER

Primary Tumor[1]	Dose Time Fractionation Schedule
Tumor Diameter	**Dose Fractionation and Treatment Duration**
< 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
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

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

References

- Athar, et al. Archives of Biochemistry and Biophysics 508 (2011) 159–163
- S. Euvrard, J. Kanitakis, A. Claudy, N. Engl. J Med. 348 (2003) 1681–1691
- B. S. Cherpelis, C. Marcusen, and P. G. Lang, "Prognostic factors for metastasis in squamous cell carcinoma of the skin,"*Dermatologic Surgery, vol. 28, no. 3, pp. 268–273, 2002.*
- M. J. Veness, D. I. Quinn, C. S. Ong, et al., "Aggressive cutaneous malignancies following cardiothoracic transplantation: the Australian experience," *Cancer, vol. 85, no. 8, pp. 1758–*1764, 1999.
- I. Nindl, M. Gottschling, E. Stockfleth, Dis. Markers 23 (2007) 247–259.
- M. Kessler, N. Jay, R. Molle, F. Guillemin, Transpl. Int. 19 (2006) 908–914.
- X. Tang, Y. Zhu, L. Han, A.L. Kim, L. Kopelovich, D.R. Bickers, M. Athar, J. Clin. Invest. 117 (2007) 3753–3764
- Stasko, et al., Dermatol Surg 2004;30:642–650
- Veness, M. J Biomed Biotechnol.2007(3):80572.
- Laramore GE et al. Int J Radiat Oncol Biol Phys. 1992;23(4):705-13
- Han and Ratner. Cancer. 2007 Mar 15;109(6):1053-9