Iatrogenic Immunosuppression and
Cutaneous Malignancy

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AAD
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Disclosures

• None
The Dermatology Foundation has supported & advanced my career.
Objectives

- Iatrogenic Immunosuppression and Malignancy
  - Introduction
  - Pathogenesis
  - Epidemiology
  - Outcomes
  - Risk Factors
  - Conclusions
I have seen bad outcomes in iatrogenically immunosuppressed patients with skin cancer in my practice…

1. Frequently
2. Fairly regularly
3. Rarely
4. Never
Introduction
Skin Cancer

- Most common human malignancy
- Over 5 million NMSC per year in US
- Increased incidence and risk in immunosuppressed
  - Solid organ transplantation
  - NHL/CLL

Original Biopsy
Organ Transplantation
Organ Transplantation

- Final defect size
  - 8.1x5.5cm
US Organ Transplants in 2015

- Total: 30,973
- > 250,000 Recipients Alive

- Heart
- Renal
- Liver
- Kidney-Pancreas
- Lung
- Pancreas
- Intestine
- Heart-Lung
Transplants per year
What would increase the number of transplant patients?
Increasing the rate of donation

• Iran has legalized the sale of human organs
• Social acceptance of deceased and living donation
• Opt-out rather than opt-in policies
  • Spain and Ireland
  • Much higher donation rates
Firefighter receives full face transplant in surgery called 'historic'

Ninety-three days after transplant, surgeons say Patrick Hardison, a retired fireman injured when a burning roof collapsed on him, is making a full recovery.

Surgeons in New York have declared the most extensive face transplant ever a success, saying the procedure to give a firefighter the face of a brain-dead man stands as a "historic" achievement.

In August surgeons at New York University's Langone Medical Center performed the transplant for 41-year-old Patrick Hardison, a retired fireman from Mississippi.
A First: Uterus Transplant Gives Parents A Healthy Baby

OCTOBER 04, 2014  10:10 AM ET

BILL CHAPPELL

In what's being hailed as a huge step in fertility and reproduction science, doctors in Sweden say a woman has given birth to a baby boy less than two years after she received a uterus transplant. The new mother, 36, had been born without a uterus, so another woman, 61, donated her womb several years after she had gone through menopause.

Dr. Mats Brännstrom and his team perform a womb transplant operation in April. Brännstrom says they delivered a healthy baby boy to a uterine transplant recipient last month, a first in medical science.

Johan Wilsborg/AP

The successful birth was reported by Dr. Mats Brännstrom of the University of Gothenburg, where a research program has performed uterine transplants on

Dr. Mats Brännstrom and his team perform a womb transplant operation in April. Brännstrom says they delivered a healthy baby boy to a uterine transplant recipient last month, a first in medical science.

Johan Wilsborg/AP
Doctors perform first successful penis transplant

Surgeons from Stellenbosch University and Tygerberg Hospital in Cape Town, South Africa, say they performed the first successful penis transplant operation on Dec. 11, 2014. / STELENBOSCH UNIVERSITY
Pathogenesis
Skin Cancer in Immunosuppressed Patients

• Multiple theories
  • Decreased immune surveillance
  • Direct carcinogenesis from medications
  • Increased infections
    • Human papilloma virus
    • Merkel Cell Polyomavirus
Risk for developing skin cancer in transplant recipients

- Basal Cell Carcinoma -- 10X
- Squamous Cell Carcinoma -- 65-250X
- Merkel Cell Carcinoma -- 20X
- Kaposi’s Sarcoma -- 84X
- Melanoma -- 2-8X
Characteristics of Skin Cancer in OTRs

- Age
  - Older = more

- Duration of immunosuppression
  - Longer = more

- Intensity of immunosuppression
  - Stronger = more

- Ultraviolet exposure
  - More = more

- HPV infection
  - Present = more

- Type I-III skin
  - Present = more

- CD4 lymphocytopenia
  - Lower = more
73 year old outdoorsman
s/p cardiac transplant 1993
Outcomes
BCC and SCC
Case

SCC – young in years, old in experience
History

- Pleasant 30 year old female
- History of ulcerative colitis
- Developed pulmonary fibrosis
  - Due to UC treatment regimen
History

- Pulmonary fibrosis
  - Progressed to bronchiolitis obliterans
- Bilateral living related lobar transplant
  - 10/15/99
- Bronchiolitis obliterans progressed
  - First transplant failed
- Double lung transplant
  - 2/2006
Non-melanoma skin cancer

- Every visit
  - At least 10-20 biopsies
  - Most superficially invasive SCC
  - Around 20-30 HAK’s
  - Around 30-40 AKs
- Deep aggressive SCC requiring Mohs every 8-12 weeks
Tumor Burden

![Graph showing tumor burden with bars for Carcinoma in situ and Invasive SCC over different time periods.](image)
Outcome

• Capecitabine stopped
  • Antibody mediated rejection of lungs
  • Bowel perforation following surveillance colonoscopy
  • Recurrence of Aspergillus pneumonia

• Tumor rebound

• Recurrent aggressive SCC left neck/scalp

• Pulmonary nocardia infection

• Pulmonary mycobacterium avium complex infection
Outcome

- Cholangiocarcinoma
- Metastases
  - Lung, bone, and multiple soft tissues
- Deceased
  - Aug 15, 2014
Lessons Learned

• The higher level of immunosuppression
  • The bigger the cutaneous challenge!
• Age sometimes not a factor
• Aggressive treatment promptly is key!
• Systemic treatment options sometimes helpful
• Very humbling!
Incidence of and Risk Factors for Skin Cancer following Cardiac Transplantation
## Mortality

<table>
<thead>
<tr>
<th>Years post transplantation</th>
<th>Cumulative incidence of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yrs</td>
<td>18.4% (95% CI 13.6%-23.0%)</td>
</tr>
<tr>
<td>10 yrs</td>
<td>37.9% (95% CI 30.5%-44.5%)</td>
</tr>
<tr>
<td>15 yrs</td>
<td>63.5% (95% CI 51.5%-72.5%)</td>
</tr>
<tr>
<td>18 yrs</td>
<td>78.7% (95% CI 57.7%-89.3%)</td>
</tr>
</tbody>
</table>

* The majority of death was due to heart failure
Mortality

- Mortality due to skin cancer
  - Only 1 person died due to skin cancer
  - Melanoma
    - 8.6 years post transplantation
Melanoma
Melanoma in OTRs

- MM prior to transplant
  - 62 cases of MM in 60 patients

- MM after transplant
  - 703 cases of MM in 633 patients

Overall Survival

Breslow Depth

- \(< 0.75\text{ mm}\) (Including in situ)
- \(0.76-1.5\text{ mm}\)
- \(1.51-3.0\text{ mm}\)
- \(> 3.0\text{ mm}\)

3 year Overall Survival

Data p value

- \(< 0.75\text{ mm}\): 88.2% 96.7%  <0.001
- \(0.76-1.5\text{ mm}\): 80.8% 93.3%  <0.001
- \(1.51-3.0\text{ mm}\): 51.2% 87.4%  <0.001
- \(> 3.0\text{ mm}\): 55.3% 76.2%  0.007

Table 1: 3 year melanoma specific survival based on Breslow depth

<table>
<thead>
<tr>
<th>Breslow Depth</th>
<th>Survival Rate</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.75mm</td>
<td>97.8%</td>
<td>98.8%</td>
<td>0.70</td>
</tr>
<tr>
<td>0.76-1.50mm</td>
<td>89.4%</td>
<td>96.6%</td>
<td>0.07</td>
</tr>
<tr>
<td>1.51-3.0mm</td>
<td>73.2%</td>
<td>91.0%</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt; 3.0mm</td>
<td>73.9%</td>
<td>81.0%</td>
<td>0.31</td>
</tr>
</tbody>
</table>

MM prior to Transplantation

- 60 patients with MM prior to Transplant
  - 2 metastases
    - 1 to LN’s (1 month post MM diagnosis)
    - 1 to lungs (14.8 years post MM diagnosis)
  - No recurrences

Conclusions

MM in OTRs

• Overall survival is worse in OTRs with MM regardless of Breslow thickness

• MM cause specific survival appears to be worse in thicker MM

• Recurrence of MM is no higher in OTRs with a prior history of MM
Risk Factors
Common Risk Factors for Skin Cancer in Transplant Patients

- Increasing incidence with increasing age
- Hereditary
  - Fair Skin, blond or red hair
  - Blue, green or gray eyes
  - Celtic background
- History of previous NMSC
- HPV
- Sun exposure
OTRs more likely to perform SSEs. During cognitive interviewing, participants stated that they did not clearly understand instructions to “stay out of the sun and use sunscreen.” Even when OTRs were aware of their increased risk, they did not recall being specifically told or taught to do SSEs during routine posttransplantation follow-up. Patients may not be performing SSEs because they do not fully understand their risks for SCC and have not received education regarding skin cancer warning signs.

Knowledge, Understanding, and Use of Preventive Strategies against Nonmelanoma Skin Cancer in Healthy and Immunosuppressed Individuals Undergoing Mohs Surgery

Alina Goldenberg, BA,* Bichchau Thi Nguyen, MD,† and Shang I. Brian Jiang, MD‡

BACKGROUND Despite various national recommendations advising individuals to reduce their exposure to ultraviolet radiation, many people still do not use these skin cancer prevention strategies.

OBJECTIVES To assess patient sources of medical information, knowledge of sun protection strategies, and barriers to implementing these strategies and to compare the overall rate of use of skin cancer prevention strategies of healthy and immunocompromised patients.

MATERIALS AND METHODS Survey-based study conducted on 140 individuals undergoing Mohs surgery.

RESULTS Seventy-three percent of healthy and 74% of immunosuppressed participants identified sunscreen use as a form of protective strategy, whereas 36% and 27%, respectively, used sunscreen daily. Participants cited physicians and the internet as equal sources of medical information. Knowing two or more strategies correlated to a higher self-rating of daily use of any protective strategy.

CONCLUSION General knowledge regarding sun protection strategies is limited, but awareness of multiple strategies correlated with greater sun protective behavior. Despite having a much higher incidence of skin cancers, the immunosuppressed group did not show more awareness of prevention strategies or higher use than healthy participants.
The Empty Vessel Concept

Does Knowledge Equal Behavior?
Conclusions
How to Unlock the Puzzle?...

• Immune system
• Behavioral factors
• Other things that affects carcinogenesis
Summary
What We Don’t Know

• Immunosuppressed patients with skin cancer
  • What is the underlying association
  • Does education and prevention effect outcomes
  • What predicts bad behavior
Future Direction and Research

• Pathogenic mechanisms
  • Genetic associations

• Optimal management
  • Formal recommendations needed

• Adjuvant therapy for high risk tumors

• Educational strategies
  • Effects on outcome
What Physicians Need to Know about Skin Cancer in Immunosuppressed Patients

• Skin cancer can ruin a life
• Skin cancer can take a life
• Prevention must come early
  • EARLY = CURE
• Less immunosuppression = less cancer
• Dermatologic surgeons and dermatologists should want to work with other specialties
• Expert help is available (www.ITSCC.org)
International Transplant Skin Cancer Collaborative

Solid organ transplant recipients are up to 65 times more likely to develop skin cancer than people without transplants. The International Transplant Skin Cancer Collaborative (ITSCC) was founded in 2001 by dermatologists from several institutions in response to this alarming phenomenon of accelerated skin cancer development in solid organ transplant recipients.

Mission Statement

1. To integrate and support basic scientific and clinical research to address the special needs of transplant recipients with skin cancer in order to improve quality of care.
2. To educate patients, scientists, primary care doctors and specialist physicians on the unique needs and clinical care issues in the transplant patients.

To become a member of ITSCC click here.

Skin cancer is the most common cancer affecting solid organ transplant recipients, affecting up to 70 percent of patients within 20 years, and is the result of intense immunosuppressive regimens.