Managing Skin Cancer in Organ Transplant Recipients

Mark Russell, M.D.
Department of Dermatology
University of Virginia

Goals

• Update Solid Organ Transplant Recipient (SOTR) data in VA and nationally
• Review skin cancer management options
How many medical centers in Virginia perform solid organ transplants?

A. 3
B. 5
C. 7
D. 9
E. 11

Organ Transplants in Virginia

<table>
<thead>
<tr>
<th>Health Resources &amp; Services Administration, Based on Organ Procurement and Transplantation Network data as of July 18, 2019</th>
<th>All Organs</th>
<th>Kidney</th>
<th>Liver</th>
<th>Pancreas</th>
<th>Kidney / Pancreas</th>
<th>Heart</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Centers</td>
<td>2,560</td>
<td>2,128</td>
<td>170</td>
<td>33</td>
<td>40</td>
<td>109</td>
<td>25</td>
</tr>
<tr>
<td>VACH-THI Children's Hosp of King's Daughters</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VAMH-THI James Eakin Hosp</td>
<td>518</td>
<td>458</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>42</td>
<td>12</td>
</tr>
<tr>
<td>VAMD-TUI Hampton General Hospital</td>
<td>174</td>
<td>174</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VAMC-TUI MC V Hospitals</td>
<td>554</td>
<td>447</td>
<td>61</td>
<td>2</td>
<td>9</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>VAMC-TUI McGuire VA Medical Center</td>
<td>22</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>VANG-TUI Sentara Norfolk General Hospital</td>
<td>534</td>
<td>484</td>
<td>0</td>
<td>6</td>
<td>8</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>VAMC-VIR Univ of Virginia HSC</td>
<td>748</td>
<td>550</td>
<td>109</td>
<td>21</td>
<td>21</td>
<td>34</td>
<td>13</td>
</tr>
</tbody>
</table>
Transplant Trends

- 112,925 - people need a lifesaving organ transplant (total waiting list candidates)
- 26,448 - transplants performed this year January - August 2019
- 12,739 - total donors January - August 2019

UNOS Website accessed 9/22/19 https://unos.org/data/transplant-trends/

2018 transplants by organ type

- Kidney 21,167
- Liver 8,250
- Heart 3,408
- Lung 2,530
- Kidney/Pancreas 836
- Pancreas 192
- Intestine 104
- Heart/lung 32
- Vascular allograft (VCA) 11
Every ten minutes, someone is added to the national transplant waiting list.
On average, 20 people die each day in the U.S. while waiting for a transplant.*

*More than 7,000 candidates died in 2016 while on the wait list, or within 30 days of leaving the list for personal or medical reasons, without receiving an organ transplant.

Data from optn.transplant.hrsa.gov (Health Resources and Services Administration web site) Accessed 09/27/2019
Organ Transplants are Increasing

2018: More transplants than ever


Skin Cancer and SOTR

- Solid organ transplants are increasing
- Survival rates post-transplant are improving
- Solid organ transplant recipients (SOTR) are at increased risk for cutaneous malignancies, a finding related to long-term immunosuppression.
- The incidence of skin cancer in these populations has been increasing, however …
Incidence

• Skin cancers account for almost 40 percent of malignancies in SOTR's
• They develop in more than 50 percent of white organ transplant recipients
• The most commonly reported skin cancers in this population include squamous cell carcinoma (SCC), basal cell carcinoma (BCC), melanoma, Merkel cell carcinoma, and Kaposi sarcoma


Introduction

• Management of these patients includes:
  – Education of the patient and PCP
  – Preventative measures
  – Appropriate physician surveillance
  – Treatments that directly target cutaneous malignancies
  – Modulation of immunosuppression
#1 - Every Dermatologist can be a Transplant Dermatologist

- 24% - Skin Infections
- 10% - Inflammatory skin conditions
- 23% - Benign skin lesions
- 11% - Premalignant lesions
- 18% - Malignant skin lesions
- 6% - Other


#1 - Every Dermatologist can be a Transplant Dermatologist

- Many hands make light work
  - Incidence of SCC and BCC may be declining in SOTR’s
  - Modified immunosuppressive treatments and close clinical follow-up may explain the decline.
  - Risk remains elevated

#2 – Early Dermatologic Intervention

• Education
  – incorporating skin cancer education into the early transplant timeline increases patient knowledge and influences positive sun-protective behavior
  – Skin cancer education before or immediately after transplant, and again one year post-transplant appears optimal

#2 – Early Dermatologic Intervention

• Prevention
  – Don’t forget the basics
  – Sun exposure is the most significant modifiable environmental risk factor for the development of cSCC in OTR

Sun Protective Hats

- ≥ 3” brim
- Flap hat
- UPF 50+
#2 – Early Dermatologic Intervention

- Education
- Prevention
- Risk Stratification
#3 – Risk Stratify Patients

- Pre-transplant
  - Used to assess skin cancer risk and appropriate timing for transplant and f/u visits

Recommended wait times pretransplant with a diagnosis of melanoma and squamous cell carcinoma

<table>
<thead>
<tr>
<th>Skin Malignancy</th>
<th>Wait Time Before Transplantation After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant melanoma</td>
<td></td>
</tr>
<tr>
<td>In situ melanoma</td>
<td>No wait necessary, follow-up post-transplant 3 mo</td>
</tr>
<tr>
<td>Stage Ia melanoma</td>
<td>2 y</td>
</tr>
<tr>
<td>Stage Iib/ila</td>
<td>2-6 y</td>
</tr>
<tr>
<td>Stage Iib/ill</td>
<td>5 y</td>
</tr>
<tr>
<td>Any stage III or IV</td>
<td>Not eligible for transplantation</td>
</tr>
<tr>
<td>Cutaneous squamous cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>No delay necessary</td>
</tr>
<tr>
<td>High-risk SCC without perineural invasion</td>
<td>2 y</td>
</tr>
<tr>
<td>High-risk SCC with perineural invasion or t2 risk factors</td>
<td>2-3 y</td>
</tr>
<tr>
<td>High-risk SCC with local nodal metastatic disease</td>
<td>5 y</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>No eligible for transplantation</td>
</tr>
</tbody>
</table>

Recommended wait times pretransplantation for patients with a history of skin cancer before transplantation

<table>
<thead>
<tr>
<th>Skin malignancy</th>
<th>Appropriate treatment pretransplantation</th>
<th>Wait time before transplantation after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>pSCC</td>
<td>Treatment of field disease</td>
<td>No delay necessary</td>
</tr>
<tr>
<td>– No history of SCC but at risk for development of SCC</td>
<td>Surgical excision with clear margins or Mohs micrographic surgery</td>
<td>No delay necessary</td>
</tr>
<tr>
<td>– Low risk</td>
<td>Surgical excision with clear margins or Mohs micrographic surgery</td>
<td>No delay necessary</td>
</tr>
<tr>
<td>– High-risk SCC (not including perineural invasion)</td>
<td>Surgical excision with clear margins or Mohs micrographic surgery</td>
<td>No delay necessary</td>
</tr>
<tr>
<td>– High-risk SCC with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Perineural invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– ≥2 Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk with local nodal metastatic</td>
<td>Surgical excision with appropriate lymph node dissection plus ART</td>
<td>5 years</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>Refer for oncology opinion</td>
<td>Not eligible for transplantation</td>
</tr>
<tr>
<td>MCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Local with negative SLN biopsy</td>
<td>Wide local excision ± ART</td>
<td>2 years</td>
</tr>
<tr>
<td>– Local with nodal metastasis</td>
<td>Wide local excision, lymph node dissection, ART</td>
<td>2 to 3 years</td>
</tr>
<tr>
<td>– Distant metastasis</td>
<td>Refer for oncology opinion</td>
<td>Not eligible for transplantation</td>
</tr>
<tr>
<td>MM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– In situ melanoma</td>
<td>Wide local excision</td>
<td>No wait necessary, follow-up posttransplantation 3 months</td>
</tr>
<tr>
<td>Stage Ia melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage Ia/II melanoma</td>
<td>Wide local excision ± sentinel lymph node biopsy</td>
<td>2 years</td>
</tr>
<tr>
<td>Stage Ia/II/III melanoma</td>
<td>Wide local excision ± sentinel lymph node biopsy</td>
<td>2 to 3 years</td>
</tr>
<tr>
<td>Any stage III or IV melanoma</td>
<td>Refer for oncology opinion</td>
<td>Not eligible for transplantation</td>
</tr>
</tbody>
</table>


#3 – Risk Stratify Patients

- Post-transplant
  - Ongoing assessment to adjust frequency of f/u visits
**Risk Factors**

- Significant predictors of post-transplant skin cancer include:
  - pretransplant skin cancer
  - male sex
  - thoracic organ transplant
  - white race
  - age at transplantation ≥50 years


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**Post-Transplantation Screening**

<table>
<thead>
<tr>
<th>Status</th>
<th>F/U Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>No history of skin cancer or AK</td>
<td>once yearly</td>
</tr>
<tr>
<td>History of AK or one low-risk nonmelanoma skin cancer</td>
<td>every six months</td>
</tr>
<tr>
<td>Multiple nonmelanoma skin cancers or a history of a high-risk SCC</td>
<td>every three months</td>
</tr>
<tr>
<td>History of pretransplant melanoma or melanoma in situ</td>
<td>every six months</td>
</tr>
<tr>
<td>Post-transplant melanoma</td>
<td>every three months for two years, then at least every six months</td>
</tr>
<tr>
<td>Rapidly developing tumors, aggressive tumors, or metastatic skin cancer</td>
<td>every four to six weeks</td>
</tr>
</tbody>
</table>

*** In all patients with a history of skin cancer, examination should include the palpation of lymph nodes.
Evaluation and management of skin cancers in organ transplant recipients before and after transplantation

#3 – Risk Stratify Patients

- Risk Stratification
#4 – Be Familiar with Skin Cancers Common in SOTR’s

Squamous Cell (SCC) and Basal Cell (BCC) Carcinoma

- SCC & BCC make up >90% of cutaneous malignancies in OTR

Epidemiology

- ratio of SCC to BCC in organ transplant recipients range from 1.5:1 to 5:1
- OTR are 65-250 times more likely to develop SCC than the general population
- 6-16 times more likely to develop BCC

Relative risk associated with cutaneous malignancies in immunosuppressed patients

<table>
<thead>
<tr>
<th></th>
<th>Basal Cell Carcinoma</th>
<th>Squamous Cell Carcinoma</th>
<th>Melanoma</th>
<th>Merkel Cell Carcinoma</th>
<th>Kaposi Sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant</td>
<td>10</td>
<td>65–250</td>
<td>2–5</td>
<td>5–50</td>
<td>80–500</td>
</tr>
<tr>
<td>CLL</td>
<td>8 *</td>
<td>8 *</td>
<td>2–4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HIV</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>2–10</td>
<td>100,000</td>
</tr>
</tbody>
</table>

* The combined relative risk for basal cell carcinoma and squamous cell carcinoma is 8.


Epidemiology

- the incidence of new skin cancers rise as the time from transplant increases.

% OTR with at least 1 NMSC

Melanoma

- Organ transplantation is associated with an increased risk of melanoma.
- A 2015 meta-analysis of 20 cohort studies found that the pooled risk of melanoma was 2.71 (95% CI 2.23-3.30), with considerable heterogeneity among studies


Melanoma

- A study of 139,991 transplant recipients followed for a median period of four years, identified:
  - Incidence increased sharply in the first four years after transplantation before declining steadily.
  - The risk of invasive melanoma was more than twofold higher than in the general population.
  - The greatest increase was noted for regional stage melanoma and for melanomas on the head and neck.
  - The risk was higher in renal transplant recipients than in liver and lung recipients. Other factors associated with increased risk included male sex, increasing age, and azathioprine maintenance therapy.

Melanoma

• In a cohort of 89,786 renal transplant recipients, the annual incidence of melanoma was 17 times greater in African-American transplant recipients than in the African-American general population.


Melanoma

• Transmission of melanoma from organ donors to organ recipients also has been reported. In a review of 104 donor-transmitted cancer cases, melanoma was the second most frequent transmitted cancer (17 percent) after renal cancer.

Melanoma

• Melanoma-specific mortality is higher in transplant recipients than in nontransplanted patients
• In a cohort study, the mortality was threefold higher in transplant recipients compared with nonrecipients


Kaposi Sarcoma
Kaposi Sarcoma

- Kaposi sarcoma (KS) is a tumor of endothelial cell origin associated with herpes human virus-8 (HHV-8) infection that occurs with increased frequency in the setting of immunosuppression
- Most cases of organ transplant-related KS have occurred in individuals of Mediterranean, Jewish, Arabic, Caribbean, or African descent


Kaposi Sarcoma

- In a South African cohort study, KS was the most common cancer detected in nonwhite renal transplant recipients

Kaposi Sarcoma

- KS often develops relatively quickly after organ transplantation; the mean interval to diagnosis is 13 months
- Men are more likely to be affected than women.
- Approximately 90 percent of patients develop cutaneous and/or mucosal lesions
- Lesions on the lower extremities are common


Merkel Cell Carcinoma
Merkel Cell Carcinoma

• Merkel cell carcinoma (MCC) is a rare tumor of neuroendocrine origin linked to the Merkel Cell polyoma virus with greatly increased incidence among solid organ transplant recipients.

• In one study of nearly 200,000 solid organ transplant recipients, the MCC risk was 24-fold higher than in the general population.

• The incidence of MCC appears to increase with:
  – age at the time of transplant, with over 70 percent of cases occurring in patients who were older than 50 years at the transplant.
  – with time since transplant, with the highest incidence observed 10 years or more after transplant.

Merkel Cell Carcinoma

- Immunosuppressive regimens may influence the occurrence of MCC
- Induction with monoclonal antibodies and maintenance immunosuppression with tacrolimus or mycophenolate mofetil seem to be associated with a lower incidence of MCC
- Incidence is highest in patients treated with a combination of cyclosporine and azathioprine


Merkel Cell Carcinoma

- In one study, solid organ transplant recipients had a nearly 12-fold increased hazard for MCC-specific death.
- Compared with immunocompetent patients, solid organ transplant recipients had a decreased one-year, MCC-specific survival (56 versus 95 percent)

#5 – Don’t Forget Non-Sun Exposed Areas

- BCC & SCC much less common in non-white patients
- African-American patients have increased incidence of HPV-related SCC in the groin and axilla


#6 – Niacinamide
Chemoprevention

• Nicotinamide (Niacinamide)
  – A randomized trial of oral nicotinamide 500 mg twice daily for 12 months in 386 immunocompetent participants with a history of two or more nonmelanoma skin cancers found a 20 percent reduction in the number of new BCCs and a 30 percent reduction in the number of new SCCs in the nicotinamide group, compared with the placebo group


Chemoprevention

• Nicotinamide (Niacinamide)
  – 24 renal transplant recipients with actinic keratoses treated with nicotinamide 250 mg three times daily or placebo for six months found that nicotinamide was more effective than placebo in inducing partial or complete regression of actinic keratoses and light-damaged skin

Chemoprevention

• Nicotinamide (Niacinamide)
  – A phase 2 trial including 22 renal transplant recipients randomized to nicotinamide 500 mg twice daily or placebo found a nonsignificant 35 percent reduction in the rate of new skin cancers at six months


Chemoprevention

• Nicotinamide (Niacinamide)
  – 38 liver and kidney transplant patients
  – Assigned to nicotinamide 500 mg daily or control for actinic keratoses (AK’s)
  – After 6 months:
    • 88% of treatment group showed significantly decreased size. 42% showed complete clinical regression. No patients develop new AK’s.
    • 91% of control group showed increase in AK size and/or developed new AK’s. Seven pre-existing AK’s progressed to squamous cell carcinoma.
  – Nicotinamide appears to be effective in preventing in treating AK’s

#7 - Retinoids

Prevention

- Chemoprevention
  - Chemopreventive measures are considered for patients who develop multiple (more than five) SCCs per year, aggressive SCCs, or accelerated development of SCCs

Chemoprevention

• Acitretin
  – Systemic retinoids such as acitretin, isotretinoin, and etretinate have been used for the prevention or reduction of nonmelanoma skin cancers
  – The major side effects of systemic retinoids include teratogenicity; dryness of the eyes, nose, lips, mouth, and skin; abnormalities in liver function tests; and hyperlipidemia.


Chemoprevention

• Acitretin
  – should be started at low doses to facilitate tolerance of adverse effects
  – Begin with 10 mg a day and gradually increase at one- to two-week intervals by increments dictated by patient tolerance of side effects
  – most patients with a maintenance dose of 25 mg per day, but the final dose is individualized to balance clinical response with side effects

Chemoprevention

• Acitretin
  – The effect of acitretin is limited to the duration of therapy
  – lesion development recurs rapidly after cessation of therapy


#8 – Immunosuppression Modification
Immunosuppressants

- Although the overall level of immunosuppression appears to be an important factor in the development of skin cancers, the contribution of individual immunosuppressive agents may not be equivalent


Immunosuppressants

- Treatment with cyclosporine or azathioprine has been linked to the development of skin cancer in multiple clinical studies


Immunosuppressants

• Data from two studies suggest that immunosuppression with mycophenolate mofetil may be associated with lower risk for skin malignancy compared with azathioprine-based regimens


Immunosuppressants

• mTOR Inhibitor – Sirolimus
  – Evidence suggests that sirolimus, compared with other immunosuppressive agents, is associated with a lower risk for skin malignancies in solid organ transplant recipients

Prophylaxis

• Voriconazole
  – broad-spectrum antifungal medication commonly used after lung transplantation
  – linked with the development of aggressive squamous cell carcinomas (SCCs) in immunocompromised patients


Summary

• Chronic immunosuppression in organ transplant recipients is associated with a high risk for cutaneous malignancies.
• Squamous cell carcinoma (SCC) is the most common skin cancer in this population and is often associated with aggressive biologic behavior.
• Early detection and treatment of cutaneous malignancies, modulation of immunosuppression, and preventive measures play an important role in the management of these patients.
Summary

• A dermatologic consultation is recommended before transplantation for the screening and treatment of skin cancer and precursor lesions.

• A careful history of previous skin cancer should be obtained to determine whether a wait time is needed before proceeding to transplantation.

Summary

• Transplant recipients should be counseled on sun avoidance, the use of sunscreens and sun-protective clothing, and the warning signs of cutaneous malignancy.

• Patients should be instructed to perform a skin self-examination on a monthly basis

• After transplantation, patients should continue to have total body skin examinations on a regular basis
Summary

• All lesions suspicious for SCC in organ transplant patients should be biopsied and sent for pathologic evaluation.
• The treatment of SCCs is based upon the presence or absence of high-risk features.

Summary

• Basal cell carcinoma (BCC), melanoma, and Merkel cell carcinoma are managed similarly in organ transplant recipients and immunocompetent patients.
• Modulation of immunosuppression is the primary treatment for Kaposi sarcoma in organ transplant recipients.
• There are no definitive guidelines regarding alteration in immunosuppressive regimens in patients with BCC, melanoma, or Merkel cell carcinoma.
Risk Factors

- Pretransplant skin cancer, in particular NMSC, may also be a risk factor for post-transplant malignancies other than skin cancer.
- Risk of post-transplant solid tumors was higher among patients with pretransplant NMSC compared with patients without pretransplant NMSC.
- Patients with pretransplant skin cancer also had an increased risk of graft failure and death.

Introduction

- The long-term immunosuppressive therapy required to maintain host tolerance of a transplanted organ contributes to an increased risk for malignancy in organ transplant recipients.
- Skin is the most common site for the development of malignancy.

Introduction

- Some skin cancers demonstrate aggressive biologic behavior in the setting of immunosuppression, and care must be taken to identify and treat lesions early and appropriately.
Pediatric Organ Transplant

- SCC, BCC, melanoma, and Kaposi sarcoma account for 13 to 55 percent of all post-transplantation malignancies in children

- 11 percent developed a nonmelanoma skin cancer over a median follow-up period of 13.4 years

PATHOGENESIS

- Proposed mechanisms through which immunosuppression may contribute to the development of skin cancer include:
  - Reduced immune surveillance, thereby facilitating the survival and proliferation of atypical cells.
  - Direct or contributory carcinogenic effects of immunosuppressive agents such as azathioprine or cyclosporine. Calcineurin inhibitors have been shown to impair cell ability to repair ultraviolet radiation-induced DNA damage
  - Proliferation of oncogenic viruses in the setting of immunosuppression. Epstein-Barr virus (EBV), human papillomavirus (HPV), Kaposi sarcoma herpes virus (KSHV), human T cell lymphotropic virus type 1 (HTLV-1), and Merkel cell polyomavirus (MCV)

Skin Cancer in Organ Transplant Recipients (OTR)

Risk Factors

- Ultraviolet radiation fair phenotypic features (Fitzpatrick types I to III with light-colored hair and eyes) are known risk factors for the development of SCC and BCC in organ transplant recipients.
- HPV infection especially in nonwhite patients in non-sun exposed areas.

Risk Factors

• A history of either SCC or BCC prior to organ transplantation significantly increased risk for the development of SCC or BCC after transplantation

• Patients with a history of pretransplant skin cancer have a nearly 3x increased risk of post-transplant malignancies, including SCC, BCC, lymphoproliferative disorders, and solid tumors


Risk Factors

• The cumulative incidence of new skin cancer after the development of an initial lesion was 32 percent after one year, 59 percent after three years, and 72 percent after five years

• A separate retrospective study of cardiac transplant patients in the United States found cumulative incidence rates of a second SCC at the same time points of 44, 67, and 76 percent, respectively. The cumulative incidence rates for a second BCC were 32, 49, and 51 percent.

Risk Factors

• Estimates of NMSC incidence after organ transplantation in the United States and Western Europe have ranged from 5 percent at 2 years, 10 to 27 percent at 10 years, and 40 to 60 percent after 20 years.

• The rates of NMSC are higher in Australia, a finding that is likely related to greater solar exposure in a predominantly fair-skinned population. Between 70 and 82 percent of organ transplant recipients in Australia are diagnosed with NMSC within 20 years after transplantation.


Risk Factors

• The degree and duration of immuno-suppression influences the risk for NMSC, particularly SCC.

• Compared treatment with a three-drug regimen (cyclosporine, azathioprine, and prednisolone) with a two-drug regimen (azathioprine and prednisolone), patients treated with the three-drug regimen had a significantly greater incidence of SCC.

Risk Factors

• A meta-analysis of 27 studies found an increased risk of SCC, but not BCC, in organ transplant recipients treated with azathioprine compared with those treated with other immunosuppressive regimens


Risk Factors

• Azathioprine has also been associated with an increased risk of melanoma and Merkel cell carcinoma


Risk Factors

• A study in 230 heart transplant patients found that the risk for SCC (but not BCC) three years after transplantation correlated with the overall level of immuno-suppression, rather than with a specific immunosuppressive drug


Risk Factors

• The risk for NMSC is greater in lung, heart, or pancreas-kidney transplant recipients than in kidney transplant patients and is lowest in liver transplant recipients

Risk Factors

• Greater age at transplantation may increase the likelihood of NMSC and may be associated with development of lesions earlier in the post-transplant period


Risk Factors

• HPV has been detected at a greater frequency in lesional versus nonlesional skin in organ transplant recipients with SCC (90 versus 11 to 32 percent of specimens positive for HPV)

Risk Factors

• HPV subtypes, such as HPV5, HPV8, and HPV9, which are considered to be nonpathogenic to the general population, can induce preneoplastic and neoplastic skin lesions in immunocompromised patients and may play a causal role in post-transplant cutaneous SCCs


Risk Factors

• In OTR, cSCC, but not BCC, was associated with an increased risk of developing second malignancies
• cSCC was also associated with increased risk of HPV-related cancers, including anal cancer and female genital cancers

PreTransplantation Screening

• A dermatologic consultation is recommended before transplantation for the screening and treatment of skin cancer and precursor lesions
• Actinic keratoses, porokeratoses, and viral warts should be treated
• A careful history of previous skin cancer should also be obtained to determine the appropriate follow-up frequency or the wait time before proceeding to transplantation


Pretransplant Screening

• Transplant candidates with extensive field disease (ie, multiple actinic keratoses, disseminated porokeratosis) but without a history of skin cancer may proceed to transplantation, with the recommendations that all field disease be appropriately managed by the dermatologist.
• For patients with basal cell carcinoma or low-risk squamous cell carcinoma (SCC) that has been surgically excised with clear margins, no waiting time is required.

Pretransplant Screening

- For patients with a history of high-risk SCC and for those with Merkel cell carcinoma stage IIa or less (local disease; any tumor size not invading bone, muscle, fascia, or cartilage; negative lymph nodes, a two- to three-year waiting time is required.
- For patients with SCC and local nodal disease, a five-year wait time is considered prudent, following appropriate treatment with lymph node dissection and adjuvant radiation therapy.


Pretransplant Screening

- For transplant candidates with a history of melanoma in situ/lentigo maligna, no waiting period is required, but the patient should be followed up with regular skin exams.
- For renal transplant candidates with a history of stage Ia/Ib/Ila melanoma, a two- to five-year wait time is required before transplantation. A five-year delay is required for patients with stage IIb/IIc melanoma.

Pretransplant Screening

• Patients with distant metastatic diseases are not eligible for transplantation in most circumstances.


Managing SCCs in Transplant Recipients

- Reduction or Discontinuation of Immunosuppression
- Systemic Chemophrophylaxis
  - Actretin, 5-FU, Nicotinamide
- Switch to mTOR Inhibitor
- Topical Treatment of Fields of AKs
  - 5-FU, PDT, Diclofenac
- Topical Retinoids
- Imiquimod
- Treat Isolated AKs
- Preventative Measures
  - Regular Skin Screenings
  - Strict Sun Protection

Prevention

• Sun Protection
  – Sun avoidance and the regular use of sunscreens and sun-protective clothing is recommended
  – In one controlled study, subjects using daily sunscreen developed fewer actinic keratoses and SCCs than subjects with intermittent sunscreen use


Prevention

• Vitamin D deficiency is more likely to occur in patients who engage in strict sun protection.
• With approval of the patient's transplant team, vitamin D supplementation can be initiated in deficient patients

Prevention

• Immunosuppressive Regimen
  – Regimens including mammalian target of rapamycin (mTOR) inhibitors such as sirolimus and everolimus rather than calcineurin inhibitors may reduce the risk for skin cancer and prolong the time to onset


Prevention

• In a 2015 meta-analysis including 39,039 kidney recipients, sirolimus was associated with a 51 percent reduction in the incidence of nonmelanoma skin cancer
  • This association was much stronger in trials comparing patients treated with sirolimus with those treated with cyclosporine suggesting that the protective effect of sirolimus may be in part driven by the withholding of cyclosporine.

Prevention

• Sirolimus was associated with an increased risk of death (HR 1.43, 95% CI 1.21-1.71)
• The increased mortality was driven by increased cardiovascular and infection-related deaths in the sirolimus group.
• An increased risk of all-cause mortality and death from malignancy associated with mTOR inhibitors (either sirolimus or everolimus) was also found in an observational study of 9353 kidney transplant recipients


Prevention

• In a five-year extension trial that compared sirolimus-based versus calcineurin inhibitor-based immunosuppression in kidney transplant recipients with one or multiple cutaneous SCCs, patients in the sirolimus group maintained a lower skin cancer rate over five years, with no difference in rejection or mortality between the two groups.

Prevention

• At five years, the rates of new skin cancers in the sirolimus group were significantly lower than those in the calcineurin inhibitor group (22 versus 59 percent for SCC, 20 versus 37.5 percent for basal cell carcinoma [BCC], and 34 versus 66 percent for other skin cancers).
• The benefit was most marked in patients who converted to a sirolimus-based regimen after the development of the first cutaneous SCC.


Prevention

• Reduction in Immunosuppression
  – reduction of immunosuppression may be considered in patients who develop numerous lesions, recurrent disease, or metastatic disease

Prevention

• Reduction in immunosuppression
  – Since reduction of immunosuppression can increase the risk for graft rejection, the risks and benefits of adjusting the level of immunosuppression must be carefully considered on an individual basis.
  – An expert consensus on the reduction of immunosuppression for specific skin cancer scenarios in organ transplant recipients has been published.


Levels of reduction of immunosuppression and associated risks to allograft

<table>
<thead>
<tr>
<th>Level of reduction of immunosuppression</th>
<th>Level of risk to allograft</th>
<th>Examples of potential risks to allograft</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>No allograft dysfunction</td>
</tr>
<tr>
<td>Mild</td>
<td>Mild</td>
<td>Risk of reversible allograft rejection or dysfunction requiring medical treatment</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate</td>
<td>Risk of partial permanent allograft dysfunction from rejection</td>
</tr>
<tr>
<td>Severe</td>
<td>Severe</td>
<td>Risk of allograft failure with potential for death (liver and heart); need to resume dialysis, undergo re-transplantation, or potential for death (kidney)</td>
</tr>
</tbody>
</table>

Chemoprevention

- Capecitabine (Xeloda)
  - Oral chemotherapeutic agent
  - Antimetabolite (Pyrimidine Analog)
  - May reduce number of new cSCC’s and improve existing lesions
  - Moderate to severe SE’s may necessitate dose reduction or discontinuation

### Prognostic significance of high-risk clinical and histologic features of SCC in organ transplant recipients

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Five-year recurrence rate (%)</th>
<th>Five-year metastatic rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large size (&gt;2 cm)</td>
<td>15.2</td>
<td>30.3</td>
</tr>
<tr>
<td>High-risk location (ear, lip, scalp, temple)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear</td>
<td>18.7</td>
<td>11</td>
</tr>
<tr>
<td>Lip</td>
<td>10.5</td>
<td>13.7</td>
</tr>
<tr>
<td>Tumor depth (&gt;2 mm Breslow depth)</td>
<td>17.2</td>
<td>45.7</td>
</tr>
<tr>
<td>Recurrence</td>
<td>23.3</td>
<td>30.3</td>
</tr>
<tr>
<td>Poor differentiation</td>
<td>28.6</td>
<td>32.8</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>47.2</td>
<td>47.3</td>
</tr>
</tbody>
</table>


### Cutaneous squamous cell carcinoma of the head and neck TNM staging AJCC UICC 8th edition

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>T category</th>
<th>T criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Primary tumor cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumor smaller than or equal to 2 cm in greatest dimension</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumor larger than 2 cm, but smaller than or equal to 4 cm in greatest dimension</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumor larger than 4 cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion*</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion</td>
<td></td>
</tr>
<tr>
<td>T4s</td>
<td>Tumor with gross cortical bone/marrow invasion</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor with skull base invasion and/or skull base foramen involvement</td>
<td></td>
</tr>
</tbody>
</table>

* Deep invasion is defined as invasion beyond the subcutaneous fat or >4 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.
Comparison of squamous cell carcinoma staging systems

<table>
<thead>
<tr>
<th>American Joint Committee on Cancer 7th Edition</th>
<th>American Joint Committee on Cancer 8th Edition</th>
<th>Brigham and Women’s Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Stage Risk factors</td>
<td>T Stage Risk factors (head and neck only)</td>
<td>T Stage Risk factors</td>
</tr>
<tr>
<td>T1 Tumor ≥2 cm with ≥2 high-risk features</td>
<td>T1 Tumor diameter ≥2 cm</td>
<td>T1 No high-risk features</td>
</tr>
<tr>
<td>T2 Tumor ≥2 cm or tumor of any size with ≥2 high-risk factors</td>
<td>T2 Tumor diameter ≥2 cm and &lt;4 cm in greatest dimension</td>
<td>T2a T2b 1 high-risk feature 2=3 high-risk features</td>
</tr>
<tr>
<td>T3 Tumor with invasion of maxilla, mandible, orbit, or temporal bone</td>
<td>T3 Tumor diameter ≥4 cm, or minor bone erosion, or perineural invasion or deep invasion</td>
<td>T3 ≥4 high-risk features</td>
</tr>
<tr>
<td>T4 Tumor with invasion of skull or perineural invasion of skull base</td>
<td>T4 Tumor with gross cortical bone/marrow invasion</td>
<td>T4 Not applicable</td>
</tr>
</tbody>
</table>

a - AJCC7 high-risk features: depth (>2 mm thickness; Clark level ≥IV), perineural invasion, location (primary site ear or nonglabrous lip), and differentiation (poorly differentiated or undifferentiated).

b - BWH high-risk factors: tumor diameter ≥2 cm, invasion beyond subcutaneous fat, poorly differentiated, and perineural invasion.

Management

• Prevention
  – UV protection
    • Broad brimmed hats
    • Long sleeve shirts and pants with UPF
    • Sun glasses with UV protection
    • Sun screen
    • Lip balm with SPF
    • Seek shade
    • Avoid sun from 10am-4pm
    • Avoid tanning beds

Management

• Actinic keratoses
  – Local destructive therapies
    • Cryotherapy
    • Electrosurgery
    • Curettage
    • CO2 laser
Management

• Actinic keratoses
  – Field Therapies
    • Fluorouracil
    • Imiquimod
    • Ingenol mebutate
    • Photodynamic Therapy

Management

• Squamous cell carcinoma
  – Most common cutaneous malignancy in OTR
  – More likely to manifest as aggressive disease when compared to immunocompetent patient
Management

• Squamous cell carcinoma
  – The SCC recurrence rate was substantially higher among organ transplant recipients than immunocompetent patients (13 versus 2 percent).
  – Histopathologic features associated with aggressive behavior, including deep tissue involvement, perineural invasion, and lymphatic invasion, were more common among transplant recipients than among immunocompetent patients.
  – In contrast, no difference in the clinical behavior of BCC was noted between the two groups.


Management

• Squamous Cell Carcinoma
  – For metastatic disease, 3 year disease specific survival was 29%.
  – Once detected, prompt appropriate management of early SCC is essential.

**Management**

- Squamous Cell Carcinoma

**Management**

- SCC - High Risk Features
  - Location in the "mask areas" of face, genitalia, hands, and feet
  - Large size – ≥10 mm on scalp, forehead, cheeks, neck or pretibial area; ≥20 mm on trunk or extremities
  - Indistinct borders
  - Rapid growth
  - Recurrent lesion
  - Lesion in site of chronic inflammation or prior radiation therapy
  - Presence of neurologic symptoms
  - Histology
  - Poorly differentiated
  - Acantholytic (adenoid), adenosquamous, desmoplastic, or metaplastic (carcinosarcomatous) histopathologic subtypes
  - Perineural, lymphatic, or vascular involvement
Management

- BCC/SCC – Treatment of primary disease
  - ED&C
  - Excision
  - Mohs Surgery
  - Radiation Therapy

Management

- Melanoma
  - Excision
  - Sentinel lymph node biopsy
Management

• Kaposi Sarcoma
  – Reduce immunosuppression
  – Consider changing cyclosporine to sirolimus


Management

• Merkel Cell Carcinoma
  – Excision
  – Radiation Therapy
  – Reduce immunosuppression

### Epidemiology

<table>
<thead>
<tr>
<th>Current U.S. Waiting List</th>
<th>All Organs</th>
<th>Kidney</th>
<th>Liver</th>
<th>Pancreas</th>
<th>Kidney / Pancreas</th>
<th>Heart</th>
<th>Lung</th>
<th>Heart / Lung</th>
<th>Intestine</th>
</tr>
</thead>
<tbody>
<tr>
<td>All States</td>
<td>116,461</td>
<td>96,556</td>
<td>14,189</td>
<td>913</td>
<td>1,692</td>
<td>3,989</td>
<td>1,374</td>
<td>43</td>
<td>273</td>
</tr>
<tr>
<td>Virginia</td>
<td>2,499</td>
<td>2,116</td>
<td>161</td>
<td>40</td>
<td>32</td>
<td>181</td>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>