Physician Opinion Survey Relating to Skin Cancer Evaluations in Immunosuppressed and Transplant Patients

A study to investigate the importance and frequency of skin cancer screening among transplant and immunosuppressed patients.

Background

Nonmelanoma skin cancer (NMSC) is the most common malignancy in immunosuppressed patients. Specifically, in transplant patients squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) account for 95% of the skin cancers. There is a 65 fold increase in incidence of squamous cell carcinoma and a 10 fold increase in incidence of basal cell carcinoma in organ transplant recipients overall. Among the patients that develop NMSC 25% will develop a second in 13 months and 50% will develop another in 3.5 years. Cardiothoracic and kidney recipients have an incidence of NMSC three times that of liver recipients. Additionally, heart and lung transplants have a higher risk of SCC development than kidney recipients due to more intense immunosuppression in the cardiothoracic group. Heart transplant recipients also develop proportionally more BCCs than kidney transplant recipients.

The increased incidence of NMSC is considered to be due to two reasons. First, the agents themselves are directly carcinogenic. For example, cyclosporine upregulates tumor growth factor β (TGF-β) and binds to the cyclophilin D receptor in the mitochondria inhibiting UVA damaged keratinocytes from undergoing apoptosis. Azathioprine is associated with the greatest increase in the development of skin cancer. Secondly, the chronic immunosuppression creates an environment where immune surveillance and eradication of precancerous change, including p53 tumor suppressor gene mutations and thymidine dimers, are impaired. NMSC is more aggressive and has higher rates of recurrence and metastasis in immunosuppressed patients. The tumors are more likely to infiltrate deeper, involve adjacent perineural and lymphatic structures and have a higher risk of metastasis when compared to NMSC in the general population. There is also a subset of patients who develop extremely aggressive and life threatening skin cancers as shown by an Australian study where 37% of heart transplant patients died due to aggressive cutaneous malignancies, most frequently poorly differentiated squamous cell carcinoma. In the general population the risk of SCC metastasis is 0.5-5%. This increases to 5-7% in organ transplant recipients. In this patient population, metastatic NMSC is often fatal. For example the Cincinnati Transplant Tumor Registry had 5.4% patients die as a direct consequence of skin cancer and an Australian study had 27% of deaths directly due to skin cancer within four years post transplant. A Swedish cohort found the principal site of metastasis to be the parotid gland with a highly increased mortality risk when compared to the general population, standardized mortality ratio of 52.2 (95% CI 21.0-107.6). The significant increase in NMSC negatively impacts the patient’s quality of life and may lead to higher anxiety levels if the patient experiences numerous nonmelanoma skin cancers.

There are well defined risk factors that place a patient at even higher risk for skin cancer. Those include Fitzpatrick skin type I to III, duration and level of immunosuppression, cumulative sun exposure, history of squamous cell carcinoma prior to transplant, pre-transplant end organ disease and increasing age at transplantation.

Integrating dermatologists into the transplant team is essential to prevent the detrimental effects of nonmelanoma skin cancer in transplant patients. This would allow for pre-transplant screening, continual surveillance, early and effective treatment, administration of chemophrophylaxis both systemically and topically, appropriate supervision of aggressive skin cancers, and evaluation for the need of sentinel lymph node biopsy. Dermatologist visits for a total body skin examination would be performed at regular intervals. Communication, collaboration and strategic development of a plan to decrease immunosuppression become streamlined. It is cost effective, and convenient for the patient. Patient education regarding daily sunscreen application, appropriate sun protective clothing, hats and monthly self examinations would be provided at each visit. Thus, patient adherence would be significantly improved if a dermatologist is integrated into the transplant team. A patent registry can be created and maintained to capture outcome data. Most importantly, the patient’s quality of life will be improved as early pre cancers are appropriately treated and many skin cancers are prevented.

Dermatologists can be integrated into the transplant team in three ways: adding a dermatologist to the transplant multidisciplinary clinic, designating dermatology transplant subspecialty clinics where all the transplant patients are referred, and finally, integrating all transplant recipients care within an onsite, local or regional dermatology clinic. A recent study found that only 39% of the United Kingdom renal transplant centers offered full skin exams and 81% of those exams were performed by nondermatologists. In contrast, 61% of the renal transplant centers offer full skin exams and 40% of those exams were performed by nondermatologists. There are a few centers in the United States with dermatology integrated into the transplant teams. Mayo, Yale and Emory are at the forefront of dermatologic care in transplant patients. Given the significantly increased
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morbidity and mortality from nonmelanoma skin cancer, the paucity of transplant centers with integrated dermatologic care has to be considered unacceptable. Dermatologists need to be an integral part of every transplant team.

We aim to determine the opinions of physicians who treat immunosuppressed and/or transplant patients regarding skin cancer and skin cancer screening. We hypothesize that transplant/immunosuppressed patients are not being adequately and routinely evaluated by dermatologists. We will determine the barriers to skin cancer screening and provide suggestions to eradicate the identified barriers. Our goal is to inspire preventative care, early intervention and the appropriate administration of prophylactic regimens against skin cancer, all of which can be accomplished by integrating dermatologists into transplant teams.

Objectives/Outcomes

1. To determine the frequency in which transplant and immunosuppressed patients are sent to dermatologists.
2. To ascertain barriers to dermatologic care in transplant and immunosuppressed patients.
3. To determine the frequency of skin cancer education provided by physicians who provide care to transplant and immunosuppressed patients.
4. To determine the referral patterns of physicians who care for transplant and immunosuppressed patients.
5. To determine the percentage of physicians who believe universal skin cancer screening is indicated among transplant/immunosuppressed patients.
6. To assess the physician awareness regarding the increased incidence of skin cancer among transplant/immunosuppressed patients.
7. We envision that this study will highlight the need for integration of dermatologist into the transplant team to allow for proper skin cancer screening, preventative measures and effective treatment.

Study design and Facilities
A web-based survey focused on skin cancer in transplant and immunosuppressed patients was created and will be distributed to all currently practicing bone marrow and solid organ transplant oncologists at Baylor University Medical Center, Dallas, Texas, USA, the medical oncologists at Texas Oncology, Dallas, Texas, USA and the transplant physicians in Texas and Oklahoma through United Network for Organ Sharing.

Recruitment
Bone marrow transplant, medical oncologists and solid organ transplant physicians will be invited to participate.

Inclusion criteria
Physicians who treat bone marrow, solid organ transplant or chronically immunosuppressed patients.

Exclusion criteria
Physicians who do not treat bone marrow, solid organ transplant or chronically immunosuppressed patients.

Statistical Methods
Statistical analysis will be performed with SAS (v9.3). Aligned with the objectives of the study, estimation methods will bet he focus of the analyses—principally estimation of proportions. Exact confidence intervals will be calculated for each estimated proportion, and, where appropriate, weighting will be employed to adjust for differential response rates. Subgroup comparisons will also be carried out, and Chi squared tests will be used to determine differences between subgroups with respect to categorical outcomes, and t-tests with respect to continuous outcomes. The demographic data will be evaluated and statistically described. A fully adjusted logistic regression model will be used to determine the association of relevant demographic covariates on the binary outcomes. Secondly backward selection will be performed on the fully adjusted model to determine important predictors of screening status. Variables which gained or lost significance as a result of the model will then be assessed further for possibility of confounding or effect modification.

Assessment

1. Demographics recorded (Appendix 1)
   1. Age
   2. Sex
   3. Physician type and setting of fellowship training (academic vs. community)
   4. Number of years practicing
   5. Number of transplant patients treated monthly
   6. Number of immunosuppressed (excluding transplant) patients treated monthly
2. Physician Assessment (Appendix 2)
   1. Physician general questionnaire
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2. Bone Marrow Transplant Physician Only questions
3. Solid Organ Transplant Physician Only questions
4. Medical Oncologist Only questions

3. Data Analysis
   a. Estimation of proportions with exact confidence intervals, potentially weighted to adjust for differential response.
   b. A logistic regression model will be created using SAS v. 9.3 to determine the barriers associated with skin cancer screening in transplant and immunosuppressed recipients.

Investigators and Qualifications
Dr. Amanda Abramson, MD, Dermatology Resident, Baylor University Medical Center
Dr Alan Menter, MD, Dermatology Department Chair, Baylor University Medical Center
Dr Steve Paulson, MD, Oncology Attending, Chairman of Texas Oncology
Dr. Alan Miller, MD, Chief of Oncology and Baylor Sammons Cancer Center Medical Director
Dr. Edward Agura, MD, Bone Marrow Transplant Chairman
Dr. Goran Klintmalm, MD, Chairman of the Baylor Regional Transplant Institute
Appendix 1: Demographics

ID# ________________________________

Date _____ / _____ / _____

Month     Day     Year

Gender     ☐ Male    ☐ Female

In which age range do you fall?
☐ 20-30 years old
☐ 31-40 years old
☐ 41-50 years old
☐ 51-60 years old
☐ 61-70 years old
☐ Above 71 years old

How large was the city in which you completed your fellowship?
☐ <50,000
☐ 50,000-500,000
☐ >500,000

What type of institution was it?
☐ Academic center
☐ Community program
☐ Combination of Academic and Community

Physician Type
☐ Solid organ transplant Surgeon
☐ Bone marrow transplant physician
☐ Surgical Oncologist
☐ Medical Oncologist
☐ Hepatologist
☐ Nephrologist
☐ Cardiologist
☐ Pulmonologist
☐ Other _________________________

Number of years practicing the above specialty?
_______ Years

How many transplant patients do you see monthly?
_______ Patients

How many oncology patients do you see monthly?
_______ Patients

What % do you consider immunosuppressed (not including transplant) patients?
☐ 0-10%
☐ 11-30%
☐ 31-50%
☐ 51-80%
☐ 81-100%
Appendix 2: Physician Survey

1. Do you have your transplant or oncology patients see a dermatologist for skin cancer screening prior to transplant or chemotherapy?
   - [ ] Never
   - [ ] 25% of the time
   - [ ] 50% of the time
   - [ ] 75% of the time
   - [ ] Always

2. Do you routinely screen the patient’s skin during each office visit?
   - [ ] No
   - [ ] Yes

3. Do you refer all your transplant or other immunocomprised patients to the dermatologist as part of your post transplant protocol?
   - [ ] No
   - [ ] Yes

4. How frequently do you send your patients to a dermatologist after the patient has received their transplant or began immunosuppression?
   - [ ] Never
   - [ ] 25% of the time
   - [ ] 50% of the time
   - [ ] 75% of the time
   - [ ] Always

5. After the initial referral, do you follow up with the patients to ensure their compliance?
   - [ ] Yes
   - [ ] No
   - [ ] I do not refer my patients to dermatology

6. Is skin cancer evaluation an important aspect of the post transplant/chemotherapy care?
   - [ ] No
   - [ ] Yes

7. Do you agree that skin cancer is an aggressive disease in transplant/immunosuppressed patients?
   - [ ] No
   - [ ] Yes

8. Are your patients educated regarding sun protection as part of their post transplant care/while they are immunosuppressed?
   - [ ] Never
   - [ ] 25% of the time
   - [ ] 50% of the time
   - [ ] 75% of the time
   - [ ] Always
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9. The following are some noted reasons for NOT referring transplant patients to a dermatologist. Please assign a value between 1 and 5 for each reason. (1= “Has no effect on my decision” and 5= “Highly influential to my decision”)
   - Skin cancer is not a significant issue in my patients
     1 2 3 4 5
   - It is difficult to see a dermatologist
     1 2 3 4 5
   - The patient already has a dermatologist who is taking care of their skin
     1 2 3 4 5
   - Skin cancer is an unavoidable side effect of the transplant, but is worth it
     1 2 3 4 5
   - Cost to patient
     1 2 3 4 5
   - I do a thorough skin examination and do not see a need, I will refer to dermatologist if I find something
     1 2 3 4 5

10. Is there sufficient medical evidence to warrant universal skin cancer screening in transplant patients?
    □ No
    □ Yes

11. Please identify the top two sources that guide your skin cancer screening practices:
    □ Practice Managers/Administration
    □ Center for Disease Control
    □ Societal Guidelines
    □ American Academy of Dermatology
    □ Colleagues
    □ Peer-Reviewed Medical Literature
    □ Media
    □ International Transplant Skin Cancer Collaborative
    □ Other ___________________________

12. The American Academy of Dermatology recommends total body skin examination every three months in solid organ transplant patients with field disease or a history of one non-melanoma skin cancer. Were you aware of this recommendation?
    □ No
    □ Yes

13. Were you aware that solid organ transplant recipients have a 65% times increased risk of squamous cell carcinoma compared to non-transplant patients?
    □ No
    □ Yes

14. Have you ever had a patient die as a result of his/her skin cancer as a direct cause of their demise?
    □ Yes
    □ No
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Solid Organ Transplant Physicians Only
1. What is the average amount of time your patients are on the transplant list?
   - [ ] 0-12 months
   - [ ] 13-24 months
   - [ ] 25-36 months
   - [ ] 37-48 months
   - [ ] >48 months

2. Do you routinely follow the patient post transplant?
   - [ ] Yes
   - [ ] No

3. At what interval do you follow the post transplant patients? Enter a 0 if you do not follow your patients post transplant.
   _______________________________________

Surgical and Medical Oncologists, Hepatologists, Cardiologists, Nephrologists, Pulmonologists Only

1. What percentage of your patients do you consider to be immunocompromised?
   - [ ] 0-25%
   - [ ] 26-50%
   - [ ] 51-75%
   - [ ] 76-100%

2. What is the average amount of time your patients are immunosuppressed?
   - [ ] 0-12 months
   - [ ] 13-24 months
   - [ ] 25-36 months
   - [ ] 37-48 months
   - [ ] >48 months
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References