January 2015

Skin Cancer Outcomes As A Function Of Referral Reason In Solid Organ Transplant Recipients

Sakil Chundydyal
Yale School of Medicine, sakil.chundydyal@yale.edu

Skin Cancer Outcomes as a Function of Referral Reason in Solid Organ Transplant Recipients

A Thesis Submitted to the

Yale University School of Medicine

in Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

by

Sakil Chundydyal

2015

Abstract

SKIN CANCER OUTCOMES AS A FUNCTION OF REFERRAL REASON IN SOLID ORGAN TRANSPLANT RECIPIENTS. Sakil Chundydyal, Fang-Yong Li, Oscar R. Colegio, Department of Dermatology, Yale School of Medicine, New Haven, CT.

Purpose of study: The purpose of this study is to examine the reason for referral of Organ Transplant Recipients (OTR) to a specialized dermatology clinic as a predictor of Non Melanoma Skin Cancer outcomes in those patients.

Methods: A retrospective chart study was conducted using the records for current OTR patients referred to a specialized transplant dermatology clinic from 1991 to 2012. The data reasons for referral as well as outcomes in terms of diagnosis of premalignant/malignant cutaneous lesions.

Results: 353 patient records were recorded. 81 patients were diagnosed with a total of 491 premalignant/malignant skin lesions. The reason for referral most closely associated with lesion diagnosis was “lesion of concern/skin cancer”, with 26% of these patients being diagnosed within 6 months, and 50% of them diagnosed over follow-up. 37% of the patients referred for “rash/acne” were diagnosed with BCC within 6 months of referral. 17.8% of patients who are referred for “acne/rash” eventually get diagnosed with malignant/premalignant lesions.

Conclusions: This is the first study to examine the link between the reason for referral of OTR to specialized dermatologic care and patient outcomes. Our results show that despite the well-established increased risk of OTR for skin malignancies, there are still significant delays in timely referrals and eventual diagnoses. A more efficient risk-stratification and referral process will likely lead to better patient outcomes and a decreased tumor burden for these patients.

Acknowledgements

I would like to express my gratitude to Dr Colegio for his invaluable mentorship and expertise throughout this research project.

Statistical expertise and assistance for this project has been provided by Fang-Yong Li from Yale Computational Biology and Bioinformatics.

The Office of Student Research at the Yale School of Medicine was also an invaluable asset throughout the process, providing ample support, guidance and resources to facilitate the undertaking of this research project.

Contents

INTRODUCTION

Presently, there are more than 170,000 solid organ transplant recipients (OTR) living in the US alone[1]. This large number is attributable to significant improvements in transplantation medicine, from surgical advances allowing more transplantations to be carried out successfully, to improved medical management of OTR resulting in their increased survival rates. This is of particular interest to dermatologists, because of OTR's increased risk for skin malignancies, particularly NMSC.

Nonmelanoma Skin Cancers (NMSC) are the most common malignancies in humans[2, 3]. NMSC can be of two types: Basal Cell Carcinoma (BCC), a malignant neoplasm that may derive from hair follicle stem cells, and Squamous Cell Carcinoma (SCC), a malignant neoplasm deriving from epidermal keratinocytes. SCC have a higher potential for metastasis than BCC [2], although BCC can invade locally and cause significant tissue damage. Another difference between SCC and BCC is in their pathogenesis: while BCC are thought to arise de novo, SCC are more likely the result of the evolution of precursor lesions such as Actinic Keratoses (AK) [3]. The latter are neoplasms arising from epidermal keratocytes that become cytologically aberrant after prolonged exposure to UV radiation. Of 165 cutaneous SCCs, Mittelbronn *et al*. found that 82·4% either arose within (26·7%) or in close proximity (55·7%) to AKs[4]. Similarly, Czarnecki *et al*. reported that 72% of SCCs

were contiguous with AKs[5], and in a review of the literature, Glogau concluded that the risk of progression of AK to SCC was 0.025–16%[6]

Organ transplant recipients (OTR) have been shown to have an increased risk for malignancies [8]. Of those, skin cancers are the most frequent [9][8][7][10]. While the prevalence of rare lesions such as melanoma, Kaposi's sarcoma and Merkel cell carcinomas are increased as compared to the general population, NMSC account for 95% of the skin cancers in organ transplant recipients (OTR) [8]

Epidemiology

Risk Factors

OTR share the same risk factors for skin cancers as the rest of the general population. Predisposing factors include light skin, eyes, and hair and tendency to get sunburned. The major carcinogen for the development of NMSC is exposure to UV radiation, especially UVB, as suggested by the fact that lesions almost exclusively occur on sun-exposed areas, and occur more frequently in sunnier countries. In addition to that, it has been shown that even for patients who develop NMSC, sun protection and avoidance after diagnosis of the first lesion decreases the likelihood of subsequent ones [11]. However, an important added risk factor that is specific to OTR is the type, dosage, and duration of immunosuppression.

Age

An important risk factor for development of NMSC in OTR is age. This has been demonstrated both in Kidney Transplant Recipients (KTR) and Heart Transplant Recipients (HTR), where the risk ratio was 12 times higher for patients who received their grafts above the age of 55 when compared to patients who received their grafts before the age of 34[12]. The higher incidence of NMSC in HTR as compared to KTR was originally thought to be due to increased levels of immunosuppression in HTR, but recent data have shown that the older age of most HTR at transplantation is more likely contributory [13] [10] [12]- indeed, the dosages of immunosuppression at the time the first NMSC was diagnosed was similar for both HTR and KTR [11]. It is therefore more likely that the increased incidence of NMSC in HTR is because of the higher age at which HTRs get transplanted compared to KTR.

Time since transplantation

Pharmacologic suppression of the immune system, which is essential to protect the transplant against rejection, increases the risk of developing malignancies, particularly cutaneous one. The duration of immunosuppression is positively associated with the number of NMSC lesions OTR will develop. One piece of evidence for this is that the number of lesions over the same follow-up period tends to be higher in KTR than HTR, [11]- this could be due to the lower age of KTR at transplantation, which means that they will have had a longer period of immunosuppression at the first NMSC diagnosis compared to HTR. The incidence of

NMSC increases steadily with time after transplantation. In the US, and Western Europe, the incidence of NMSC at 2, 10 and 20 years post-transplant increase from 5% to 10-27% to 40-60%, respectively [13-16].

Geography

The incidence of NMSC has been reported to be higher in countries and regions with higher exposure sunlight. In an Australian cohort, the cumulative incidence of NMSC has been reported to be 45% by 10 years after transplantation, and 70% by 20 years post-transplantation[17]. In the UK, by comparison, the mean annual risk for developing NMSC was found to be 3.27% for OTR less than 5 years post –transplant, 5.86% for OTR 5-10 years post-transplant, and 11.1% more than 10 years post-transplantation, which is markedly lower than the Australian cohorts. [15]

Type of transplant

The type of transplant also influences the incidence of NMSC in OTRs. There is evidence that Heart Transplant Recipients (HTR) have a two to fourfold increased incidence of NMSC as compared to Kidney Transplant (HTR) [10], [13] [12]

Type of tumor

The ratio of SCC to BCC is 4:1 in the population at large. This ratio is reversed in OTRs, and this reversal is even more pronounced with decreasing latitude, sun

exposure, and the time elapsed in between follow-up dermatologic appointments. [8], [10].

The considerable acceleration of SCC incidence in SOTR is such that the diagnosis of a first SCC has been shown to be highly predictive of multiple subsequent NMSC within 5 years [11]. Not only do these tumors occur with a higher incidence, they are also clinically more aggressive in OTR than in the general population in terms of growth, local recurrence and metastasis (the rate of metastasis is approximately 8%)[18, 19].

Another important risk factor among OTR is pre-transplant personal history of AK, BCC, SCC or melanoma, which places the patient at a significantly higher risk for developing post-transplant skin cancer[20].

Clinical Features

Clinically, NMSC tend to appear on sun-exposed area about 8-10 years after transplantation, and as described by Bouwes-Bavinck, are often associated with other keratotic lesions that can be confused with SCC, such as Actinic Keratoses, Bowen's disease, and Keratoacanthoma [20]. Multiple Keratotic lesions have been linked with an increased risk for SCC. Patients who have less than 50 keratotic lesions have a 4-fold elevated risk of having an SCC, and patients with greater than 50 keratotic lesions have a 12-fold elevated risk, both compared to patients with no such lesions [20]. This correlation characterizes the concept of field cancerization, in

which sun-exposed areas undergo actinic damage resulting in visible and sub-clinical lesions of epidermal dysplasia.

Compared to BCC, SCC are considered to be more aggressive in terms of growth, recurrence, and ability to metastasize. The rate of local recurrence is 13.4%, and metastasis is 5-8% [21]. A 18.6% rate of extracutaneous tumors has been reported for OTR diagnosed with SCC, which confirms previous reports that OTR diagnosed with skin cancers have a higher overall tumor burden than others [22].

Management of NMSC in OTR

The management of OTR risk for NMSC is best done in a multidisciplinary manner, conjugating the care of the transplant physician with that of a specialized dermatologist. The transplant dermatologist has not only a role to play in the treatment of lesions, but also in preventive education, chemoprophylaxis, and surveillance of OTR to both decrease the incidence, and manage NMSC.

Preventive education

The most important element of patient education for OTR with regard to their skin cancer risk is photo-education. Sun avoidance and protection is the cornerstone of any prevention program. The dermatologist's role in this process is crucial, because several studies have shown that OTR who have a dermatologist involved in their care are more likely to be knowledgeable about and compliant with photoprotection

recommendations. Ismail et al reported that among patients attending their specialist OTR clinic, 98% recalled receiving photo-protection advice and 95% reported regular sunscreen use, compared with 77% and 67%, respectively, for patients who did not have specialized dermatologic care [23]. The dermatologist working in an OTR clinic has an important role to play in encouraging all OTR to apply sunscreen with sufficient sun protection factor daily, instead of only when sun exposure is anticipated, and recommend that OTR avoid sun between the hours of 10 am and 2 pm. OTRs should also avoid artificial exposure to UV radiation (tanning beds) and dress in sun-impermeable clothes shielding their skin from sunlight for optimal protection.

Chemoprophylaxis

The concept of field cancerization was first proposed by Slaughter et al in 1953 to refer to histologically abnormal tissue adjacent to tumor tissue. Environmental carcinogens influence whole areas of the skin surface leading to simultaneous (usually actinic) damage of a large proportion of epithelial cells, thus contributing to premalignant states within the entire exposed surface. The whole area has accumulated enough mutations to be at much greater malignant potential, even after the original tumor has been removed. Therefore, for OTR at high risk for cancer development, these high-risk areas must be eliminated, or at least controlled, nonsurgically[24]. Retinoid derivatives have been investigated and been demonstrated to have some clinical use in preventing NMSC in OTR. Oral acitretin has been shown to decrease the incidence of both AK and SCC in two randomized

controlled trials[25, 26]. The current guidelines recommend adjuvant chemoprophylaxis for OTR at high risk for developing multiple, recurrent and aggressive NMSC[27]. The barrier to chemoprophylaxis is poor compliance due to poor tolerability of systemic retinoid. Patients complain of mucocutaneous xerosis, cheilitis and arthralgia and discontinue therapy. Upon discontinuation of the drug, a rebound effect is observed, where SCC relapses occur. Therefore, chemoprophylaxis should be life-long.

Surveillance

After appropriate photoeducation about sun protection/avoidance and possible chemoprophylaxis, OTR must be followed closely and routinely to screen them for the development of cutaneous malignancies. To that end, a multidisciplinary clinic is considered the best approach, providing maximum efficiency in scheduling appointments and allowing for standardization of follow-up intervals in conjunction with the primary transplant team. It is recommended that all OTR undergo a full body skin exam prior to transplantation to establish a baseline and to determine the initial frequency at which the patient will be seen for screening. At each subsequent visit, the patient must be screened and any lesions treated. In addition to that, the dermatologist has a role to play in educating the OTR in self-examination and monitoring of changing skin lesions. Patients at risk for metastatic skin cancers should be taught to do lymph node self- exams. Such an approach facilitates early detection and treatment of skin cancer, which improves outcomes.

Treatment

Actinic Keratoses, consistent with the concept of field cancerization, represent pre-malignant lesions that have the potential of developing into SCC, and therefore should be managed aggressively with therapies such as cryotherapy, or Electrodessication and Curettage (ED&C). In high-risk patients, it is not sufficient to treat the lesion, but also to use prophylaxis on the potentially malignant surrounding tissue. For this purpose, 5-FU or photodynamic therapy can be used[28].

Squamous Cell Carcinomas are graded into low-risk and high risk, which influences the way they are treated. Factors which make an SCC high-risk include size, multiplicity, recurrence, ulceration, presence of satellite lesion, high-risk location and histology[29]. The options for low-risk SCC include Mohs micrographic surgery, traditional surgical excision, and ED&C for multiple lesions that cannot be excised [24]. High-risk SCC requires more aggressive and early intervention. Mohs micrographic surgery is the treatment of choice; however excision with post-operative margin assessment is also used. Adjuvant radiation therapy can be used for surgical resections where the margins have not been found to be clear of malignancy.

Goals of Study

It has been well-documented that OTR are at an increased risk for cutaneous malignancies. Therefore, a proactive approach is required in managing this health risk, with preventative education, prevention, and surveillance being the cornerstone of morbidity reduction. The optimal management of NMSC risk in OTR requires a multidisciplinary approach, involving the transplant physician and dermatological specialists. A proactive risk reduction model would reduce the morbidity of skin cancers OTR through an optimal referral system whereby OTR who are at highest risk for developing NMSC are referred to dermatologic care for preventative measures and surveillance, in a timely fashion, allowing early prophylactic interventions to decrease the patient's potential tumor burden, as well as early diagnosis and treatment of malignant lesions. Since dermatologists are the most qualified at educating OTR about how to prevent skin cancer, and at diagnosing malignant lesions, OTR should be sent for preventative screening when they are identified to be at risk, rather than after malignant lesions are suspected by a non-dermatologist, leaving no window for prophylaxis. Within such a multidisciplinary clinic model, a key component of care is the referral process from non-dermatologic providers to dermatologic care. The reason for which an OTR is referred by a non-dermatologist for dermatologic care has not been previously studied as a variable that could predict NMSC outcomes.

The aim of our study is to examine the referral process for OTR to be sent for specialized dermatologic care. We hypothesize that the reason for which an OTR is referred for dermatologic care has a significant effect on his/her outcomes in terms of NMSC diagnoses. We will look at the reasons for which OTR are being referred to dermatologic care and compare their outcomes, in order to answer several research questions:

1. What is the referral reason that yields the highest proportion of NMSC diagnoses?
2. Which referral group bears the highest tumor burden?
3. Is the current referral process resulting in missed opportunities for early NMSC prevention/surveillance?

Materials and methods

We conducted a retrospective chart study, using patient records from the Yale Transplant Dermatology Clinic, located in New Haven for patients referred from 2007 to 2012. The clinic specializes in the care of OTR referred by transplant physicians for dermatologic evaluation and works in a multidisciplinary fashion with transplant physicians to manage OTR risk for cutaneous malignancies or other lesions. Upon admission into the clinic, data is recorded by the dermatologist on dedicated input forms containing fields corresponding to factors for developing skin cancer, general medical history, transplant history, as well as reason for referral. A full body skin exam is then performed by the dermatologist during the initial visit. Information about cutaneous lesions found for these patients is also recorded in the paper charts, including biopsy reports, location, and date of diagnosis. Patients referred to the clinic are followed up periodically after initial referral, with follow-up appointments scheduled according to clinical need. The medical records used for the purpose of this study were in paper form.

Data collection took place from May to August 2012, during which 353 patient records were reviewed. The protocol was submitted to the Human Investigations Committee (IRB), and approval was obtained prior to data collection. (protocol #1206010335) Two separate databases were created: the first one contained data from the initial input forms, excluding any patient identifiers to maintain patient

anonymity. The second database was created to record data about NMSC lesions diagnosed on patients. For each AK, BCC, and SCC, an entry was created in the database, containing the date of diagnosis, type of diagnosis and location on the patient's body. AK were diagnosed both clinically and by biopsy, whereas BCC and SCC were always diagnosed using a biopsy. The two databases were linked to allow each NMSC lesion record to be traced back to the subject on whom it was diagnosed.

In order to assess the impact on referral reasons and outcomes, reason for referral was divided into 5 categories, namely "skin screening", "rash or acne", "lesion of concern", "unknown" or "other". "Skin screening" describes referrals where no specific lesion has been identified by the referring provider but he/she deemed that the patient needed specialized dermatological care due to their risk for cutaneous malignancies. "Rash or Acne" describes referrals where a non-malignant lesion has been identified by the referring provider. "Lesion of concern", on the other hand, entails a lesion which the referring provider suspects might be skin cancer. "Unknown" describes patients for which the "reason for referral" field was left empty in the intake form, while "other" describes a referral reason outside of the 4 other categories.

Statistical analysis focused on comparing variables of OTR who ended up being diagnosed with a NMSC with those who did not. Patient variables were summarized as mean and standard deviation for continuous variables, or frequency and percentage for categorical variables. Bivariate analyses were performed to compare

OTR who ended up being diagnosed with malignant/premalignant lesions vas those who never being positive.

Reason for referral was one of the variables compared between the two groups. This analysis enables us to discern which referral reasons were more likely to result in diagnoses of AK, BCC and SCC as opposed to those who are were not.

We also compared the time elapsed between transplantation and first visit for patients who were diagnosed with AK/BCC/SCC and those who remained skin cancer-free throughout their follow-up time. This gives us pertinent information as to how timely referrals might affect skin cancer outcomes.

Similar analyses were carried out to compare OTR who were diagnosed with AK, BCC, SCC within 6 months of their first visit to those who are not. . The reason why we specifically examined these patients was that they would have most likely benefitted from an earlier referral.

We also compared the tumor burden across referral categories. This will allow us to discern any referral groups bearing a disproportionately large tumor burden, which is useful in terms of risk-stratification and targeted interventions to reduce morbidity.

Chi-square test or t test were used as appropriate. All the statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC). Significance level was $p < 0.05$, two-sided.

Results

Age and sex distribution

A total of 353 records were input into the database. 224 were male and 127 female. The mean age was 54.1 (std deviation 15.1).

Demographics	N, (%),
Age*	54.1± 15.1
Gender	
Male	224 (63.5)
Female	127 (36.0)

Table 1: OTR demographics

Transplant History

A majority of the patients (179, or 50.7%) were KTR followed by HTR (82, or 23.2%). There were 55 patients with liver transplants, accounting for 15.6% of the sample. 17 patients (4.8%) had more than 1 transplants. For 16 patients (4.5%), the type of transplant was not recorded.

Transplant Hx	
Transplant type	**N, (%)**
Kidney only	179 (50.7)
Kidney plus other	17 (4.8)
Heart	82 (23.2)
Liver	55 (15.6)
Pancreas	3 (0.9)
Lungs	1 (0.3)
Other/unknown	16 (4.5)

Table 2: Transplant History

Dermatologic History

The majority of patients (273 patients, or 77.3) had no prior dermatologic history upon admission to the clinic. However, 26 patients (7.4%) had a history of BCC, 25 (7.1%) had a history of SCC, and 12 (3.4%) had a history of SCC in situ.

Derm History	N, (%)
No history	273 (77.3)
Hx of AK	27 (7.7)
Hx of BCC	26 (7.4)
Hx of SCC	25 (7.1)
Hx of SCC in Situ	12 (3.4)
Hx of Melanoma	5 (1.4)
Hx of Atypical Nevi	3 (0.9)
Hx of Cutaneous warts	36 (10.2)
Hx of Genital warts	4 (1.1)

Table 3: Dermatologic History

Reason for referral

The referral reason was recorded for most patients, with only 4 patients (0.01%) with missing referral information. The most common reason why patients were referred to the clinic was for skin screening (159 patients, 45%), followed closely by "Rash/Acne" (140 patients, or 39.7%). There was a considerable group referred for lesion suspicious for cancer (34 or 9.6%).

Reason for referral	N, (%)
Skin screening	159(45.0)
Rash/Acne	140(39.7)
Lesion of concern	34 (9.6)
Unknown	4 (0.01)
Other	1(0.0)

Table 4: Reason for referral

NMSC diagnoses

Among the 353 patients, 81 were diagnosed with one or more malignant/premalignant lesions. 50 (14.2%) were eventually diagnosed with one or more AK, 44 (12.5%) were diagnosed with one or more BCC, and 70 (19.8%) were diagnosed with one or more SCC.

Lesion	N (%)
AK	50 (14.2)
BCC	44 (12.5)
SCC/SCC in situ	70 (19.8)

Table 5: NMSC diagnoses

As shown in table 5, 19 patients were diagnosed with AK within 6 months of their first visit to the clinic. 16 were diagnosed with BCC, 12 with SCC and 11 with SCC in situ.

Lesion	N (%)
AK	19 (5.3)
BCC	16 (4.8)
SCC	12 (3.4)
SCC in situ	11 (3.1)

Table 6: diagnoses within 6 months of referral

Exclusion of certain data fields

Some variables were collected from the intake forms, e.g. family history of cancer, use of sun barriers/sunscreen had many missing values due to the information not being present on the forms, and therefore were excluded from data analysis. Those variables were not directly related to our hypothesis and therefore their exclusion did not have a significant impact on the study.

OTR who develop malignancies *versus* others:

Bivariate analysis was performed to compare OTR who ended up being diagnosed with NMSC with those who never get diagnosed. This allowed us to correlate specific variables with subsequent diagnosis of NMSC.

Reason of referral	**AK positive (%)**	**BCC positive (%)**	**SCC/SCC in situ positive (%)**	**Negative (%)**
p value	P=0.0002	P=0.001	P=0.001	
N	50	44	52	272
Referral categories				
Skin screening	20 (40.8%)	15 (34.1%)	18 (35.3%)	123 (47.1%)
Rash or Acne	15 (30.6%)	17 (38.6%)	16 (31.4%)	115 (44.1%)
Lesion of concern or skin cancer	13 (26.5%)	11 (25.0%)	15 (29.4%)	17 (6.5%)
Unknown	1 (2.0%)	1 (2.3%)	1 (2.0%)	6 (2.3%)
Other			1 (2.0%)	

Table 7: comparing OTR who get diagnosed v/s those who do not

The data in table 7 can be used to assess which referral reasons were more likely to yield positive diagnoses for the lesions listed (AK, BCC, SCC). The percentages in brackets indicate the distribution of referral reasons for patients diagnosed with a particular lesion. For example, 40.8% of patients who got diagnosed with AK were referred for skin screening, as compared to 47.1% who were without any malignancy referred for same reason. From the table, it is clear that patients who end up being diagnosed with AK/BCC/SCC were more likely referred due to lesion of concern/skin cancer, who only made up 6.5% of patients who were negative for such lesions.

OTR who are diagnosed with malignancies within 6 months of initial visit *versus* those who are not

	AK diagnosed within 6 mo (N, %)	BCC diagnosed within 6 mo(N, %)	SCC/SCCIS diagnosed within 6 mo (N, %)	No NMSC diagnosis in first 6 months
Total number	19	16	19	272
Skin screening	9 (47.3)	5 (31.3)	8 (42.1)	123 (47.1)
Rash/Acne	3 (15.8)	6 (37.5)	3 (15.8)	115 (44.1)
Lesion of concern/skin cancer	7 (36.8)	4 (25.0)	7 (36.8)	17 (6.5)
Unknown	0	1 (6.2)	1 (5.3)	6 (2.3)
Other	0	0	0	

Table 8: Comparing OTR who had an early NMSC diagnosis vs those who did not

The above table shows the comparison of patients who were diagnosed with NMSC within 6 months of referral v/s those who aren't. Of the 50 patients who were

diagnosed with AK at the clinic, 19 (38%) had their AK diagnosed within 6 months of their initial visit at the clinic. Of the 44 patients who were diagnosed with BCC during their followup, 36.3%, were diagnosed within 6 months of referral, and of the 52 patients diagnosed with SCC/SCC in situ, 44% were diagnosed within 6 months of referral.

Patients diagnosed with a lesion within 6 months were mostly likely to be referred for "lesion of concern/Skin cancer" comparing to those no NMSC diagnosed in first 6 months,, since those referrals made up only 6.5% of the "lesion negative" group, while making up 36.8% of AK diagnoses ($p<0.001$), 25% of the BCC diagnoses ($p=0.03$) and 36.8% of the SCC diagnoses ($p<0.001$). It is however interesting to note that a considerable proportion of cancerous or pre-cancerous diagnoses were made within 6 months for patients who were referred for rash/acne (non-cancer referral), particularly for BCC. These patients made up 37.5% of those who were diagnosed with a BCC within six months, making them the most represented referral reason for early diagnoses of BCC.

A total of 3 patients were diagnosed with an invasive form of skin cancer (BCC/SCC), who had been referred for Rash/Acne. This is a concerning finding, because these skin cancer diagnoses are incidental, reflecting the fact that these patients would have benefitted from a timelier referral.

Tumor Burden

For the purpose of our study, we define the tumor burden as the number of malignant/premalignant lesions diagnosed, including AK, BCC and SCC. The total number of AK lesions diagnosed for the patients was 192, total number of BCC was 106, while the total number of SCC/SCC IS is 193. Therefore the SCC:BCC ratio in our sample is 2.79.

Reason for referral/Lesion	AK N/n=192/50	BCC N/n=106/44	SCC/SCC In situ N/n=193/52
Skin Screening	1.0 (1.0 to 6.0)	1.0 (1.0 to 6.0)	5.0 (3.0 to 8.0)
Acne/Rash	2.0 (1.0 to 14.0)	1.0 (1.0 to 5.0)	5.0 (2.0 to 9.0)
Lesion of concern/Cancer	3.0 (1.0 to 37.0)	3.0 (1.0 to 7.0)	5.0 (2.0 to 22.0)
Other/UK	2.0 (1.0 to 3.0)	8.0	9.0 (6.0 to 10.0)

Table 9: tumor burden (total number of lesions) across reasons for referral

As shown in table 9, patients referred for lesion of concern/skin cancer contributed far more to the tumor burden, across tumor categories (for AK, BCC and SCC) than any other referral reason, even though they only accounted for 9.6% of the sample size. Another noteworthy observation is that even though there were fewer patients referred for Acne/Rash than for Skin Screening (39.7% of total patients vs 45.0% respectively), the tumor burden across both groups is comparable for BCC and SCC, while the Acne/Rash group actually had a higher number of AK diagnoses.

Time between transplant and first visit *versus* lesion diagnosis

Outcomes	Skin screening	Rash or Acne	Lesion of concern or skin cancer	Other (including UK)
Time from transplant to first visit (years)	6.3 (8.5) 3.5 (0 to 66) N=143	5.6 (6.7) 2.6 (0.1 to 34.9) N=125	5.4 (7.1) 2.3 (0 to 27.5) N=31	7.5 (11.6) 1.4 (0.7 to 27.8) N=5
For those no-cancer found	5.4 (7.8) 2.8 (0 to 66) N=110	5.0 (6.2) 1.8 (0.1 to 30.1) N=102	4.8 (5.9) 2.2 (0 to 19.8) N=14	2.7 (3.0) 1.4 (0.7 to 6.1) N=3
For those diagnosed with AK, BCC or SCC	8.9 (10.1) 6.0 (0 to 47.9) N=33	8.4 (8.5) 5.9 (0.2 to 34.9) N=23	5.9 (8.2) 2.3 (0.1 to 27.5) N=17	1.3 and 27.8 N=2

Table 10: Time from transplant to first visit for patients diagnosed with NMSC vs patients negative for NMSC
[Data is presented as mean (SD) upper panel, and median (min, max) lower panel.

Table 10 compares the time elapsed from transplant to first visit. Across referral categories, patients who were diagnosed with AK/BCC/SCC the mean time from transplantation to first dermatological visit is higher than those who are not diagnosed with such lesions. For example, for patients referred for rash/acne, the mean time from transplant to first visit for patients who were diagnosed with a lesion was 8.4 years as opposed to 5.0 years for patients who were not diagnosed with any lesions.

Discussion

Because OTR are treated by multiple physicians and have many comorbid conditions along with their well-established increased risk for NMSC, it is clear that a proactive rather than reactive approach to NMSC prevention, surveillance, and treatment is needed. The multi-disciplinary system of care whereby dermatologic specialists collaborate closely with transplant physicians and surgeons has been described as a superior model for such proactive care to be delivered [29]. Within a multi-specialty context, the referral process is a crucial component of quality of care, because it constitutes the liaison between the different specialties, and specifically in this case, between the non-dermatologist and the dermatologic specialist. Our study is the first, to our knowledge, to examine the reason for referral of patients referred to a multidisciplinary dermatology clinic specializing in the care of OTR and examine its relationship with patient outcomes.

Patient demographics

There were significantly more males in our OTR sample than females (63.5% males). This is not unexpected, since there are more male OTR than females; a study of OTR patients in Queensland Australia had a similar percentage of male patients of 61.3% [30]. The overall incidence of NMSC diagnoses was 22.9%. This number is known to increase with lower latitudes. As comparisons, the cumulative incidence of NMSC in Australian cohorts over 20 years post-transplantation is 70-82%

[31]compared to 30-52% in the UK. Our incidence is lower than the UK cohort[32], but that can be explained by our shorter median follow-up time.

Reason for referral and NMSC diagnosis

Patients referred for "Lesion of concern/Skin Cancer"

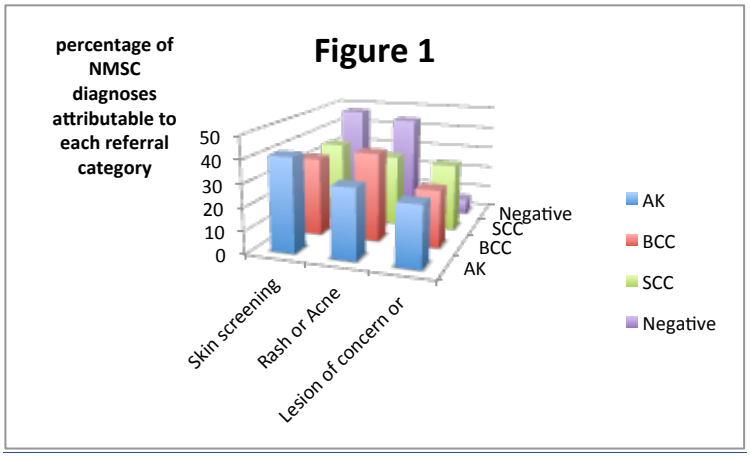

Figure 1: NMSC diagnoses(%) across referral groups (bars for "unknown" and "other" excluded because of very low number of patients in these categories)

Analysis of our data revealed that the referral reason that was most closely associated with cancer diagnoses among OTR was "lesion of concern/skin cancer". Of the 34 OTR who were referred under this category, 17 (50%), were eventually diagnosed with either AK, BCC or SCC. 9 patients (26%) in this category were diagnosed with SCC within 6 months of their first visit, highlighting the urgency with which they needed to be seen. In figure 1, each bar represents the percentage of NMSC diagnoses attributable to each referral category. As expected, "lesion of concern/skin cancer" is the only category where the percentage for "negative"

diagnosis is lower than for AK, BCC, and SCC. This is a graphical illustration of the higher risk for these OTR to be diagnosed with these lesions.

Based on figure 1, in terms of risk-stratification, patients referred for "lesion of concern/skin cancer" constitute a relatively higher-risk group among which diagnosis of NMSC is particularly likely. This is important for two reasons: first, it validates the non-dermatologist's suspicion that a particular OTR is at risk for skin cancer. Second, it raises the concern that these patients should have been referred earlier, for surveillance, in a more proactive, rather than reactive, manner. Indeed, the data in table 7 shows that while this group only makes up 9.6% of our sample size, it bears the largest share of the total tumor burden compared to all the other referral groups. It also bears the largest share of early SCC diagnoses: 26% of patients under this category were diagnosed with an SCC within 6 months of their first visit, as compared to 5.7% of patients who were referred for "skin screening". This highlights the need for better risk-stratification, using current, well-established risk factors for NMSC in OTR, and early referral of those high-risk patients to dermatologic care for effective photoeducation, prevention and surveillance. Numerous studies have shown that both knowledge of the importance of photoprotection and compliance with photoprotective measures are consistently deficient among OTR [33] [34, 35]. Seukeran and colleagues have proposed that these attitudes might be due to the lack of exposure to dermatologic care for those OTR[36]. Several other studies have shown that the intervention of a dermatologist in a multi-disciplinary context is particularly well suited to accomplish effective

patient photoeducation [23]. The data gathered in our study emphasizes the need for earlier intervention in this group of patients, who would benefit from a timelier referral. Effective photoeducation and prevention among this group could achieve a considerable reduction in the overall tumor burden (table 7).

Patients referred for rash/acne

As opposed to OTR referred for "lesion of concern/skin cancer", those under "Acne/Rash" have been referred for lesions that were not suspected to be malignant, indicating a relatively lower level of suspicion for NMSC from the referring provider. 140 OTR in our study fell under this referral category, out of whom 25 (17.8%) ended up being diagnosed with either AK, BCC or SCC. 3 patients in this group were diagnosed with SCC within 6 months of their first visit to the clinic, and 6 were diagnosed with BCC within 6 months of their first visit to the clinic. While those patients constitute a small percentage of the total number of people referred for rash/acne, those early diagnoses are particularly worrisome because NMSC were not suspected in these patients. They might not have been referred to dermatologic care had their referring physician not believed they had a rash or acne, which could have resulted in delayed diagnosis and therefore increased morbidity for these patients. The high proportion (17.8%) of patients referred for a rash/acne who eventually get diagnosed with AK/BCC/SCC during their follow-up at the clinic raises the question of whether these patients should have been more effectively risk-stratified and referred for dermatologic care even in the absence of their rash/acne, for education, prevention, and surveillance. This is further evidenced by

the data in table 10 which shows that for these patients, the time elapsed from transplant to the first dermatological visit is positively associated with an increased risk for them to be diagnosed with AK/BCC/SCC.

Strengths and Weaknesses of the Study

The strength of the study is the large number of OTR followed as well as follow up time (median follow up time is 36 months), which allows us to look at the short and long-term outcomes of patients referred to the clinic. The presence of individual record lesions and pathology reports prevents recall bias for AK/BCC/SCC diagnoses. However, since our study looked at prevalent patients only, we might encounter survivor bias, i.e, if patients with NMSC are more or less likely to die, our patient sample will not be representative of all OTR. Another possible source of bias might stem from our changing awareness about UV exposure and NMSC prevention over the years, and how this information is disseminated to OTR, which might induce bias when comparing patients who had organs transplanted at different points in the past. Lastly, the patient data we collected were from 1 institution only, which might introduce biases specific to that institution or the patient population it serves.

In conclusion, analysis of the electronic medical records of 353 OTR referred to a New Haven, CT Dermatology clinic revealed that 159 of them had been referred for

Skin Screening, 140 for Acne/Rash and 34 for Lesion of Concern/Skin Cancer. The overall incidence of skin cancer amongst those patients was high, at 22.9%, but that number was still lower than published skin cancer rates in OTR in different studies. Further analysis reveals that most of the tumor burden for those patients was borne by the patients referred for lesion of concern, even though they are far less numerous than patients in the other referral categories. Among the 140 OTR referred for acne/rash, 9 were diagnosed with invasive NMSC within six months of their first visit, and 25 were eventually diagnosed with skin cancer over follow-up appointments. These observations lead to the conclusion that despite the fact that risk factors for OTR to develop NMSC are well-documented within the literature, patients are still experiencing delayed or missed referrals to specialized dermatologic care, resulting in sub-optimal outcomes. This paves the way for better risk-stratification and referral strategies to ensure timely and appropriate referrals, which would reduce the overall tumor burden for OTR.

References

1. USDHHS/HRSA/HSB/DOT. *Annual Report of the US Organ producrement and transplantation network and the scientific registry of trnansplant recipients: transplant data 1998-2007, Rockville (MD):* . December 28th, 2014]; Available from: http://www.ustransplant.org.
2. Carucci, J.A., Leffel DJ., *Basal Cell Carcinoma*, in *Fitzpatrick's Dermatology in General Medicine.* 2007, Mc Graw Hill: New York. p. 1036-42.
3. Grossman D, L.D., *Squamous Cell Carcinoma*, in *Fitzpatrick's dermatology in general medicine*. 2007, Mc Graw Hill: New York. p. 1028-36.
4. Mittelbronn, M.A., et al., *Frequency of pre-existing actinic keratosis in cutaneous squamous cell carcinoma.* International Journal of Dermatology, 1998. **37**(9): p. 677-681.
5. Czarnecki, D., et al., *The Majority of Cutaneous Squamous Cell Carcinomas Arise in Actinic Keratoses.* Journal of Cutaneous Medicine and Surgery: Incorporating Medical and Surgical Dermatology, 2002. **6**(3): p. 207-209.
6. Glogau, R.G., *The risk of progression to invasive disease.* Journal of the American Academy of Dermatology, 2000. **42**(1, Part 2): p. S23-S24.
7. Duncan KO, G.J., Leffel DJ, *Epithelial precancerous Lesions*, in *Fitzpatrick's dermatology in General Medicine*. 2007, Mc Graw hill: New York. p. 1007-27.
8. Euvrard, S., J. Kanitakis, and A. Claudy, *Skin cancers after organ transplantation.* N Engl J Med, 2003. **348**(17): p. 1681-91.
9. *<ulrich et al .pdf>.*
10. Ulrich, C., et al., *Comparative epidemiology and pathogenic factors for nonmelanoma skin cancer in organ transplant patients.* Dermatol Surg, 2004. **30**(4 Pt 2): p. 622-7.
11. Euvrard, S., et al., *Subsequent skin cancers in kidney and heart transplant recipients after the first squamous cell carcinoma.* Transplantation, 2006. **81**(8): p. 1093-100.
12. Otley, C.C., et al., *Skin cancer in organ transplant recipients: effect of pretransplant end-organ disease.* J Am Acad Dermatol, 2005. **53**(5): p. 783-90.
13. Fortina, A.B., et al., *Skin cancer in heart transplant recipients: frequency and risk factor analysis.* J Heart Lung Transplant, 2000. **19**(3): p. 249-55.
14. Kasiske, B.L., et al., *Cancer after kidney transplantation in the United States.* Am J Transplant, 2004. **4**(6): p. 905-13.
15. Ramsay, H.M., et al., *Seven-year prospective study of nonmelanoma skin cancer incidence in U.K. renal transplant recipients.* Transplantation, 2007. **84**(3): p. 437-9.
16. Bordea, C., et al., *Skin cancers in renal-transplant recipients occur more frequently than previously recognized in a temperate climate.* Transplantation, 2004. **77**(4): p. 574-9.
17. Bouwes Bavinck, J.N., Hardie DR, Green A et al, *The risk of skin cancer in renal transplant patients in Queensland, Australia. A followup Study.* Transplantation, 1996. **65**(5): p. 715-21.

18. Jensen, P., et al., *Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens.* Journal of the American Academy of Dermatology, 1999. **40**(2): p. 177-186.
19. Martinez, J.C., et al., *Defining the clinical course of metastatic skin cancer in organ transplant recipients - A multicenter collaborative study.* Archives of Dermatology, 2003. **139**(3): p. 301-306.
20. Bouwes Bavinck, J.N., et al., *Keratotic skin lesions and other risk factors are associated with skin cancer in organ-transplant recipients: a case-control study in The Netherlands, United Kingdom, Germany, France, and Italy.* J Invest Dermatol, 2007. **127**(7): p. 1647-56.
21. Ulrich, C., et al., *Skin cancer in organ transplant recipients--where do we stand today?* Am J Transplant, 2008. **8**(11): p. 2192-8.
22. Dantal, J., et al., *Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens.* Lancet, 1998. **351**(9103): p. 623-8.
23. Ismail, F., et al., *Specialist dermatology clinics for organ transplant recipients significantly improve compliance with photoprotection and levels of skin cancer awareness.* Br J Dermatol, 2006. **155**(5): p. 916-25.
24. de Graaf, Y.G., et al., *The occurrence of residual or recurrent squamous cell carcinomas in organ transplant recipients after curettage and electrodesiccation.* Br J Dermatol, 2006. **154**(3): p. 493-7.
25. Bavinck, J.N., et al., *Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study.* J Clin Oncol, 1995. **13**(8): p. 1933-8.
26. George, R., et al., *Acitretin for chemoprevention of non-melanoma skin cancers in renal transplant recipients.* Australas J Dermatol, 2002. **43**(4): p. 269-73.
27. Kovach, B.T., H.H. Sams, and T. Stasko, *Systemic strategies for chemoprevention of skin cancers in transplant recipients.* Clin Transplant, 2005. **19**(6): p. 726-34.
28. Weiss, J., et al., *Effective treatment of actinic keratosis with 0.5% fluorouracil cream for 1, 2, or 4 weeks.* Cutis, 2002. **70**(2 Suppl): p. 22-9.
29. Greenberg, J.N. and F.O. Zwald, *Management of Skin Cancer in Solid-organ Transplant Recipients: A Multidisciplinary Approach.* Dermatologic Clinics, 2011. **29**(2): p. 231-+.
30. Mackintosh, L.J., C.C. Geddes, and R.M. Herd, *Skin tumours in the West of Scotland renal transplant population.* Br J Dermatol, 2013. **168**(5): p. 1047-53.
31. Ramsay, H.M., et al., *Non-melanoma skin cancer risk in the Queensland renal transplant population.* Br J Dermatol, 2002. **147**(5): p. 950-6.
32. Webb, M.C., et al., *Skin tumours posttransplantation: a retrospective analysis of 28 years' experience at a single centre.* Transplant Proc, 1997. **29**(1-2): p. 828-30.
33. Robinson, J.K. and D.S. Rigel, *Sun protection attitudes and behaviors of solid-organ transplant recipients.* Dermatol Surg, 2004. **30**(4 Pt 2): p. 610-5.
34. Donovan, J.C., C.F. Rosen, and J.C. Shaw, *Evaluation of sun-protective practices of organ transplant recipients.* Am J Transplant, 2004. **4**(11): p. 1852-8.

35. Cowen, E.W. and E.M. Billingsley, *Awareness of skin cancer by kidney transplant patients.* J Am Acad Dermatol, 1999. **40**(5 Pt 1): p. 697-701.
36. Seukeran, D.C., C.G. Newstead, and W.J. Cunliffe, *The compliance of renal transplant recipients with advice about sun protection measures.* Br J Dermatol, 1998. **138**(2): p. 301-3.