A Case Controlled Study of Risk factors for Metastatic Squamous Cell Carcinoma in Organ Transplant Recipients: Single Academic Medical Center

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Background/Rationale

Malignancy is the third leading cause of death in solid organ transplant recipients.[1] Currently, cutaneous squamous cell carcinoma (SCC) is the most common neoplasm found in transplant patients and is associated with increased morbidity and mortality. Medication exposures like Voriconazole have also been associated with sun induced changes and phototoxic reactions (Goyal, 2015). Patient factors like age and thoracic transplant (Garret, 2016) are known risk factors for increased mortality from cutaneous squamous cell carcinoma. Prior studies have identified risk factors in metastatic disease such as tumor characteristics like maximum clinical diameter, histologic differentiation and perineural invasion (Brougham, Dennett et al. 2012) as well as head/neck location, older age at transplantation and older age at diagnosis of first cSCC (Genders, Osinga et al. 2018), however, mortality remains unchanged.

OBJECTIVE

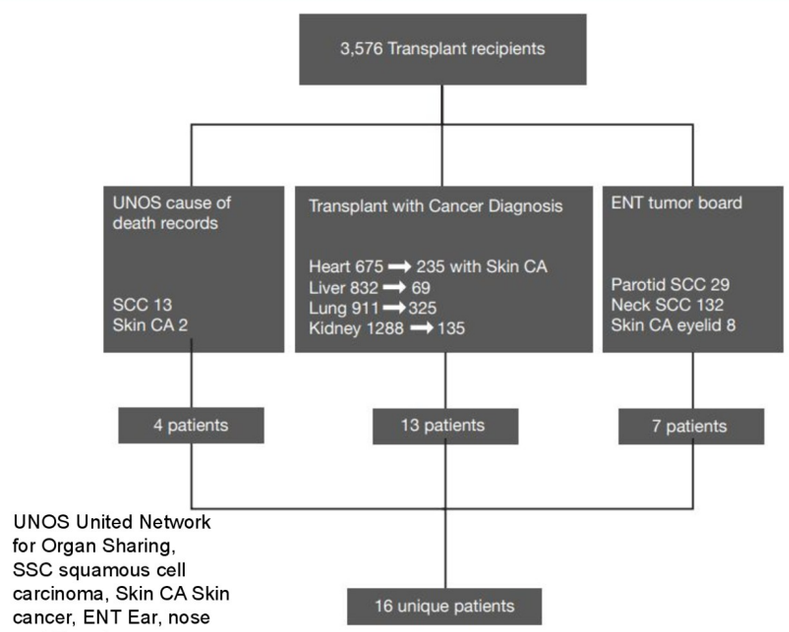
The primary outcome of this study is to investigate potential risk factors for SCC and determine predictive variables for metastasis in the context of solid organ transplant recipients.

The results of this study will enable clinicians to accurately identify transplant patients at an increased risk of MetSCC and decrease mortality in this population.

METHODS

Data from the University of Texas Southwestern Medical Center (UTSW) and the Organ Procurement Transplant Network (OPTN) database identified 3576 cases of heart, lung, kidney, and liver transplants from January 1991 to July 2022.

FIGURE 1 Method for Triangulation of Patients with Metastatic Squamous Cell Carcinoma from Institutional Organ Transplant Recipients



UNOS United Network for Organ Sharing, SSC squamous cell carcinoma, Skin CA Skin cancer, ENT Ear, nose and Throat

Age, organ matched control cohorts: one with a history of SCC but without nodal metastases, and the other patients with no history of SCC. Manual chart review of the charts for predictive factors was performed.

RESULTS

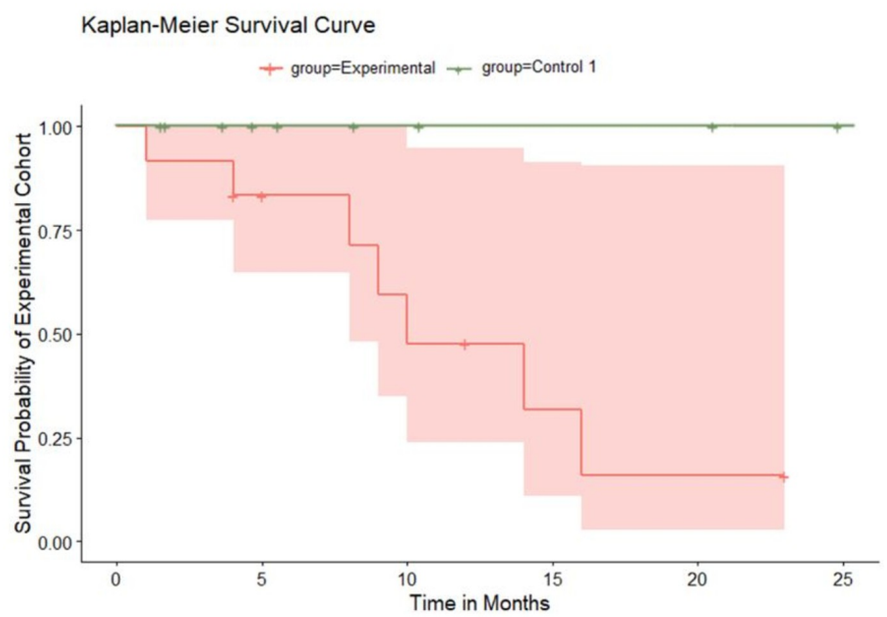
TABLE 1: Characteristics of Patients with Metastatic Squamous Cell Carcinoma

Age at transplant	Transplant	Sex	Race	Years Transplant to Metastasis	Months Metastasis to death	Tumor Location	Tumor Depth (mm)	Location Node Met	Death due to SCC
68	Heart	Male	White	8	8	L ear and neck	79	L neck	Yes
58	Heart	Male	White	17	14	L cheek	Unknown	R neck	Yes
48	Kidney	Female	White	13		R thigh	5	R inguinal	Alive
67	Kidney	Male	White	6		R occipital neck	Unknown	Unknown	Alive
51	Liver	Male	White	5	9	L cheek	7	L parotid	Yes
55	Liver	Male	White	14		Right Occipital scalp	19	R neck	Alive
54	Liver	Male	White	2		L ear	Unknown	L intraparotid and L neck	Alive
52	Lung	Male	White	8	10	Penile shaft	16	R inguinal	Yes
58	Lung	Male	White	11	23	Back	3.9	R axillary	No
57	Lung	Male	White	3	4	R cheek	1	R periparotid	Yes
73	Lung	Male	White	3	1	L ear	Unknown	Cervical	yes
61	Lung	Male	White	6	5	R antihelix	3-4	R Cervical	No
57	Lung	Female	White	3	16	R shoulder	2	R Axillary	Yes
69	Lung	Male	White	3	4	L temple	11	Posterior Parotid	No
54	Lung	Male	White	12	12	R neck	12	R parotid	No
69	Lung	Male	White	8	5	R ear	3	R postauricular	No

L Left, R Right, mm millimeters

MetSCC cohort

- >1% of our institutional cohort developed MetSCC
- Primarily males (88%)
- Average age of 59 years at transplantation
- Over half (62%) lacked a vocational history involving sun exposure
- Average time from transplant to metastatic event was approximately 7 years
- Average 9.8 months from primary excision to metastasis and a subsequent 9.25 months from the metastatic event to death
- Alarmingly, 43% succumbed to MetSCC.



Immunosuppression:

- Patients with MetSCC had significantly lower mean cylex $t(15) = -2.1$, p=0.05 and WBC counts $t(15)= -2.1$, p=0.04 compared to patients with SCC.
- Patients with lung transplants were significantly more likely to develop MetSCC $x^2(12)=41$, p=0.0004.

RESULTS CONTINUED

Cancer and Cancer Treatment history:

- MetSCC cohort more likely to have 5-fluorouracil than nonSCC cohort (OR=9,95%CI [1.5,53.4]).
- MetSCC cohort more likely to have cryotherapy than nonSCC patients (OR=5,95%CI [1.1,22.8]).
- MetSCC cohort more likely to have basal cell carcinoma than nonSCC OTRs (OR=33,95%CI [3.36,323.8]

Drug exposures

- Patients with no history of SCC have significantly lower cumulative doses of Voriconazole $t(15)=2.09$,p=0.04.
- The metastatic cohort had the highest levels of Voriconazole exposure significantly higher than patients no cancer history $t(15)=2.29$,p=0.03.
- MetSCC cohort more likely to be maintained on higher immunosuppression regimen (OR=0.06,95%CI [0.009,0.42]

DISCUSSION

Prior studies have shown Voriconazole exposure and cumulative dose are associated with increased risk of SCC,[2] our study showed patients with no history of SCC have significantly lower cumulative doses of Voriconazole $t(15)=2.09$,p=0.04. The metastatic cohort had the highest levels of Voriconazole exposure, significantly higher than patients with no cancer history $t(15)=2.29$,p=0.03.

Our institutional cohort was in line with Garret et al; our metastatic cohort was largely white men over the age of 50 with lung transplant.[3] The rate of metastasis was lower in our cohort than has been previously reported.[4]

Interestingly our patients with MetSCC had significantly lower mean cylex $t(15) = -2.1$, p=0.05 and WBC counts $t(15)= -2.1$, p=0.04 compared to patients with SCC. These measures of immunosuppression were lower in our metastatic cohort and may be important markers to consider for metastatic disease progression. This has not been previously associated with skin cancer in OTRs.

CONCLUSION

This study highlighted the strong association of MetSCC with lung transplant patients, the short time between primary excision, metastasis and death and the high mortality due to MetSCC. Identification and management of critical factors, including mean cylex levels and rate of immunosuppression as measured by lowest WBC count and medication exposure specifically Voriconazole, emerge as imperative strategies for enhancing outcomes in this vulnerable population.

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