A protocol for skin cancer screening for solid organ transplant recipients based on a single-centre retrospective series in South Australia

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Summary

Long-term survival after organ transplantation is increasing and as a result, health practitioners across multiple disciplines are encountering more patients with complications of transplantation. Immunosuppressive treatment is associated with an increased risk of various cancers, including skin cancers. Regular outpatient dermatological review of solid organ transplant recipients (SOTRs) is routine in South Australia, however at present, no data exists to outline the frequency of review required in a tertiary setting for these patients. We carried out a single-centre retrospective series to examine which transplant recipients were at highest risk of developing skin cancer and at what point in time post transplant. The clinical outcome was to identify a set of patient criteria and recommend a time-effective protocol for dermatology outpatient skin cancer surveillance of SOTRs. Our results support increasing age, time since transplant and male gender as risk factors for the development of skin cancer post solid organ transplantation. Our series did not identify any risk factors for multiple skin cancers, but it did demonstrate that in our SOTR population, nearly 2/3 of those who develop one skin cancer will develop at least a second. Our results also demonstrate over half of second skin cancers occur by 1 year and nearly all within 3 years from the first skin cancer detection. Our results are consistent with a number of larger publications. This study provides evidence to support the current practice of annual full skin examination of all patients following transplantation for the first 8 years post transplantation. Once a skin cancer is detected, follow up every 6-12 months would be an appropriate initial practice, and increased to 3-6 monthly after a second skin cancer occurs.

KEY WORDS: solid organ transplant; screening; surveillance; skin cancer; non-melanoma skin cancer, NMSC.

Introduction

Long-term survival after organ transplantation is increasing and as a result, health practitioners across multiple disciplines are encountering more patients with complications of transplantation. In most cases, adequate graft function requires lifelong immunosuppressive treatment, and the resultant suppression of the immune system is associated with an increased risk of various cancers (1).

Skin cancers are the most common malignant conditions in solid organ transplant recipients (SOTRs) (2) and account for substantial morbidity and mortality in such patients (3). The most common forms of skin cancer in transplant recipients include basal cell (BCC) and squamous cell carcinoma (SCC), melanoma, Kaposi's sarcoma and lymphoma (1, 4). It has been estimated that the incidence of cutaneous SCC in immunosuppressed individuals is 65-100 times over that of the general population and 10 times for BCCs (5, 6). SCCs in these individuals are often more pathologically aggressive with increased risk of loco-regional and distant metastasis (5, 6). SCCs also tend to occur at a younger age with a higher tumor burden in SOTRs (7).

The pathogenesis of skin carcinoma is multifactorial, with extrinsic and intrinsic factors. Ultraviolet radiation appears to be the most important factor, and the highest incidence of skin carcinomas is in countries with high sun exposure, such as Australia (6, 8, 9).Tumors tend to develop in sun-exposed areas and in transplant recipients with a history of high sun exposure after, or even before, transplantation (10-12).

Regular examination and management of premalignant and early malignant lesions leads to early detection and treatment of skin cancers, which decreases associated morbidity and mortality (11, 13). Regular outpatient dermatological review of SOTRs is routine in South Australia. At present, however, no data exists to outline the frequency of review required in a tertiary setting for these patients.

Objective

We examined which transplant recipients were at highest risk of developing skin cancer and at what point in time post-transplant. The clinical outcome was to identify a set of patient criteria and recommend a time-effective protocol for dermatology outpatient skin cancer surveillance of SOTRs.

Methods

Study design
We carried out a single-centre retrospective series on all SOTRs who had been registered with the transplant co-ordinators at Flinders Medical Centre in South Australia. The study was approved by the Flinders Medical Centre Human Research Ethics Committee.

Study setting and population
The data were obtained by analysing case notes of SOTRs reviewed in Dermatology outpatients for full skin examination and review of histology results on the computerised electronic record up until August 2014 or date of death.
287 patients were registered at our centre. Of these 35 were excluded from the series as they did not attend the outpatient department for surveillance. Of the 252 patients included in the series, 208 were reviewed as 44 case notes were unable to be obtained given the high volume of frequent appointments and admissions for these patients as part their clinical care. The study population comprised 142 men and 66 women.

Statistical analysis

Negative binomial regression was used to model the incidence of BCCs and SCCs, with time followed as the exposure. The dependent variable was BCC or SCC count. Cox proportional regression modelling was used for time to first, second and third skin cancer. The independent variables in all models were age at transplant, gender, rural location and transplant type. Results are reported as incidence rate ratios (IRR) or hazard ratios (HR) with 95% confidence intervals (CI). A p-value of less than 0.05 (two-tailed) was considered statistically significant. Descriptive figures were created using Microsoft Excel. All analyses were performed using STATA 14.1 (StataCorp, College Station, Texas).

Results

Of the 208 SOTRs in the study 120 had had renal transplants, 61 liver and 25 heart/lung (or both). There were 2 subjects who received both renal and liver transplants. The median age of the patients at time of first transplant was 45.6 years.
A total of 71 individuals (34%) developed a combined total of 404 skin cancers over a mean follow up period of 42 months (interquartile range 21-93 months). Forty-five (22%) developed multiple cancers (Figure 1). The ratio of SCC to BCC was 2.75:1. One patient developed an atypical fibroxanthoma, which was recurrent, another developed microcystic adnexal carcinoma and 1/3 developed cutaneous lymphoma. No melanomas were detected. The cutaneous lymphoma was included in the analysis.
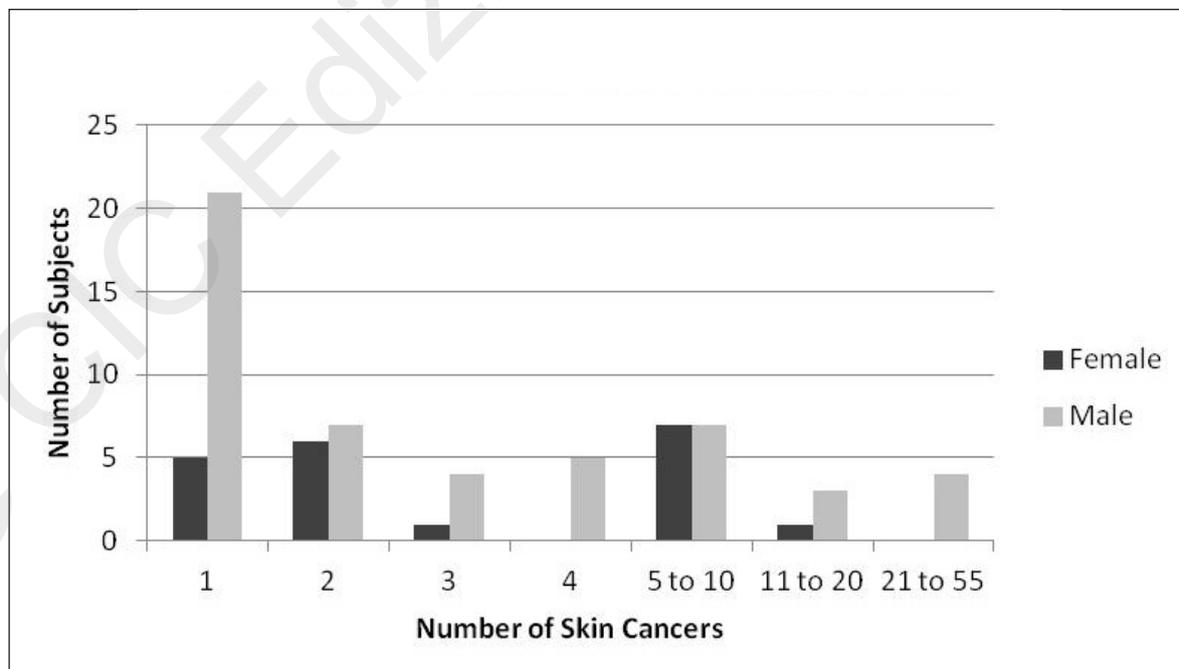

Figure 1 - Number of subjects with one more skin cancers following solid organ transplantation (by gender).
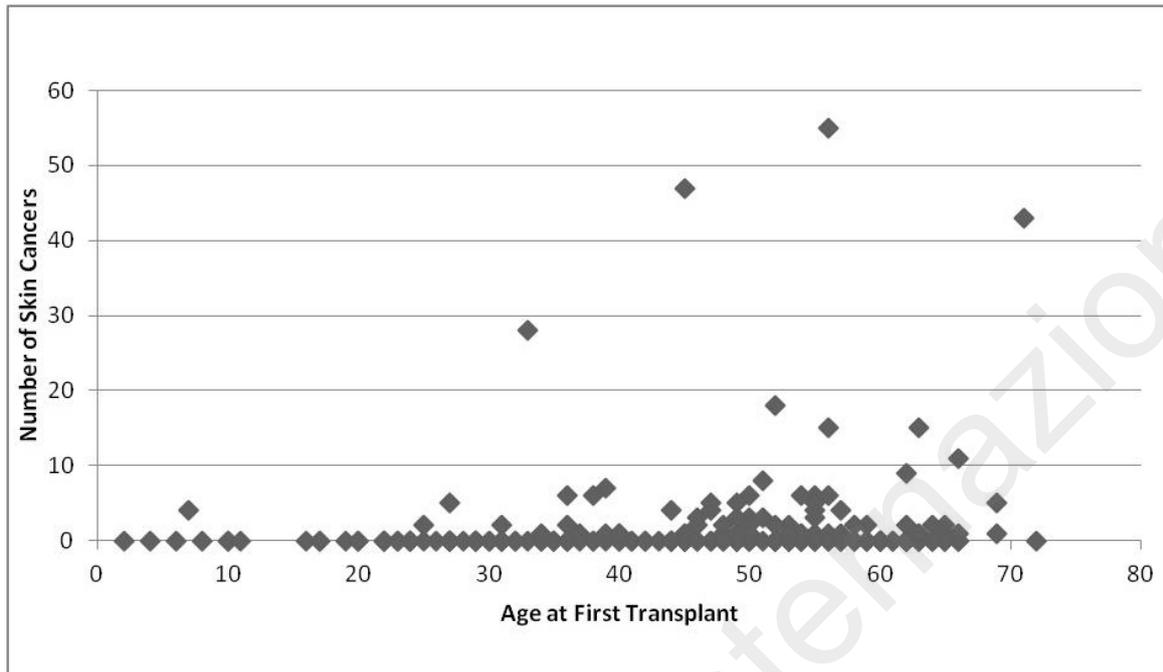
Figure 2 - Number of skin cancers per age at first transplant.

Cox regression analysis demonstrated that type of transplant was not a predictor of skin cancer development but age at the time of first transplant was a significant predictor of skin cancer post transplant. For each additional year of age at time of first transplant, the risk of developing skin cancer increased by 5% HR=1.05 (1.02, 1.08), p<0.001. Figure 2 demonstrates the distribution of skin cancers per age at first transplant.

Negative bimodal regression showed that patients are expected to have 9% more BCCs with each increasing year of age IRR=1.09 (95% CI 1.036, 1.12). SCC risk also increased with age IRR=1.04 (95% CI 1.01, 1.07). Female gender was protective for BCC with women in our study developing 59.5% less BCCs than men IRR=0.41 (95% CI 0.17, 0.97).

Gender did not play a role in the development of SCC. Survival analyses were conducted for time to first, second and third skin cancers. These established that in our study cohort, half of all SOTRs developed a skin cancer within the first 21 years (Figure 3). Median time to first skin cancer was 42 months. Figure 4 demonstrates that of those subjects who developed at least one skin cancer, 50% had done so by 3.5 years and 75% by 8 years.
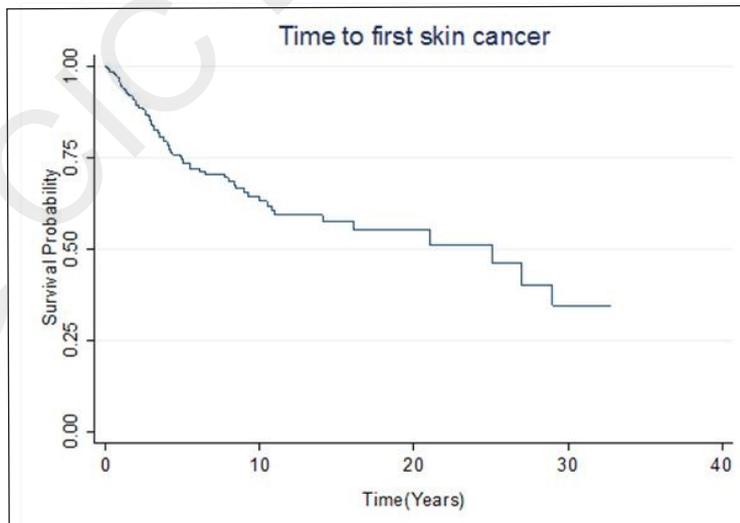

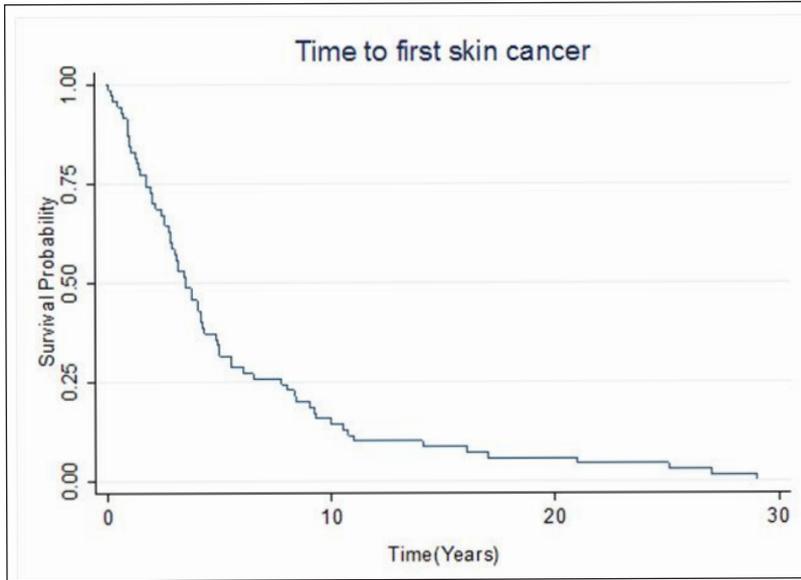Figure 3 - Time to first skin cancer detection for all subjects.

Figure 4 - Time to first skin cancer detection for the subjects who developed a skin cancer.

50% of patients who developed a second skin cancer, did so within 37 months of their initial skin cancer. 75% developed their second skin cancer within 62 months. Median time to second skin cancer was 24 months. Nearly all patients who went on to develop a third skin cancer did so within the subsequent 3 years (50% by 11 months) (Figures 5, 6). Median time to third skin cancer was 10 months. These figures also demonstrate that length of time from transplant increases risk of skin cancer. No significant risk factors for developing second or third skin cancers were identified in our study.

Discussion

Our results support increasing age, time since transplant and male gender as risk factors for the development of skin cancer post solid organ transplantation. European studies have also shown time since transplant (12), male gender (12, 14) and age at transplant in the 6th or 7th decade to be associated with a higher risk of skin cancer development in SOTRs. Other factors identified include multiple tumors at presentation (15) and fair eye, skin and hair colour (15). A Swedish Registry study showed heart and lung transplant recipients are at a higher risk than other organ types (14), however organ type was not found to be a significant factor in our study.

The risk of multiple tumors has been associated with male gender (12) and the number of previous SCCs has been shown to be strongly predictive of subsequent SCCs (14). Our series did not identify any risk factors for multiple skin cancers, but it did demonstrate that in our SOTR population, nearly 2/3 of those who develop one skin cancer will develop at least a second.
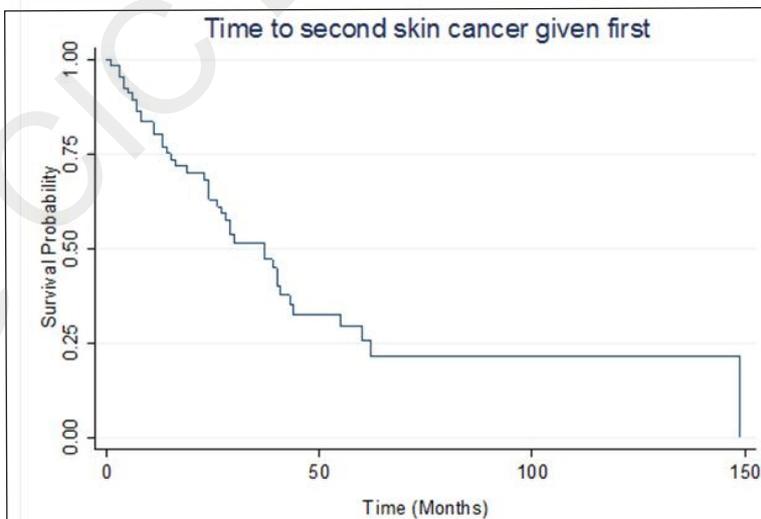

Figure 5 - Time to second skin cancer detection following first skin cancer.
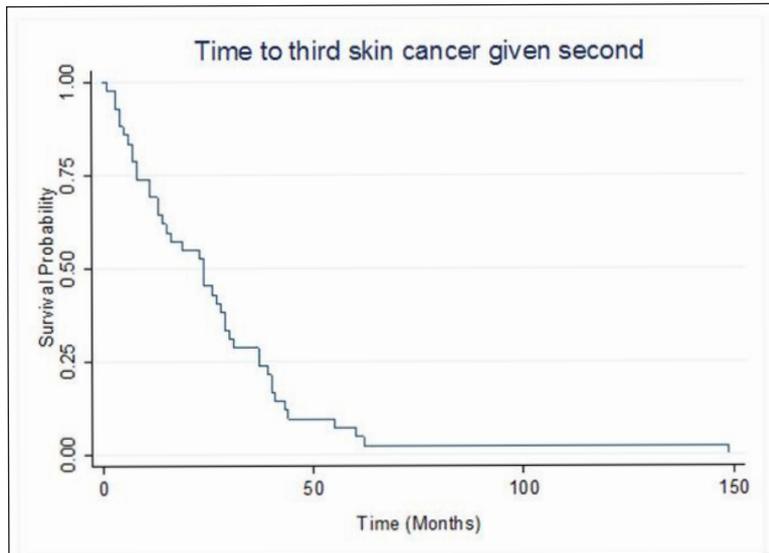
Figure 6 - Time to third skin cancer detection following second skin cancer.

The rate of skin cancer post transplantation varies depending on region. A Northern Californian paper demonstrated prevalence of initial SCC of 81.7% by 5 years (7), whilst a Brazilian publication found a much lower incidence of skin cancer following renal transplantation at 6.67% at just over 3 years (16). In a single-centre south-east Queensland study, Ramsay et al. found that 51.8% of subjects developed skin cancers with cumulative risks of 52.2 and 82.1% at 10 and 20 years, respectively (9), higher than the > 30% 10 year cumulative risk that Ramsay et al. identified in a UK cohort (17). At 5 years post transplant, approximately 25% of our cohort had developed an initial skin cancer, with a total of 34% developing skin cancer during follow up.

Our results have shown that nearly 1/4 of our cohort who developed one skin cancer, went on to develop two or more. A second skin cancer was identified by approximately 5 years in 75% of these subjects, with a median time of 2 years. This is in contrast with results from a Swedish study that found 50% of patients with one NMSC developed a second within 5 years (12), and a French study with 88 -100% of SOTRs (depending on transplant type) developing a second SCC within 5 years (15).

Other studies have not looked into time to third skin cancer in SOTR patients, in which our results demonstrate over half occur by 1 year and nearly all within 3 years from the second skin cancer detection.

It has been suggested that length and strength of immunosuppression increases risk of developing skin cancer in SOTRs due to a combination of decreased immunosurveillance and direct oncogenic effects of some immunosuppressants (6, 15, 18, 19). Immunosuppression was not examined in our study given that the majority of our patients had regimes that were quite variable during their lifetime. It was interesting that in our cohort, most subjects who were transplanted in childhood did not go on to develop multiple skin cancers, despite long periods of immunosuppression. This may be in part due to effective preventative health measures regarding sun protection at an early age. The American Society of Transplantation's protocol suggests annual full skin examinations for all SOTRs and to increase the frequency of surveillance if they have a history of skin cancer (20) Ulrich et al. and Otley et al. suggested more structured schedules of quarterly, biannual and annual reviews stratified by risk assessment based on the presence or history of actinic damage or skin cancer (19, 21).

34% of the subjects in our cohort developed skin cancers suggesting that up to 65% of SOTRs in South Australia do not develop skin cancer. This indicates that the majority of patients (those at low to medium risk) may therefore be adequately monitored in a primary care setting rather than a tertiary centre and referred for rapid review should a skin cancer be found.

A limitation of our study was that a retrospective series and the data obtained were dependant on the quality of documentation during outpatient review. This meant that several variables could not be examined in the statistical analysis, including skin type, personal/family history of skin cancer and sun exposure pre- and post-transplant. Rural location was used as a surrogate marker for sun exposure in our study but was found not to be a significant predictor of risk.

Given our series was conducted retrospectively and at a single centre, we suggest that a similar study should be undertaken prospectively across multiple centres to further identify any extrinsic and intrinsic patient factors that affect the timing of skin cancers in this population, in order to better predict those at highest risk of multiple cancers and at what point post transplant.

Conclusion

Our results are consistent with a number of larger publications. What is novel about our findings is that they elaborate on the timing of skin cancers in SOTRs in Australia. This study provides evidence to support the current practice of annual full skin examination of all patients following transplantation for the first 8 years post transplantation. Once a skin cancer is detected, follow up every 6-12 months would be an appropriate initial practice, and increased to 3-6 monthly after a second skin cancer occurs.

As the numbers of these patients continue to rise, it may be more appropriate for SOTR screening to be integrated into primary health care settings with access to rapid tertiary dermatology support for those patients that develop skin cancer rather than annual screenings in a tertiary centre for the vast majority of patients, as is currently the practice in our state. Tertiary dermatology follow-up could then be ongoing for those patients who have already developed skin cancer, given their increased risk of subsequent NMSC. Such a screening program has the potential to improve continuity of care and facilitate more accurate data collection allowing rapid identification of high risk patients and potentially result in improved patient outcomes.

Given the variation in population demographics and ultraviolet exposure across the world it is unlikely that an adequate overarching global protocol for surveillance of SOTRs can be achieved.

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