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A Surveillance Model for Skin Cancer in Organ Transplant Recipients: A 22-Year Prospective Study in an Ethnically Diverse Population

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Skin cancer is a frequent complication of organ transplantation. Current guidelines advise specialist skin surveillance but there are limited data on how these should be implemented. This study determines overall burden of cancer and relevant intervals for strategic surveillance in an ethnically diverse transplant population. Prospective data on time to first and subsequent cancers and cumulative burden with respect to defined risk factors were analyzed in a cohort of 1010 patients in a UK center over 22 years. Among 931 individuals transplanted >6 months (mean 10.3 years), 1820 skin cancers occurred in 267 (29%) individuals and were multiple in 66%. Cumulative incidence at 5, 10, 20 and 30 years was 11%, 25%, 54% and 74%, with median time to second, third and fourth cancers of 24, 14.7 and 8.4 months, respectively. Tumors were overwhelmingly squamous and basal cell carcinomas (73% and 24%, respectively). Skin phototype, ultraviolet radiation exposure, age at transplant and duration of transplant were significant risk predictors and were used to construct clinically relevant surveillance intervals. This study provides a comprehensive, prospective analysis of skin cancer morbidity and risk in an ethnically diverse transplant population from which we derive an evidence-based skin cancer surveillance program.

Key words: Basal cell carcinoma, melanoma, skin cancer, squamous cell carcinoma, skin cancer prevention, skin cancer surveillance, ultraviolet radiation

Abbreviations: CI, 95% confidence interval; CIS, carcinoma *in situ* (Bowen's disease); HPV, human papillomavirus; KSC, keratinocyte skin cancer; OTR, organ transplant recipient; KTR, kidney transplant recipient; SCC, squamous cell carcinoma; UVR, ultraviolet radiation.

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Introduction

Organ transplant recipients (OTRs) are at significantly increased risk of malignancy compared to the general population (1–4), predominantly for cancers with a known or suspected infectious cause (5–7). Posttransplant cancer patterns differ worldwide; Kaposi sarcoma (KS) is the most common tumor in Saudi Arabia (8) and urogenital cancers and hepatocellular carcinoma in Taiwan (9). In populations of European descent, keratinocyte skin cancers (KSC), comprising squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are overwhelmingly the most common posttransplant malignancies (10). Indeed, cutaneous SCCs were among the first malignancies to be reported in Australian OTR (11). Further reports from the USA, Australia and Europe confirmed a predominance of SCC over BCC and a progressive increase in KSC incidence with duration of immunosuppression (12–15). Ultraviolet radiation (UVR) exposure in sunlight is an important determinant of risk, but other factors contribute (16), including immunosuppressive drugs (e.g. ciclosporin (17–23) and azathioprine (24–27)), host genetic factors(29) and, possibly, human papillomavirus infection (30).

The need for posttransplant skin cancer surveillance has been recognized in many international expert consensus guidelines. In the United Kingdom, the National Institute for Health and Clinical Excellence recommend surveillance in dedicated dermatology clinics (31). Other guidelines in

Europe and the USA also advise specialist full skin examination of OTR every 6–12 months (32–36). However, these recommendations do not take account of individual risk and are thus not adequately tailored to the needs of the practicing dermatologist or physician with limited resources. To date there have been no studies examining practical aspects of their implementation.

This study aims to provide a comprehensive, prospective analysis of skin cancer morbidity and mortality in an ethnically diverse cohort of OTR and to use these data to construct an evidence-based surveillance program for post-transplant skin cancer.

Materials and Methods

Patients

At Barts and the London NHS Trust (London, UK: 56′ latitude), the first kidney transplant was performed in 1968. A specialist skin cancer surveillance clinic was started in 1989. All kidney transplant recipients (KTR) were referred by their transplant clinician and seen within 6–12 months of transplantation by a consultant dermatologist (37). Patients underwent full skin examination and completed a standardized questionnaire detailing cause of organ failure, length of pretransplant dialysis, age at transplant, type of transplant, immunosuppressive drug regimen, family history, past history of skin disease including skin cancer, Fitzpatrick sun-reactive skin phototype (I: always burns/never tans; II: usually burns/sometimes tans; III: usually tans/sometimes burns; IV: always tans/rarely burns; V: Asian; VI: Black), ethnic origin (categorized as white European, Indian subcontinent, Far-Eastern, African-Caribbean, African), country of birth, history of recreational and occupational sun exposure. Patients were then categorized as having high chronic UV exposure (38) if there was a history of an outdoor occupation for longer than 5 years, residence in a sunny climate for over 6 months or more than 11 sunny holidays during which they had sunbathed. All other patients were considered to have low/intermediate exposure unless no information was available. Acute UV exposure (sunburn episodes), was recorded for childhood, adult, pre- and posttransplant and categorized as never, 1–2, 3–5, 6–10 and 11+ episodes. During this initial assessment, patients are provided with verbal and written advice regarding self-skin examination and photoprotection.

At the time of this study, subsequent follow-up was at least annual in patients with no (pre)-skin cancer and at least 3–4 monthly in those with skin cancer. Consultations included full skin examination, treatment of precancerous lesions and diagnostic biopsy or excision of all suspicious lesions. All patients have rapid access to the clinic through a telephone contact service if they are concerned about specific skin lesions between routine consultations.

Data collection

Clinicopathological information was collected prospectively between 1989 and 2006. Outcome data for each primary tumor were available for a further 60 months after the end of the study period (June 2011). Patients excluded were those whose transplant had failed within 6 months of transplantation, or who had less than 6 months follow-up. Patients with a history of skin cancer pretransplantation were analyzed separately. A total of 260 KTR were not seen during the study period; the reasons included death or graft failure, transfer to other institutions, lost to follow-up or declined to attend.

Statistical analysis

The main outcome measure was development of histologically confirmed skin cancer. Differences in the number of tumors, age at transplantation and time to presentation between subgroups were initially compared using Pearson's chi-square test, Student's *t*-test or regression analysis as appropriate. The number of patient-years at risk was calculated from the date of the first lasting transplant to the date of last clinical examination, the date of rejection of the last transplant, or the patient's death. The statistical relationship between incidence of skin cancer and potential risk factors, including age at transplantation, duration of immunosuppression, skin phototype, ethnic origin and UV exposure was evaluated using the log-rank test. Cox proportional hazards regression was used to perform time-to-event univariate and multivariate risk factor analyses. Graphical representations were produced using the Kaplan–Meier estimation. Plots by sex, ethnicity and UV exposure were adjusted for age at transplant; the plot by sunburn was adjusted for age at transplant and skin type.

Risk stratification

Assessing cumulative incidence of skin cancer over time since transplantation, we constructed five risk groups for KSC risk assignment posttransplant, based upon age at transplant, skin phototype and sunburn history. We used this risk stratification to derive a clinical surveillance interval for each group after baseline assessment, which aimed to keep estimated cumulative incidence of KSC below 5%. Analysis of required surveillance intervals was also assessed for patients after the first and subsequent skin cancers. The statistical package used was Stata 10.

Results

Patient characteristics (Table 1)

Of 931 patients examined in this study and transplanted >6 months, 604 (64.9%) were male and 327 (35.1%) female. Mean duration of transplant was 10.3 years (range 0.5–34.4 years), representing 9571 patient years at risk. Mean age at transplant was 41.0 years (range: 7.7–72.2 years).

Overall, 705 patients (75.8%) were white European, with 35 (5.0%) of Mediterranean origin (skin types III and IV from Turkey, Greece, Cyprus and Italy). Almost one-quarter five patients, 24.2%) were non-White: 130 (14.0%) were from the Indian subcontinent, 78 (8.4%) African/African-Caribbean and 17 (1.8%) from the Far East. All non-whites, with the exception of 25 Indian and three African–Caribbeans, were born outside the United Kingdom. There were no significant differences in sex or age at transplantation between ethnic groups. However, mean duration of follow-up was lower for Indian (8.1 years) and African (6.6 years) but not Far Eastern OTRs (12.4 years) compared with white OTRs (11.0 years).

Patients with skin cancer (Tables 2 and 3)

A total of 267 (28.7%) patients developed skin cancer; 178 (66.7%) males and 89 (33.3%) females, mean age at transplant 54.9 years (range: 27.1–77.8 years). The majority were white European (247/267; 92.5%), but skin cancers were also recorded in 5/130 (3.8%) Indian and 2/17 (11.8%) Far-Eastern OTRs. Thirteen of 78 (16.7%) African/African-Caribbean OTRs developed KS (n = 11, 14.1%) and two developed SCC (n = 2, 2.6%).

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Table 1: Clinical characteristics of organ transplant recipients with and without skin cancer

	Number of individuals	Mean follow-up (years)	Number of individuals with skin cancer (%)	Median time to first cancer (years)	Estimated proportion with cancer at 10 years† (%)	Number of individuals with metastatic disease	Number of cancers	Mean rate of cancers per year**
Age at transplant (years)								
<30	238	12.2	38 (16.0)	22.7	4.4	1	209	0.61
30–39	199	11.3	39 (19.6)	24.1	15.0	2	344	1.25
40–49	215	10.2	74 (34.4)	13.8	28.6	6	343	0.69
50–59	201	8.3	85 (42.3)	10.3	47.7	8	658	0.98
≥60	78	7.0	31 (39.7)	7.6	53.7	3	266	1.58
Sex								
Male	604	10.0	178 (29.5)	16.8	26.4	15	1373	1.15
Female	327	10.8	89 (27.2)	20.1	21.7	5	447	0.61
Ethnicity/skin phenotype								
Caucasian/far eastern*								
I	135	10.1	51 (37.8)	12.8	37.4	9	557	1.30
II	229	12.1	98 (42.8)	14.5	32.4	7	778	1.05
III	224	11.0	72 (32.1)	15.5	21.9	3	365	0.84
IV	62	11.1	15 (24.2)	19.2	20.3	0	66	0.70
Missing	66	9.3	*12* (*18.2*)	–	21.2	0	35	0.25
Indian / Far Eastern*								
V	137	8.4	6 (4.4)	–	4.8	0	6	0.00
Black								
VI	78	6.6	13 (16.7)	–	15.1	1	13	0.00
Total	931	10.3	267 (28.7)	17.5	24.8	20	1820	0.96

Of 17 Far Eastern Individuals; 2 skin type II, 1 skin type III, 8 skin type IV, 6 skin type V.
**Mean rate of cancers per year following first cancer in those with at least two years follow-up after the first cancer.
†Sex and ethnicity adjusted for age at transplantation.

Table 2: Number of tumors by cancer subtype*

		Total OTR	Total cancers	SCC	CIS	BCC	Kaposi sarcoma	Other cancers**
Sex	Male	604	1373 (227.3)	740 (122.5)	281 (46.5)	319 (52.8)	11 (1.8)	22 (3.6)
	Female	327	447 (136.7)	192 (58.7)	124 (37.9)	114 (34.9)	4 (1.2)	13 (4)
Skin phototype	I	135	557 (412.6)	310 (229.6)	112 (83)	117 (86.7)	1 (0.7)	17 (12.6)
	II	229	778 (339.7)	415 (181.2)	170 (74.2)	186 (81.2)	1 (0.4)	6 (2.6)
	III	224	365 (162.9)	169 (75.4)	93 (41.5)	98 (43.8)	0 (0)	5 (2.2)
	IV	62	66 (106.5)	20 (32.3)	20 (32.3)	23 (37.1)	1 (1.6)	2 (3.2)
	V	137	6 (4.4)	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)	2 (1.5)
	VI	78	13 (16.7)	2 (2.6)	0 (0)	0 (0)	11 (14.1)	0 (0)
	Missing	66	35 (53)	15 (22.7)	9 (13.6)	8 (12.1)	0 (0)	3 (4.5)
Ethnicity	Caucasian	705	1800 (255.3)	929 (131.8)	404 (57.3)	431 (61.1)	3 (0.4)	33 (4.7)
	Far-Eastern	17	2 (11.8)	1 (5.9)	0 (0)	1 (5.9)	0 (0)	0 (0)
	Indian	130	5 (3.8)	0 (0)	1 (0.8)	1 (0.8)	1 (0.8)	2 (1.5)
	Black	78	13 (16.7)	2 (2.6)	0 (0)	0 (0)	11 (14.1)	0 (0)
Age (years)	<30	238	209 (87.8)	114 (47.9)	53 (22.3)	37 (15.5)	1 (0.4)	4 (1.7)
	30–39	199	344 (172.9)	196 (98.5)	68 (34.2)	76 (38.2)	0 (0)	4 (2)
	40–49	215	343 (159.5)	197 (91.6)	46 (21.4)	92 (42.8)	3 (1.4)	5 (2.3)
	50–59	201	658 (327.4)	278 (138.3)	165 (82.1)	191 (95)	9 (4.5)	15 (7.5)
	≥60	78	266 (341)	147 (188.5)	73 (93.6)	37 (47.4)	2 (2.6)	7 (9)
Total		931	1820 (195.5)	932 (100.1)	405 (43.5)	433 (46.5)	15 (1.6)	35 (3.8)

*In brackets is the average number of tumors per 100 organ transplant recipients.
**Other cancers' include appendageal cancers, dermatofibrosarcoma protruberans, cutaneous lymphoma, melanoma and Merkel cell carcinoma.

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Table 3: Number (percentage) of individuals by rate of cancer after first cancer in those with 2+ years of follow-up after the first cancer

		0–0.5 per year	0.5–1 per year	1–2 per year	≥2 per year	Total
Sex	Male	19 (22.1)	16 (18.6)	24 (27.9)	27 (31.4)	86 (100.0)
	Female	18 (38.3)	9 (19.2)	16 (34.0)	4 (8.5)	47 (100.0)
Skin phenotype	I	8 (27.6)	2 (6.9)	9 (31.0)	10 (34.5)	29 (100.0)
	II	15 (25.9)	12 (20.7)	20 (34.5)	11 (19.0)	58 (100.0)
	III	9 (27.3)	7 (21.2)	8 (24.2)	9 (27.3)	33 (100.0)
	IV	2 (22.2)	4 (44.4)	2 (22.2)	1 (11.1)	9 (100.0)
	Missing	3 (75.0)	0 (0.0)	1 (25.0)	0 (0.0)	4 (100.0)
Age (years)	<30	7 (35.0)	6 (30.0)	5 (25.0)	2 (10.0)	20 (100.0)
	30–39	6 (26.1)	3 (13.0)	6 (26.1)	8 (34.9)	23 (100.0)
	40–49	14 (37.8)	10 (27.0)	7 (18.9)	6 (16.2)	37 (100.0)
	50–59	8 (22.9)	5 (14.3)	13 (37.1)	9 (25.7)	35 (100.0)
	≥60	2 (11.1)	1 (5.6)	9 (50.0)	6 (33.3)	18 (100.0)
UV risk*	Low	19 (30.2)	11 (17.5)	22 (35.0)	11 (17.5)	63 (100.0)
	High	13 (22.4)	13 (22.4)	14 (24.1)	18 (31.0)	58 (100.0)
	Missing	5 (41.7)	1 (8.3)	4 (33.3)	2 (16.7)	12 (100.0)
Total*		37 (27.8)	25 (18.8)	40 (30.1)	31 (23.3)	133 (100.0)

All patients (except one) with 2+ years of follow-up after the first cancer were White so this individual is excluded from the table. The exception is from Indian subcontinent with skin type 5, aged over 60 years and female.
*UV high risk defined as 11+ sunny holidays OR having an outdoor occupation OR living abroad for 6 months or more. All other individuals considered low risk unless no information.

Skin tumor subtypes (Table 2)

A total of 1820 skin cancers were confirmed, a rate of 190.2 tumors per 1000 person years at risk. Squamous cell malignancies accounted for 1337/1820 (73.5%) and BCC 433/1820 (23.8%), giving a SCC/BCC ratio of 3.1:1. Fifty other skin cancers occurred; 15 KS (0.8%), 10 melanoma/melanoma *in situ* (0.54%), 20 appendageal cancers (1.1%), 2 primary cutaneous lymphoma, 2 dermatofibrosarcoma protuberans and 1 Merkel cell carcinoma (MCC).

Anatomical location of tumors (Figure 1)

A total of 70% tumors were on sun-exposed sites. There were significant differences in distribution, with 36.3% SCC versus 5.2% BCC occurring on the hands/forearms. Conversely, 8.5% SCC versus 22.2% BCC were truncal. Anatomical location also varied with gender; tumors were more frequent on the scalp/ears in males (233/1159 vs. 22/407, $p < 0.001$) and on the legs/feet in women (34/1159 vs. 68/407, $p<0.001$). Tumors on the legs were overrepresented in African/African-Caribbean individuals, attributable to the distribution of KS.

Cumulative incidence and multiple skin cancers (Figures 2 and 3)

With a mean follow-up of 10.3 years, the mean time from transplant to first skin cancer in those with skin cancer was 8.8 years (range: 0.3–24.3 years), but varied with subtype (SCC, 9.9 years; BCC, 7.6 years; melanoma, 5.7 years; KS, 4.9 years). Overall cumulative incidence was 10.6%, 24.8%, 53.9% and 73.9% at 5, 10, 20 and 30 years post-transplant, respectively. The 30-year cumulative incidence was 65.4% for SCC and 46.5% for BCC. A total of 175 (65.5%) individuals had multiple cancers (range: 2–105, median 6), with almost one-half of all cancers (870/1820, 47.8%) occurring in 10% (26/267) of patients. 46 (17.2%) OTR had >10 tumors each; all were white and 36/46 (78.3%) were skin phototypes I/II.

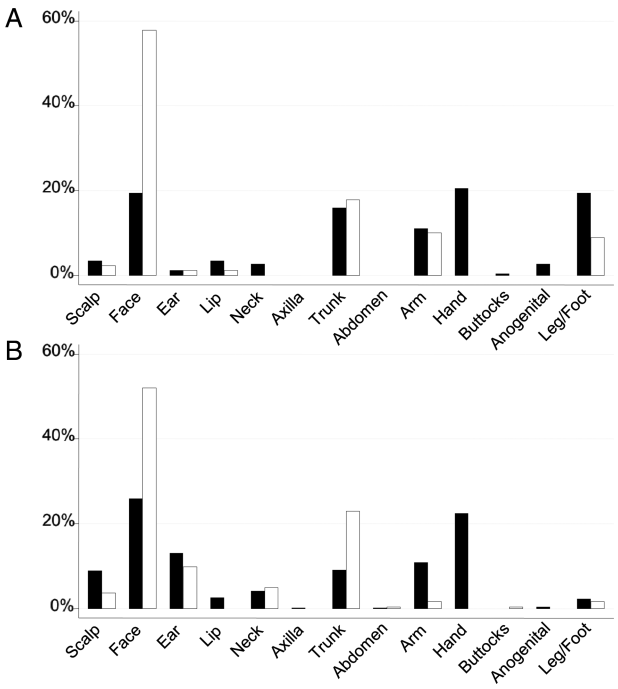
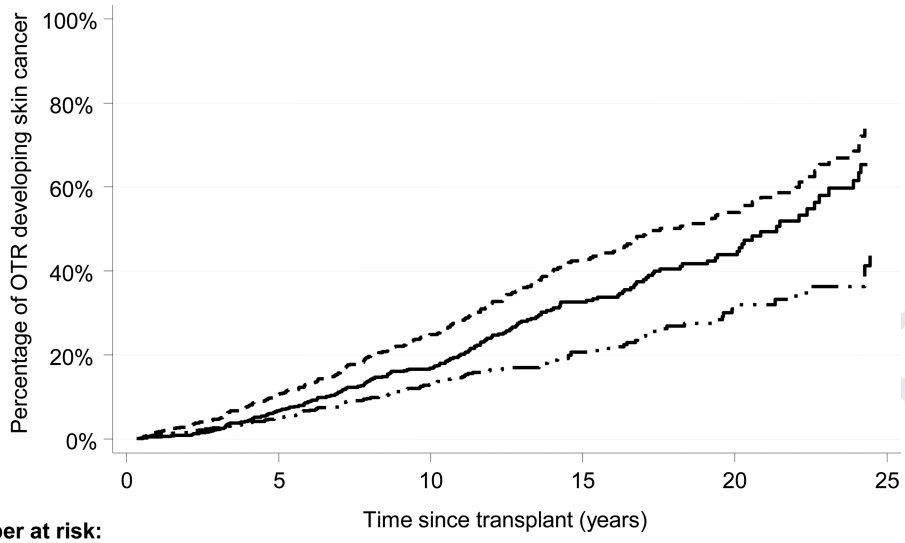


Figure 1: Anatomic distribution of keratinocyte skin cancers (SCC and BCC) in (A) female and (B) male organ transplant recipients. Solid black bars represent percentage of SCC/CIS tumors and white bars represent BCC tumors.



Number at risk:

All cancers	**931**	**599**	**348**	**159**	**61**	**14**
SCC/CIS	**931**	**622**	**378**	**178**	**69**	**16**
BCC	**931**	**631**	**386**	**196**	**77**	**23**

Figure 2: Cumulative incidence for skin cancer developing in OTRs derived from Kaplan–Meier estimation for all cancers (dashed line), SCC/CIS (solid line) and BCC (dash-dot line).

Rates of cancers and time to subsequent cancers after the first cancer (Table 3, Figure 3)

Patient characteristics according to rate of cancer per year after the first cancer are shown in Table 3. To allow for variation in follow-up, only individuals with surveillance for 2 years or more following the first cancer are included. Approximately one-third developed at least one cancer per year, with 29/197 (14.7%) developing two or more per year. After a first skin cancer, the proportion of OTR with a further cancer was 33.4% at 1 year, increasing to 73.3% at 5 years (Figure 3A). There was a median of 24 months from first to second skin cancer and 14.7 and 8.4 months respectively to third and fourth cancers. For SCC, time to second and third cancer was shorter at 12.7 and 8.3 months respectively (Figure 3B). If SCC was the first cancer, the second cancer was more likely to be an SCC. Similarly, if BCC was a first cancer, the second tumor was more frequently a BCC. In those with an initial SCC, a second SCC occurred more rapidly than a BCC (Figure 3C).

Nine patients had a history of pretransplant skin cancer. Their mean time to first posttransplant cancer was 71.0 months (range: 7.1–161.1), shorter than 104.9 months (range: 4.0–372.3) for those with no history of pretransplant skin cancer ($p = 0.006$), and comparable to time from first to second cancer in the latter group ($p = 0.099$, stratified for age at transplant).

SCC age and sex-matched relative risk

Based upon local data available between 1999–2003 (Thames Tumour Registry), the expected number of SCC in our cohort was 1.1, whereas 168 were observed, giving a 153-fold increased risk compared with the general population ($p < 0.001$). Relative risk was proportionately higher

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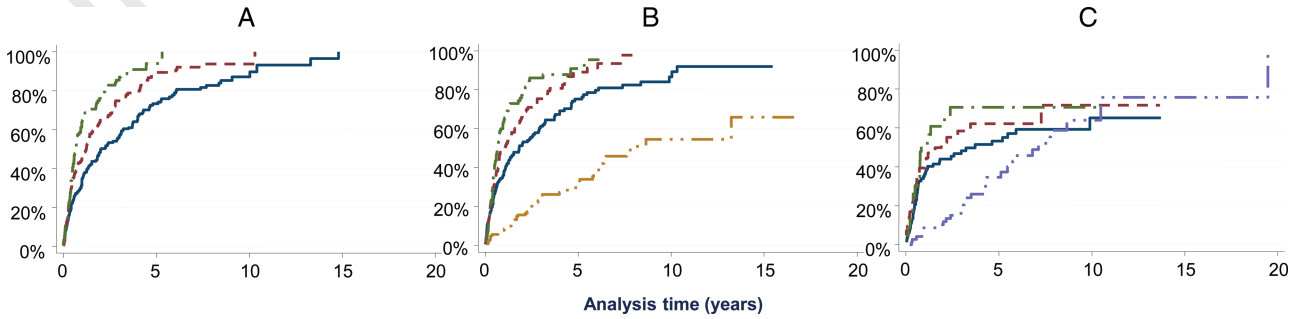

Figure 3: Cumulative incidence of subsequent skin cancer developing in organ transplant recipients who have had a first skin cancer for (A) All cancers (B) CIS/SCC and (C) BCC. Solid blue line represents first to second skin cancer; dashed red line second to third skin cancer and dot-dash green line third to fourth cancer. Yellow line represents cumulative incidence of BCC after SCC/CIS and purple line represents cumulative incidence of SCC/CIS after BCC.

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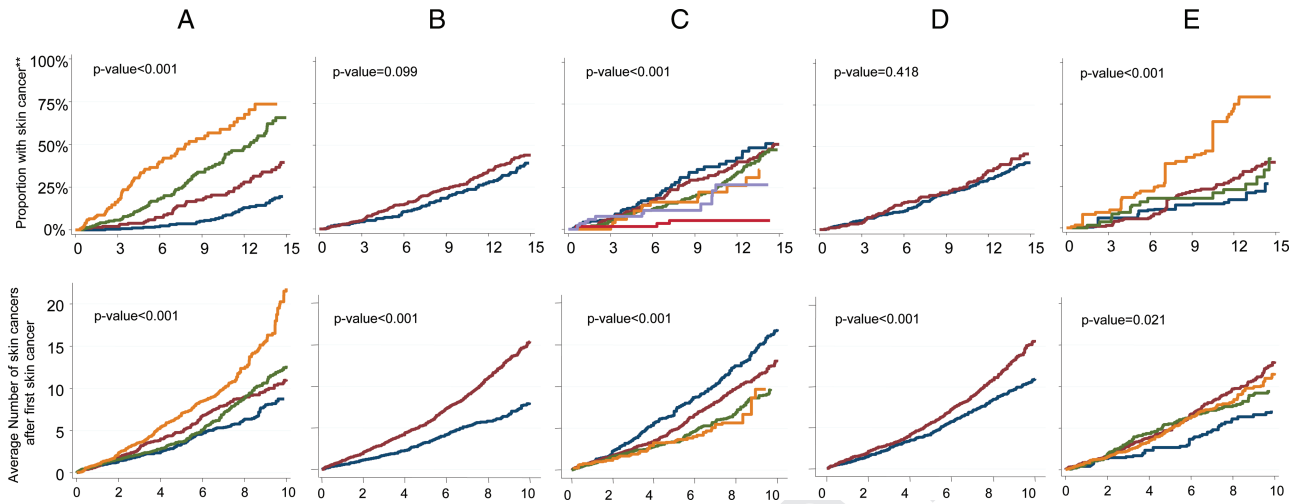

Figure 4: Cumulative incidence of skin cancer and average number of skin cancers after first skin cancer according to clinical risk factors. Sex, ethnicity and UV sunburn were adjusted for age at transplant. Sunburn was adjusted for age at transplant and skin type. P-values from the log-rank test. (A) Age group. Blue = <35 years; Maroon = 35–45 years; green = 45–55 years; yellow = 55 or more years. (B) Sex. maroon = male; blue = female. (C)sSkin type/ethnicity (average number of cancers among Caucasians only): blue = skin type I; maroon = skin type II; green = skin type III; yellow = skin type IV; purple = black; red = Indian subcontinent. (D) UV exposure (patients were categorized as having 'high' chronic UV exposure if there was a history of an outdoor occupation for longer than 5 years or residence in a sunny climate for over 6 months of more than 11 sunny holidays during which they had sunbathed. All other patients were considered to have 'low' exposure unless no information was given on any of these exposures): maroon = high risk; blue = low risk. (E) Sunburn pre-transplant. Blue = never; maroon = 1–5 times; green = 6–10 times; yellow = 11 or more times.

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for younger OTR (<50 years) than for those >50 years, with incident ratios of 480 (72 observed/0.15 expected) and 139 (96 observed/0.69 expected), respectively. However, it is recognized that most tumor registries do not capture data on nonmelanoma skin cancers and that the SCC numbers recorded may be an underestimate of the true incidence. Unfortunately, it is not possible to accurately quantify the extent of this possible underestimate. We were unable to calculate incident ratios for BCC as there were no comparable data available from the general population.

Metastatic disease and death from skin cancer (Table 1)

Excluding KS, there were 20 cases of metastatic disease (14 SCC, 3 melanoma, 2 appendageal cancers, one MCC) and 14 attributable deaths (9 SCC, 3 melanoma, one appendageal tumor and 1 MCC). Seven deaths occurred after the end of the study period (June 2006) but metastasized within the subsequent 60-month period for which follow-up information was available (i.e. June 2006–June 2011). All metastatic cancers arose in white European OTRs, with the exception of one SCC in an African-Caribbean patient. Age- and sex-matched data on death from skin cancer in England and Wales were used to calculate expected number of deaths. For melanoma, the expected number of deaths was 0.48 with three observed deaths, giving a standardized mortality ratio 6.19. The expected number of KSC deaths was 0.07 with 11 observed, giving a standardized mortality ratio of 148.26.

Kaposi sarcoma

Fifteen individuals were diagnosed with KS; eight African, three African-Caribbean, one Indian and three white European OTRs, at a median of 36.2 (range 6.7–230.8) months posttransplant. In all cases the skin was clinically involved; in 13/15 (87%), lesions arose on the legs/feet with edema, usually unilateral, preceding skin involvement in 12/15 (80%). Visceral KS affected 4 (26.7%) cases. Graft loss directly attributable to treatment for KS occurred in 6/15 (40%) individuals.

Immunosuppressive drug regimens and era effects

OTRs transplanted pre-1984 received azathioprine and corticosteroids as a standard immunosuppressive regimen. After 1984, ciclosporin was introduced. From the late 1990s, azathioprine was largely replaced with mycophenolate mofetil and tacrolimus was used as an alternative calcineurin inhibitor. At time of first skin cancer, 24% of individuals were receiving prednisolone and azathioprine; 58.8% prednisolone, azathioprine and ciclosporin; 7.9% prednisolone and ciclosporin; 3% azathioprine and ciclosporin; 4.1% prednisolone, mycophenolate and ciclosporin and 1.1% prednisolone, tacrolimus and ciclosporin. However, immunosuppressive drug regimens were dependent not only on the year of transplantation, but also varied within individuals on a temporal basis; drug doses were often altered and patients were also switched to different agents. In view of this and also the inherent problems of assessing individual immunosuppressive burden, data relating to specific associations with

Table 4: (Panel A) Risk levels and surveillance intervals after baseline assessment. (Panel B) Risk levels and surveillance intervals after confirmed skin cancer

Panel A Risk level	Definition	Surveillance interval/months or years
1	Skin type V and VI	KS surveillance only at 2-year intervals
2	I–IV; <35 years at transplant	At 5 and 10 years and then every 2 years
3	I–IV; 35–44 years at transplant; < 5 sunburns	At 5, 7, 9, 11 years and then annually
4	I–IV; 35–44 years at transplant; > 5 sunburns I–IV; 45–54 years at transplant	At 2 and 4 years and then annually
5*	I–IV; ≥55 years at transplant	Annual for first 2 years and then every 6 months

Panel B Risk level	Definition	Surveillance interval/months or years
First SCC	First posttransplant SCC (or pretransplant SCC)	4, 8 and 12 months; then annually if no further cancers
First BCC	First post-transplant BCC (or pretransplant BCC)	6 and 12 months; then annually if no further cancers
Second or third cancer	Second or third posttransplant SCC/BCC	3, 6, 9, 12 months; then annually if no further cancers

*Patients with actinic keratoses are included as risk level-5 for the purposes of surveillance. See the text.

immunosuppressive drug regimens were not analyzed in detail as part of this study.

Many eras were encompassed by our cohort analysis and a number of confounders, in addition to immunosuppressive drug regimens, may have influenced skin cancer risk over this time. Nonetheless, we initially subjected the data to an era analysis in three groups, pre-1985, 1985–2000 and post-2000. However, as follow-up was limited for the post-2000 cohort, this group was excluded. We found no significant era effect for pre-1985 versus 1985–2000 (p-value for trend 0.895).

Clinical risk factors (Table 3)

Age at transplant was significantly related to subsequent skin cancer incidence ($p < 0.001$), with median time to diagnosis of 8, 12 and 19 years for those >55, 45–54 and 35–44 years at transplant, respectively. Skin phototype was also a risk factor ($p < 0.001$), as was pretransplant sunburn, both overall ($p < 0.001$), and separately both in childhood ($p = 0.003$) and as an adult ($p < 0.001$). Time to first skin cancer was shortest in white OTRs, but also occurred in African/African-Caribbeans in the first 5 years posttransplant, exclusively due to KS. Independent risk factors for cumulative skin cancer burden were older age at transplant ($p <0.001$), skin phototype in white Europeans (I/II vs. III/IV, $p < 0.001$), high UVR exposure ($p <0.001$) and pretransplant sunburn ($p = 0.021$). Males were at increased risk and were more likely to develop two or more cancers per year (Table 3).

Assignment of skin cancer risk groups and surveillance intervals before first skin cancer (Table 4A)

Assessing cumulative incidence of skin cancer over time since transplantation, we constructed five risk groups for KSC risk assignment posttransplant, calculated risk on the basis of age, age at transplant and UV exposure (including sunburn episodes). This model is designed to allow assignment of risk at any point posttransplant before development of (pre)malignant lesions. The risk groups are: level-1 (OTRs with skin types V/VI); level-2 (OTRs with skin types I–IV, <35 years of age at transplant); level-3 (OTRs with skin types I–IV, 35–45 years at transplant with <5 sunburns); level-4 (OTRs with skin types I–IV, 35–45 years at transplant with >5 sunburns and all those aged 45–55 years at transplant); level-5 (OTRs with skin types I–IV, ≥55 years of age at transplant). Although this model assumes no other clinical indicators of risk, the presence of actinic keratoses (AKs), potential precursors of SCC, is known to confer additional risk (38,39). However, the current study was based upon histologically confirmed lesions and information was therefore not systematically analyzed for AK as these are usually diagnosed clinically. In a previous case–control study that included a subgroup of 89 OTR with SCC and 271 controls drawn from the 1010 OTR included in the current study, we confirmed AK to be a significant SCC risk factor ($p <0.001$), with odd ratios of 62.1(16.8–229.49) (39). In view of this, once patients develop AK, we assign them to risk level-5 for surveillance until the point of first skin cancer.

We used this risk stratification to derive a clinical surveillance interval for each group after baseline assessment, which aimed to keep estimated cumulative incidence of KSC below 5%.

For level-1 OTRs, no routine surveillance for KSC is necessary as the risk is negligible (but see discussion for KS risk in this group). Intervals for KSC surveillance in levels 2–5 range from 5 yearly to 6 monthly (Table 4A).

Assignment of surveillance intervals after first skin cancer (Table 4B)

After a first skin cancer, the risk of second and subsequent cancers is high. Applying the same 5% threshold for interval second skin cancers, gave an impractical surveillance interval of 0.5 months. Even after excluding second cancers occurring within the subsequent 2 months as potentially nonindependent events and restratifying for age at

transplantation, the required surveillance interval remained <4 weeks. A less stringent threshold of <15% was therefore applied and requires surveillance every 4 months after a first SCC; if no further cancer of any type is identified within the first year, our data indicate that this can be reduced to annually. After BCC as a first cancer, a 15% threshold requires 6-monthly surveillance intervals for the first year, reduced to annually if no further cancer is found within 12 months. Based on a 15% threshold, 3-monthly surveillance intervals are sufficient after subsequent cancers, reducing to annually if no further cancer is found within the following 12 months.

Discussion

National Institute for Clinical Excellence in the United Kingdom (31), and other expert consensus guidelines in Europe and the USA (32–36) recommend that OTRs should be managed in dedicated skin cancer clinics. This study addresses practical aspects of these recommendations by stratifying for skin cancer risk within a diverse patient population. Skin cancer and demographic data on more than 1000 patients with almost 10,000 patient years at risk were analyzed over a 22-year prospective follow-up period. It extends information from studies in geographically similar regions (e.g. 14, 40–43) by providing longer follow-up and a wider ethnicity profile. From these data we derive an evidence base to determine who should be monitored for skin cancer and how often.

Scale of the skin cancer burden in OTRs is considerable and predictable

A total of 1820 skin cancers were documented within approximately one-third (almost 30%) of our cohort. This represents a 150-fold excess risk for both developing an SCC and dying from it, compared with the general population. Among those with KSC, two-thirds develop more than one tumor. Median time to first KSC was 8.8 years with median intervals to second, third and fourth tumors of 24, 14.7 and 8.4 months, respectively. Almost three-quarters of individuals had at least one further cancer within 5 years of the first, consistent with findings in other cohorts (43–48), and considerably higher than the general population (49). Those individuals with >10 skin cancers (almost 10% of the skin cancer population) developed a mean of 2.39 new tumors each per year, contributing almost 50% total KSC burden across the study period. This exponential skin cancer growth occurs in a small, predictable group of patients with a high mortality; in our cohort, 27% (7/26) of OTRs with >10 skin cancers died from metastases.

Most studies report data from white populations in Europe, Australia and the United States and few have included nonwhites living in these countries (40,41,43,46). Twenty skin cancers occurred in nonwhite individuals in our cohort; KS was the most frequent, affecting 8/78 (14%) African/African-Caribbeans compared with 1% of white Europeans. Our data on African OTRs KS are similar to that previously reported in a Portuguese study in which 8/52 (15.4%) Africans developed KS compared with 3/364 (0.8%) white European patients in a cohort of 416 OTRs (50). It also accords with the endemic prevalence of human herpes virus-8 (HHV8) infection in countries of birth (51,52).

A diversity of other skin cancers occur at higher frequency posttransplant

A total of 35 patients presented with other skin malignancies, including melanoma and melanoma *in situ,* which was found in 10 cases (0.54%). We previously documented a 7.8-fold increased melanoma risk in our cohort (53) and, in a multicenter European study, found a worse prognosis for melanoma stage T2 and above compared with the general population (54), subsequently confirmed in a separate cohort in the United States of America (55). Appendageal cancers, estimated to be 100-fold more common in OTRs (56), accounted for 20 skin malignancies and were metastatic in two cases. They are usually of sebaceous or eccrine origin (particularly sebaceous carcinoma and eccrine porocarcinoma) rather than follicular or apocrine and are uncommonly diagnosed prior to surgery and often present as nonspecific, ulcerated, red nodules (57). MCC, a highly aggressive neuroendocrine skin cancer with a possible viral etiology (7), is significantly overrepresented with a worse prognosis in OTR (58,59). In our cohort there was one MCC, which was fatal.

Identification of OTR at risk and assignment of surveillance intervals (Table 4A)

The purpose of posttransplant surveillance is to facilitate preventative strategies, although further studies are required to confirm the cost-effectiveness of this approach (59) (and, similarly, to determine the benefits of pretransplant screening (60)). The primary aim of this study was to define surveillance intervals that would allow close follow up of at-risk individuals posttransplant whilst not burdening the clinical service with routine follow-up of those who were at much lower risk. We defined five risk levels using characteristics that translate into straightforward clinical protocols, requiring knowledge of skin type, age at transplant and sunburn history.

Surveillance intervals were set to ensure that fewer than 5% of all first skin cancers would have arisen which we considered a stringent but clinically relevant threshold. We found that only patients in the highest risk group (level-5) required annual surveillance (i.e. had a 5% or greater risk of developing skin cancer within a 12-month period), although current guidelines recommend a minimum of annual surveillance for *all* OTR (33,34,36,62). Our data indicate that for those in level 2–4 risk groups, surveillance intervals can be spaced more widely, initially every 2–5 years. At each visit, a risk assessment is undertaken again to determine the subsequent surveillance interval. For level-1

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patients (skin types V/VI), surveillance is not routinely required for KSC, but KS risk should be assessed. Risk is currently based on HHV8 endemicity in country of birth, but studies are underway to quantify risk of KS virologically. In the absence of specific virological data, annual review is justifiable during the first 5 years posttransplant when our data and others indicate that the majority of KS presents (63–65).

Assignment of surveillance intervals after first skin cancer

Following a first skin cancer, in our cohort, 4-monthly surveillance is sufficient to ensure that fewer than 15% of all further cancers would arise by the planned surveillance visit, and can be reduced to annually if there is a cancer-free period of 1 year thereafter. After second and subsequent cancers, 3-monthly surveillance for a year is recommended, reduced to annually after a cancer-free year. These recommendations are intended to maximize detection of skin cancer whilst retaining clinically practicable surveillance intervals. Clinical judgment should determine those individual patients requiring closer surveillance than that derived from the population risk. The rapid response component of the specialist clinic has proven valuable in this respect, since OTRs are encouraged to present between scheduled surveillance intervals should they develop suspicious skin lesions. In our experience many, if not all, 15% of cancers that might present between surveillance visits are still diagnosed at an early stage and brought to our attention through this rapid access system.

Summary

Our study provides an algorithmic approach to defining individual risk and calculates appropriate skin cancer surveillance intervals. This should be of practical use to those setting up posttransplant skin clinics and will facilitate targeted surveillance and active management to those that need it most. We estimate that this model is sensitive enough that fewer than 5% of first skin cancers would arise within the defined surveillance visit. Similar modeling for detection of subsequent cancers, with slightly reduced sensitivity to ensure practical application, would expect fewer than 15% of tumors would arise within the defined surveillance periods. A patient-activated, urgent access pathway for those at high risk of second and subsequent cancers should address this shortfall. We consider that these recommendations provide a cost-effective means of deploying limited service resources in delivering selective surveillance and management of patients at high risk of skin cancer following organ transplantation.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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