Immunosuppressive regimens and skin cancer risk in solid-organ transplant recipients

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Abstract

Background Solid organ transplant recipients (SOTRs) are at increased risk of developing skin cancer due to long-term immunosuppressive (IS) therapy. Calcineurin inhibitors (CNIs), particularly tacrolimus and ciclosporin, are associated with elevated skin cancer risk. Mammalian target of rapamycin inhibitors (mTORi) are considered protective, but real-life evidence of their effectiveness, especially when combined with reduced-dose CNIs, is limited. Understanding the impact of current IS regimens on skin cancer risk is essential for improving patient outcomes.

Objectives To evaluate the relative risk of different IS drugs and regimens on skin cancer development in SOTRs.

Methods We conducted a prospective observational study at Vall d'Hebron University Hospital, Barcelona, Spain, from 2011 to 2021. The study included 1055 SOTRs from a mixed-organ cohort, with a combined follow-up of 3336 person-years. Real-life IS drug regimens were recorded during scheduled posttransplant screenings or dermatological follow-

ups. Cox proportional hazards models with shared frailty were used to assess skin cancer risk, accounting for multiple events and adjusting for time-varying drug exposure.
Results Skin cancer occurred in 131 of 1055 SOTRs (12.4%). A total of 450 skin cancer events were registered, including 317 squamous cell carcinomas (70%), 118 basal cell carcinomas (26%) and 15 melanomas (3%). mTORi-based regimens were associated with significantly lower skin cancer rates [hazard ratio (HR) 0.66, 95% confidence interval (CI) 0.47–0.92; $P = 0.01$]. Everolimus appeared more protective than sirolimus (HR 0.38, 95% CI 0.21–0.69; $P < 0.001$). Reduced-dose CNI combined with mTORi was linked to a 37% reduction in skin cancer rates in high-risk patients (HR 0.63, 95% CI 0.42–0.93; $P = 0.02$) and a 32% reduction in patients with posttransplant events (HR 0.68, 95% CI 0.47–0.98; $P = 0.04$). The reduction was mainly driven by decreased squamous cell carcinoma incidence.
Conclusions mTORi-based regimens, particularly with reduced-dose tacrolimus, appear to offer a safer and more effective alternative to CNI-heavy regimens for skin cancer prevention in SOTRs. Real-life data support the integration of mTORi into IS strategies to reduce skin cancer risk, particularly for high-risk patients and those who developed skin malignancies.

Lay summary

People who receive a solid organ transplant (SOT) need medicines to stop their immune system from rejecting the new organ. These medicines are ‘immunosuppressant’ (IS) drugs, which suppress the immune system. However, the IS drugs must be taken long term and they increase the risk of developing skin cancer. Such skin cancers can be more aggressive.
We conducted a study at Vall d’Hebron University Hospital in Barcelona, Spain. We followed over 1000 people with SOTs for 10 years (2011–2021). We looked at which IS drugs, alone and combined, were best at reducing skin cancer risk. We focused on two types of drugs, ‘mTOR inhibitors’ such as everolimus and sirolimus, and ‘calcineurin inhibitors’ such as tacrolimus.
We found that everolimus plus reduced-dose tacrolimus lowered skin cancer risk. Higher-dose tacrolimus alone was linked to a greater risk of skin cancers. The greatest risk reduction was for people with a high skin cancer risk or who had skin cancer after their transplant. Everolimus seemed to be more protective than sirolimus.
These drug combinations could help SOT recipients who have higher skin cancer risks. Such a change could help SOT recipients reduce their skin cancer risk. This would improve their long-term health and quality of life.

What is already known about this topic?

- Solid organ transplant recipients (SOTRs) face a high risk of developing skin cancer due to lifelong immunosuppressive (IS) therapy, particularly with calcineurin inhibitors (CNIs) like tacrolimus and ciclosporin.
- While mammalian target of rapamycin inhibitors (mTORi) like everolimus and sirolimus have been linked to reduced skin cancer risk, real-life evidence on their effectiveness, especially when combined with reduced-dose CNIs, is limited.

What does this study add?

- This real-life study shows that mTORi-containing regimens, especially with reduced-dose tacrolimus, were associated with lowered skin cancer risk in SOTRs, particularly for squamous cell carcinoma.
- mTORi combined with reduced-dose tacrolimus were associated with 32–37% lower skin cancer rates in high-risk patients and those with posttransplant skin cancer.
- Among mTORi, everolimus appeared more protective than sirolimus.

Solid organ transplant recipients (SOTRs) face a significantly higher risk of developing skin cancer, especially keratinocyte carcinomas, which are major contributors to morbidity and mortality.[1–4] This increased risk is primarily driven by exposure to ultraviolet radiation and long-term immunosuppressive (IS) therapy.[1,2,5]

Previous trials have linked traditional IS drugs, such as ciclosporin and azathioprine, to an increased skin cancer risk, whereas mammalian target of rapamycin inhibitors (mTORi) have been associated with a reduced risk.[5–13] However, many of these studies do not reflect current clinical practices, where potentially less carcinogenic calcineurin inhibitors (CNIs), such as tacrolimus, and newer antimetabolites (ATMs), like mycophenolate mofetil (MMF), are routinely used.[9,12,14–17] Combining different drug families is common to reduce toxicity and improve organ survival, with most SOTRs now receiving a regimen that includes a CNI or mTORi along with an ATM and oral corticosteroids (OCS).[5,12,14,16]

These regimens are not static over the posttransplant period.[12] When skin cancer becomes a concern, a common strategy is to introduce mTORi, discontinue ATMs and reduce the CNI dose (mTORi + rCNI combination).[14,18] Despite its frequent use, this regimen has not been studied in clinical trials focusing on skin cancer.[14,19–22] Some retrospective and registry-linked

studies found that reduced-exposure ciclosporin + mTORi lowered the incidence of skin malignancy compared with standard exposure to ciclosporin + ATM.[20,23,24] However, two meta-analyses yielded differing results: one showed a borderline benefit, while the other found no significant effect of these combinations on skin cancer reduction.[19,25] Notably, there is limited information on the effects of reduced-exposure tacrolimus, a CNI that is now preferred over ciclosporin.[12,20,26]

Given this context, our prospective study aimed to provide important real-life evidence on the relative skin cancer risks associated with current IS drugs and regimens in a mixed-organ SOTR cohort. Specifically, we sought to determine whether the now common rCNI + mTORi regimen offers protection against skin cancer in patients with posttransplant events, and whether it can reduce cutaneous malignancy in high-risk patients. To comprehensively capture the high tumour burden in SOTRs, we included all events occurring during follow-up, not just the first or second events, as is typical in clinical trials.[6,7,27,28]

Patients and methods

Study design, participants, exposures and outcomes

A prospective observational study was conducted at Vall d'Hebron University Hospital (Barcelona, Spain) from July 2011 to July 2021. The study included all adult SOTRs who attended per protocol dermatological screenings and routine follow-up visits at the dermatology department's SOTR unit during the study period. There were no specific exclusion criteria.

Data were collected prospectively during this period from electronic medical records and through structured interviews conducted during routine clinical visits. This included demographic information, clinical details and transplant-related factors. Exposure to various induction and maintenance IS drugs was systematically recorded at each follow-up visit, including the duration, dosage and any adjustments made, along with the reasons for these modifications. High-risk patients were retrospectively identified as those categorized within the high- and very high-risk groups by the Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator (SUNTRAC) at the time of transplant.[29–31]

The primary outcome was incidence of skin cancer, including squamous cell carcinoma (SCC), basal cell carcinoma (BCC), Merkel cell carcinoma and cutaneous melanoma. Diagnosis of skin cancer was made through clinical examination and skin biopsy. At each visit, type and number of tumours were recorded by board-certified dermatologists

specializing in skin cancer. Date of last follow-up was defined as the date of last dermatological visit with recorded information. The study was approved by the Vall d'Hebron University Hospital Ethics Committee and the national drug committee (CFP-AZA-2020-01).

Statistical analyses

Descriptive statistics were calculated for baseline clinical characteristics and exposure variables.[32] To compare patients who developed skin cancer with those who did not, we used the Kruskal–Wallis rank sum test for continuous variables, Fisher's exact test for categorical variables and a trend test for ordinal variables.[32]

Cox proportional hazards regression models with shared frailty were employed to assess the impact of IS drugs/regimens on the risk of skin cancer events. These models accounted for individual patient susceptibility to developing multiple skin cancer events, while allowing time-varying IS drug exposure.[20,27,33,34] Crude models were adjusted by other coadministered IS drugs. Adjusted models included additional covariates such as age; sex; race and ethnicity; smoking; induction with immunoglobulins; acute graft rejection; year and type of transplant; time since transplant; frequency and number of dermatology visits; baseline actinic damage; and pre- and posttransplant skin cancer events. This minimum set of adjustment variables was selected using directed acyclic graphs based on their potential association with both exposure (IS drug/regimen) and outcome (skin cancer) (Figure S1; see Supporting Information).[34–36]

The effect of IS drugs and regimens on skin cancer risk was estimated for all patients, high-risk patients, and those who developed skin cancer after transplant. We also stratified our analyses by SCC and BCC events. Due to few melanoma cases, risk estimates for this neoplasm could not be computed.

Sensitivity analyses, considering cumulative IS drug exposure as a percentage of follow-up time, were performed to confirm the robustness of the primary findings and to account for carry-over effects of previous IS.[34] Occasional missing data were addressed using the last observation carried forward method or, if no prior information was available, a missing category was defined. Statistical significance was evaluated using two-tailed tests at an alpha level of 0.05. All statistical analyses were conducted using R version 4.2.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) from June 2024 to August 2024.

Results

Clinical and demographic characteristics

The study included 1055 SOTRs, with a combined follow-up of 3336 person-years. The majority (64.5%) were White men, with a median transplant age of 57 years (Table 1). Transplants of lung (42.9%) and kidney (42.5%) were most common, followed by liver (13.6%). Organs were from deceased donors in 93% of cases, and 12.6% of patients experienced acute rejection episodes.

Skin cancer affected 131 SOTRs (12.4%), leading to 450 recorded events, including 317 SCCs (70%), 118 BCCs (26%) and 15 cutaneous melanomas (3%) from 3705 dermatological visits. Multiple skin cancer events were common: 69 of 131 patients (52.7%) had more than one, and 14 (10.7%) had more than five (Figure 1a).

Patients who developed malignancy were significantly older, predominantly White men, with greater baseline sun damage, higher rates of pretransplant skin cancer and longer median follow-up (Table 1). At the time of transplant, most would have been classified as high- or very high risk according to the SUNTRAC risk score. Those in higher SUNTRAC risk groups also had a greater burden of multiple tumours (Figure S2a; see Supporting Information). Regarding transplant type, there were no significant differences in skin cancer risk between transplanted organs (Table 1).

Maintenance immunosuppressive drugs and regimens

Most patients received maintenance IS regimens featuring triple therapy, that is a CNI combined with an ATM and OCS (Figure 1a, b). In this prospective real-life cohort, IS regimens changed over time, as patients often switched therapies due to tolerability issues, toxicity, organ rejection, viral replication or malignancy (Figure 1a).

CNI exposure was nearly universal (97.6% of exposure time), with tacrolimus as the predominant choice (98.6%) and minimal use of ciclosporin (1.4%). ATMs were used in 69.6% of follow-up time, with MMF (70%) and mycophenolic acid (29.1%) being the most prescribed, while azathioprine use was rare (0.9%). mTORi were used 19.1% of the time, with sirolimus accounting for 60.6% and everolimus for 39.4% of the exposure. A switch to an mTORi-containing regimen occurred in 15% of patients and was more frequent in those who developed skin cancer (33.6% vs. 12.3%; $P < 0.001$) (Table 1; Figure S2b).

Corticosteroid use was frequent (77.9%), mainly prednisone (65%) and methylprednisolone (35%).

The most prevalent IS regimen was CNI + ATM ± OCS (68%), followed by rCNI + mTORi ± OCS (18%) (Figure 1b). mTORi-containing regimens were more common in patients with skin cancer, particularly in those with a high tumour burden (Figure 1b). In contrast, simpler regimens with just CNI ± OCS were less common and were mostly seen after liver transplant (Figure 1b).

Skin cancer risk by immunosuppressive drugs

The use of mTORi, after adjusting for coadministered IS drugs, was linked to a 40% decrease of skin cancer rates in high-risk patients [hazard ratio (HR) 0.6, 95% confidence interval (CI) 0.35–1.02; $P = 0.06$] and a 72% reduction in those with posttransplant events (HR 0.28, 95% CI 0.17–0.46; $P < 0.001$) [Figure 2; Figure S3 (see Supporting Information)]. In the latter group it reduced rates of both BCC and SCC (Table S1; see Supporting Information).

Among the two mTORi, everolimus was associated with the lowest skin cancer rates, providing substantial protection across all subgroups (Figure 3). Everolimus outperformed sirolimus in reducing cancer rates across all patients (HR 0.38, 95% CI 0.21–0.69; $P < 0.001$). However, among patients with skin cancer, everolimus was not clearly superior to sirolimus (HR 0.69, 95% CI 0.37–1.28; $P = 0.24$). Regarding skin cancer subtypes everolimus proved protective for both SCC and BCC in this group (Table S2; see Supporting Information).

In contrast, exposure to a CNI, primarily tacrolimus, was associated with a four- to five-fold increase in the rate of skin cancer across all subgroups (Figures 2, 3). This increased risk was particularly high for SCC (Table S2).

Exposure to an ATM drug, primarily MMF, showed a largely neutral association in the overall cohort. However, among patients who developed skin cancer, it was associated with lower risks (HR 0.41, 95% CI 0.26–0.67; $P < 0.001$) for both SCC and BCC [Figures 2, 3; Table S2]. In our analysis, patients receiving MMF doses above the median did not show an increased risk of SCC (HR 0.53, 95% CI 0.10–2.89; $P = 0.47$).[5] OCS use was not clearly associated with increased cancer risk or protection in our study (Figures 2, 3). As sensitivity analyses, we also explored models that accounted for cumulative previous exposure to IS drugs as percentage of follow-up under a certain drug with similar results (Figure S3).

Skin cancer risk by immunosuppressive regimens

Regimens incorporating an mTORi were associated with a protective effect against overall occurrence of skin cancer, particularly benefiting high-risk patients and those with a history

of posttransplant skin cancer (Figure 4a). This effect was primarily driven by lower SCC rates (Table S3; see Supporting Information). This benefit was less clear in preventing the initial occurrence of skin malignancy in high-risk patients (HR 0.83, 95% CI 0.48–1.44; $P = 0.51$). In contrast, mTORi-containing regimens stood out in reducing the rate of subsequent skin cancer events in patients who had already experienced an initial posttransplant malignancy (HR 0.43, 95% CI 0.26–0.72; $P < 0.001$) (Figure 4a). Conversely, patients on a CNI-only scheme faced a two-fold increase in skin cancer rates compared with those on CNI + ATM (Figure 4b). The combination of mTORi with reduced-exposure CNI was associated with 37% lower event rates in high-risk patients (HR 0.63, 95% CI 0.42–0.93; $P = 0.02$) and 32% lower rates in those who developed posttransplant skin cancer (HR 0.68, 95% CI 0.47–0.98; $P = 0.04$) (Figure 4b). Stratifying by cancer type, mTORi + rCNI regimens were associated with SCC risk reductions (HR 0.52, 95% CI 0.34–0.78; $P < 0.001$) but showed no significant impact on BCC rates (HR 0.93, 95% CI 0.59–1.47; $P = 0.76$) (Table S4; see Supporting Information). Although the mTORi + ATM regimen was rarely prescribed in our cohort, it showed the most substantial reduction in malignancy rates, particularly among patients who developed posttransplant skin cancer (HR 0.07, 95% CI 0.01–0.53; $P = 0.01$) (Figure 4b).

Discussion

This study explored the real-life impact of current IS drugs and maintenance regimens on the risk of skin cancer among a prospective cohort of 1055 SOTRs. We found significant differences in skin cancer risk between IS regimens, underscoring the importance of regimen and drug selection in clinical practice.[12]

Regimens including mTORi were associated with substantial protection against the overall occurrence of skin cancer in SOTRs, especially in high-risk patients and in those who developed posttransplant skin cancer, with rate reductions ranging from 33% to 46%. These numbers are in line with those from clinical trials and meta-analyses (33–44%).[7,10,11,19,25] The anticancer properties of mTORi are linked to their capacity to suppress cell growth, angiogenesis and viral replication along with their involvement in boosting DNA repair and enhancing memory T-cell function.[18,37–39]

In the context of primary prevention, while mTORi-containing regimens seemed effective in reducing the overall skin cancer burden, their benefit was not clear in preventing the occurrence of a first event in high-risk patients. Interestingly, animal and clinical studies also show that mTORi do not play a major role in tumour initiation, but rather in progression by

decreasing tumour vascularization, thickness and diameter.[7,39,40] This suggests that we still need to identify high-risk patients who might benefit from early switching (e.g. patients with several precancerous or *in situ* lesions), and insist on other preventive measures such as rigorous sun protection, treatment of actinic keratoses, chemoprevention and timely dermatological screening.[3,13,29,41,42]

For secondary skin cancer prevention, mTORi-containing regimens appeared particularly effective, with a 57% rate reduction among patients with posttransplant cutaneous malignancy. This supports the early switch to mTORi-based regimens for SOTRs after invasive SCC diagnosis, as the ability of mTORi to reduce subsequent cancers is well demonstrated from animal, observational and clinical trial studies.[7,10,11,39,43,44]

The combination of mTORi + ATM, although infrequent, was associated with the most substantial reductions in skin cancer risk, particularly in patients who developed skin cancer. This could be attributed to the full withdrawal of the CNI, the antitumoral properties of mTORi, and the mostly neutral or protective effect of MMF.[16–18] In our study, after adjusting for concomitant immunosuppressive therapies, MMF was associated with a nearly 60% reduction in the risk of posttransplant skin cancer, suggesting a potential protective effect in patients who develop skin cancer. Similarly, in the study by Vos *et al*., sequential switching from azathioprine to MMF in lung transplant recipients was associated with a significantly lower risk of cutaneous SCC (HR 0.24, 95% CI 0.10–0.56).[45] This protective effect may be explained by MMF's known ability to inhibit tumour growth and angiogenesis in animal models and, by the fact that, unlike azathioprine, it does not promote incorporation of 6-thioguanine pseudobases that photosensitize DNA.[17,39,46]

Unexpectedly, everolimus seemed more effective than sirolimus in reducing overall skin cancer rates, including among high-risk patients. Although it did not significantly surpass sirolimus in those with posttransplant skin cancer, our findings suggest that everolimus could be the preferred choice, with sirolimus remaining an option for secondary cancer prevention.[7,8,12]

Despite the outlined benefits, exposure to mTORi was low, accounting for less than 20% of cohort exposure, with the majority on a tacrolimus/CNI-based regimen, as is common practice worldwide.[8,16] This low proportion may be partly explained by the discontinuation of mTORi in some patients, primarily due to poor tolerability. In our cohort, ciclosporin use was rare, with tacrolimus in combination with mycophenolate (CNI + ATM) being the predominant regimen, aligning with recent US data.[8,16]

We found that exposure to tacrolimus was associated with a significant increase in skin cancer incidence, with rates elevated four- to five-fold across all subgroups. In fact, a meta-analysis and a nested case–control study found no reduction in skin cancer rates with tacrolimus compared with ciclosporin.[17,41] The carcinogenic effects of CNIs are well-documented, with mechanisms involving Ras pathway activation, disruption of the p53 pathway, and interference with immune surveillance, DNA repair and apoptosis.[47–51] These findings indicate that tacrolimus still remains a major driver of carcinogenesis in SOTRs.[41,47] To mitigate carcinogenic risk, while also improving nephrotoxicity and tolerability, regimens combining low-exposure CNI with mTORi are increasingly favoured.[14,20,23] This approach is supported by evidence that reducing or discontinuing ciclosporin lowers skin cancer rates, although data on tacrolimus remain limited.[6,7,47,52,53] In our study, reduced-dose tacrolimus combined with an mTORi was associated with lower skin cancer risk, particularly for SCC events, with observed rate reductions of 37% in high-risk patients and 32% in those with posttransplant events. These findings add novel evidence to support the clinical shift to this regimen, which had limited and conflicting support regarding skin malignancies.[20,23–25,41]

In contrast, regimens relying solely on CNIs were linked to a significantly higher skin cancer risk. These findings highlight the need for clinicians to reconsider the use of CNI-heavy regimens in patients at elevated risk for skin cancer, particularly after an SCC event or a high tumour burden is observed.

The strengths of this study include its prospective design, large cohort size, extended follow-up period, high number of skin cancer events and detailed documentation of current immunosuppressive drug use and confounding factors. We also accounted for time-varying drug exposure using frailty models and recurrent event analysis with extensive covariate adjustment. The inclusion of subgroup analyses and the SUNTRAC tool for risk stratification were used to improve the relevance of the results for clinical decision-making.

Despite these strengths, several limitations must be acknowledged. The observational nature of the study may have led to residual confounding by indication, including potential time-varying confounding of the association between drugs/regimens and skin cancer, as well as selection bias.[34] Additionally, some immunosuppressive regimens and drugs were infrequently used in our cohort, limiting our ability to provide precise estimates for these treatments. The single-centre design may also restrict the generalizability of our findings to other transplant populations.

Ultimately, IS modification should be a multidisciplinary decision tailored to each transplant recipient, focusing on minimizing cancer risk, preserving graft function, managing adverse

events and ultimately reducing mortality risk.[12,41] Our data strongly support the preferential use of mTORi, even in combination with low-dose CNIs, in high-risk patients and those who develop posttransplant skin cancer. While our findings are promising, clinical trials focusing on skin cancer are necessary to confirm these benefits. Trials are needed to assess the benefit of early introduction of mTORi-based regimens in patients identified as high- or very high risk by the SUNTRAC tool at the time of transplant.[3,29] Ongoing research is also needed to clarify the skin cancer risk associated with newer IS drugs.[16,41,54,55]

In conclusion, this real-life prospective study provides updated knowledge on the differences in skin cancer risk among various IS regimens, emphasizing the need for careful IS drug selection in clinical practice. mTORi-based regimens, when paired with reduced-dose CNIs or ATMs, like MMF, seem to offer a safer alternative to CNI-heavy approaches regarding skin cancer risk. Transplant teams should consider switching to these regimens to improve skin cancer outcomes in high-risk SOTRs.

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Conflicts of interest

A.G.-T. has received support from Almirall, Galderma, LEO Pharma, Novartis and UCB for congress attendance and speaker honoraria outside of the submitted work. **C.G.C.** has received support from Almirall, Johnson & Johnson, LEO Pharma and Sun Pharma for congress attendance, advisory boards, consultancy or speaker honoraria outside of the

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

This study was approved by the Vall d'Hebron University Hospital Ethics Committee and the national drug committee (CFP-AZA-2020-01). All procedures were conducted in accordance with the Declaration of Helsinki and relevant institutional guidelines.

Patient consent

Written patient consent for publication was obtained.

AI disclosure

ChatGPT 4.0 (OpenAI, 2025) was used sparingly to assist in editing certain sentences of the manuscript, but not for data analysis, table generation or figure creation. Image creation mode was used to create illustrations for the graphical abstract which were further modified by the authors.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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Figure legends

Figure 1 (a) Patient timelines of immunosuppressive (IS) treatments, visits and skin cancer events in those with more than three events. Black dots indicate dermatology visits with at least one skin cancer diagnosis; white dots indicate visits without skin cancer events. (b) Relative cohort exposure to immunosuppressive therapies by clinical characteristics. Colour of bar indicates type of IS therapy exposure. ATM, antimetabolite; CNI, calcineurin inhibitor; rCNI, reduced-exposure calcineurin inhibitor; mTORi, mammalian target of rapamycin inhibitor.

Figure 2 Skin cancer risk by immunosuppressive drug family: hazard ratios and 95% confidence intervals (CIs) from multivariate Cox regression models. *N* (events) is the number of patients and number of visits with at least one skin cancer event. High-risk patients are those in the high- or very high-risk categories of the SUNTRAC (Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator) tool at the time of transplant. ‘Skin cancer patients’ refers to patients with posttransplant skin cancer events. Crude models were adjusted by other coadministered immunosuppressive drugs. Adjusted models included

additional covariates such as age; sex; race and ethnicity; smoking; induction with immunoglobulins; acute graft rejection; year and type of transplant; time since transplant; frequency and number of dermatology visits; baseline actinic damage; and pre- and posttransplant skin cancer events. mTOR, mammalian target of rapamycin.

Figure 3 Skin cancer risk by immunosuppressive drug: hazard ratios and 95% confidence intervals (CIs) from multivariate Cox regression models. *N* (events) is the number of patients and number of visits with at least one skin cancer event. High-risk patients are those in the high- or very high-risk categories of the SUNTRAC (Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator) tool at the time of transplant. 'Skin cancer patients' refers to patients with posttransplant skin cancer events. Crude models were adjusted by other coadministered immunosuppressive drugs. Adjusted models included additional covariates such as age; sex; race and ethnicity; smoking; induction with immunoglobulins; acute graft rejection; year and type of transplant; time since transplant; frequency and number of dermatology visits; baseline actinic damage; and pre- and posttransplant skin cancer events. MMF/MPA, mycophenolate mofetil/mycophenolic acid.

Figure 4 Skin cancer risk by immunosuppressive regimens: hazard ratios and 95% confidence intervals (CIs) from multivariate Cox regression models. *N* (events) is the number of patients and number of visits with at least one skin cancer event. High-risk patients are those in the high- or very high-risk categories of the SUNTRAC (Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator) tool at the time of transplant. 'Skin cancer patients' refers to patients with posttransplant skin cancer events. All models were adjusted by corticosteroid use. Adjusted models included additional covariates such as age; sex; race and ethnicity; smoking; induction with immunoglobulins; acute graft rejection; year and type of transplant; time since transplant; frequency and number of dermatology visits; baseline actinic damage; and pre- and posttransplant skin cancer events. ATM, antimetabolite; CNI, calcineurin inhibitor; rCNI, reduced-exposure calcineurin inhibitor; mTORi, mammalian target of rapamycin inhibitor.

Table 1 Cohort characteristics by posttransplant SC (skin cancer)

	SC (*n* = 131)	**No SC (*n* = 924)**	**Total (*N* = 1055)**	***P*-value[a]**
Transplant age (years), median (IQR)	60.5 (56.0–67.0)	56.0 (46.0–63.0)	57.0 (47.0–63.0)	< 0.001[b]
Sex				0.02
Female	34 (26.0)	341 (36.9)	375 (35.5)	
Male	97 (74.0)	583 (63.1)	680 (64.5)	
Race and ethnicity				0.002
Asian	0 (0)	7 (0.8)	7 (0.7)	NA
Black	0 (0)	15 (1.6)	15 (1.4)	NA
Latinx	1 (0.8)	52 (5.6)	53 (5.0)	0.02[c]
Middle Eastern and North African	0 (0)	34 (3.7)	34 (3.2)	NA
White	130 (99.2)	816 (88.3)	946 (89.7)	0.02[c]
Type of transplant				0.03
Kidney	66 (50.4)	382 (41.3)	448 (42.5)	0.19[c]
Liver	17 (13.0)	127 (13.7)	144 (13.6)	0.99[c]
Single lung	19 (14.5)	138 (14.9)	157 (14.9)	0.99[c]
Double lung	26 (19.8)	269 (29.1)	295 (28.0)	0.18[c]
Heart–lung	1 (0.8)	0 (0)	1 (0.1)	NA
Other	2 (1.5)	8 (0.9)	10 (0.9)	0.99[c]
Type of transplant, grouped				0.06
Renal	66 (50.4)	382 (41.3)	448 (42.5)	
Nonrenal	65 (49.6)	542 (58.7)	607 (57.5)	
Baseline sun damage				< 0.001[d]
Absent	7 (5.5)	199 (22.3)	206 (20.2)	
Mild	68 (53.5)	564 (63.2)	632 (62.0)	
Moderate	47 (37.0)	128 (14.3)	175 (17.2)	
Severe	5 (3.9)	2 (0.2)	7 (0.7)	
Previous transplant	6 (5.0)	46 (5.4)	52 (5.4)	0.99
Previous immunosuppression	24 (21.2)	169 (21.2)	193 (21.2)	0.99
Type of induction regimen				0.11
Thymoglobuline®	18 (13.7)	164 (17.7)	182 (17.3)	
Basiliximab	38 (29.0)	200 (21.6)	238 (22.6)	
No antibodies or plasmapheresis	74 (56.5)	558 (60.4)	632 (59.9)	
Other	1 (0.8)	2 (0.2)	3 (0.3)	

Pretransplant history of skin cancer	12 (9.2)	26 (2.8)	38 (3.6)	0.001
SUNTRAC group				< 0.001
High- & very high risk	107 (81.7)	495 (53.6)	602 (57.1)	
Low- & medium risk	24 (18.3)	429 (46.4)	453 (42.9)	
mTORi introduction during follow-up				< 0.001
mTORi switch	44 (33.6)	114 (12.3)	158 (15.0)	
No mTORi switch	87 (66.4)	810 (87.7)	897 (85.0)	
Death during follow-up	22 (16.9)	163 (17.9)	185 (17.8)	0.90
Follow-up (years), median (IQR)	5.5 (3.4–7.4)	2.3 (0.6–4.5)	2.5 (0.8–5.2)	< 0.001[b]

All values are presented as *n* (%) unless otherwise indicated. IQR, interquartile range; mTORi, mammalian target of rapamycin inhibitor; NA, not applicable; SUNTRAC, Skin and Ultraviolet Neoplasia Risk Assessment Calculator. [a]*P*-values were calculated via Fisher's exact test unless otherwise indicated. [b]Kruskal–Wallis rank sum test. [c]Post hoc tests: row-wise Fisher's exact test with Holm's correction. [d]Trend test for ordinal variables.