ORIGINAL ARTICLE

Cumulative incidence and risk factors for cutaneous squamous cell carcinoma metastases in organ transplant recipients: The Skin Care in Organ Transplant Patients in Europe-International Transplant Skin Cancer Collaborative metastases study, a prospective multicenter study

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Introduction: Solid organ transplant recipients (SOTRs) are believed to have an increased risk of metastatic cutaneous squamous cell carcinoma (cSCC), but reliable data are lacking regarding the precise incidence and associated risk factors.

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Methods: In a prospective cohort study, including 19 specialist dermatology outpatient clinics in 15 countries, patient and tumor characteristics were collected using standardized questionnaires when SOTRs presented with a new cSCC. After a minimum of 2 years of follow-up, relevant data for all SOTRs were collected. Cumulative incidence of metastases was calculated by the Aalen-Johansen estimator. Fine and Gray models were used to assess multiple risk factors for metastases.

Results: Of 514 SOTRs who presented with 623 primary cSCCs, metastases developed in 37 with a 2-year patient-based cumulative incidence of 6.2%. Risk factors for metastases included location in the head and neck area, local recurrence, size > 2 cm, clinical ulceration, poor differentiation grade, perineural invasion, and deep invasion. A high-stage tumor that is also ulcerated showed the highest risk of metastasis, with a 2-year cumulative incidence of 46.2% (31.9%-68.4%).

Conclusions: SOTRs have a high risk of cSCC metastases and well-established clinical and histologic risk factors have been confirmed. High-stage, ulcerated cSCCs have the highest risk of metastasis. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2024.01.040.)

Key words: immunosuppression; organ transplantation; skin cancer; squamous cell carcinoma.

INTRODUCTION

Solid organ transplant recipients (SOTRs) have a 50- to 100-fold increased risk of cutaneous squamous cell carcinoma (cSCC) development compared with immunocompetent patients.[1-6] In addition, multiple cSCCs often develop in SOTRs.[7] In immunocompetent patients, the lifetime risk of cSCC metastases development varies between 2% and 4%.[8-10] In SOTRs, although reliable data are lacking, cSCC metastasis is thought to occur in up to 10%.[11] cSCC metastases usually develop within 2 years of the primary cSCC.[12,13]

CAPSULE SUMMARY

- Solid organ transplant recipients have an increased risk of cutaneous squamous cell carcinoma metastases. It is unknown whether this is caused by a more aggressive behavior or the presence of multiple cutaneous squamous cell carcinomas.
- Prevention of subsequent tumors in these patients is important in reducing the lifetime-risk of metastasis.

In the general population, various clinicopathologic criteria are associated with an increased risk of metastasis, including tumors in the head and neck area, increasing size, depth and histologic grade, perineural invasion, and local recurrence.[10,14,15] Risk factors for metastases in SOTRs are similar, but it is thought that drug-induced immunosuppression also contributes to worse outcomes.[4,16] Furthermore, cSCCs in SOTRs might present with a higher proportion of histologic high-risk cSCCs compared with immunocompetent patients.[17]

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Patient consent: All patient information in this article has been anonymized. Nevertheless, informed consent off all patients was obtained by the authors and included at the time of article submission to the journal stating that all patients gave consent with the understanding that this information may be publicly available.

IRB approval status: The study was conducted according to the principles of the Declaration of Helsinki (adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, Korea, October 2008) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). The ethics committee of the Leiden University Medical Center (LUMC) had approved the proposal (P12.117), and separate ethical approval was obtained in all participating centers.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Abbreviations used:

AJCC: American Joint Committee on Cancer
BWH: Brigham and Women's Hospital
cSCC: cutaneous squamous cell carcinoma
SHR: subdistribution hazard ratio
SOTR: solid organ transplant recipient

Tumor classification systems have been developed to predict poor outcomes. Most commonly used are the American Joint Committee on Cancer (AJCC), Union for International Cancer Control, and Brigham and Women's Hospital (BWH) staging systems. Although immunosuppression is often mentioned as a risk factor for metastases, it is not incorporated into these staging systems. The positive predictive value of AJCC8 for poor outcomes is only 17%[15,18,19] as the majority of "high-risk" cSCCs do not develop advanced disease, and this system does not allow accurate prediction of which cSCCs are more likely to progress to metastatic disease or disease-specific death.[14,18] The BWH staging system performs better, but positive predictive value for poor outcomes is just 24% to 38%.[19] Better insight into contributions of possible risk factors to cSCC metastasis will help to develop better staging systems in the future.

The aim of this study was to prospectively determine the cumulative incidence of metastases 1 and 2 years after diagnosis of cSCC in SOTRs. The second objective of the study was to assess risk factors for metastases.

METHODS

This study was a collaboration between SCOPE (Skin Care in Organ Transplant Patients in Europe, http://www.scopenetwork.org/) and ITSCC (International Transplant Skin Cancer Collaborative, http://www.itscc.org/) networks. Nineteen centers in the Netherlands, Switzerland, France, Belgium, Italy, Spain, Portugal, United Kingdom, Poland, Turkey, Czech Republic, Austria, United States, New Zealand, and Brazil were included.

Between 2013 and 2018, SOTRs undergoing routine surveillance in specialized dermatology clinics (university hospitals and clinics led by dermatologists specialized in skin cancer in SOTRs), who had no cSCC metastases, were recruited at diagnosis of a first or a subsequent primary cSCC (the "index-cSCC," ie, the cSCC with which the patient presented to the outpatient clinic and which lead to inclusion in the study). In the case of SOTRs presenting with concurrent multiple primary cSCCs, there were multiple index-cSCCs. *In situ* cSCCs were excluded.

If there was suspicion of cSCC metastasis, most patients underwent various additional procedures including lymph node palpation, ultrasonography, aspirate, sentinel node biopsy, lymph node dissection, X-ray, computed tomography scan, magnetic resonance imaging scan, and/or positron emission tomography-computed tomography scan. After a minimum of 2 years of follow-up, relevant data for all included SOTRs were collected according to a prespecified study protocol.

Medical history including age, sex, type of transplant, number of skin cancers before inclusion, index tumor characteristics, and histopathologic data were collected at inclusion in the study using standardized questionnaires (Supplementary Materials, available via Mendeley at https://data.mendeley.com/datasets/458kxcvxcg/1).

During the 2-year follow-up period the occurrence of metastasis was recorded. For patients in whom cSCC metastases developed during the follow-up period, we collected data of all cSCCs that developed since transplantation in order to be able to determining the primary metastasizing cSCC.

Details of the immunosuppressive regimen at study inclusion were collected, including the use of sirolimus and everolimus. We also recorded the chemopreventive use of acitretin.

Medical ethics

The data of all patients were collected separately in the participating clinical centers. After assigning a unique study number to each patient the data were sent to the Leiden University Medical Center, Leiden, the Netherlands, and entered anonymously in a digital access database.

Statistical analysis

Baseline demographics and characteristics of index-cSCCs stratified by patients with no metastasis and patients with metastasis, were analyzed using descriptive statistics and frequency tabulations to evaluate for differences between groups. The date of inclusion in the study was used as the starting date for analysis and the end date for analysis was date of first metastasis, death, or end of 2-year follow-up. Patients in whom an outcome of interest was not developed were censored for analysis on their date of death or at last follow-up. The Aalen-Johansen estimator was used to calculate the cumulative incidence of metastases, considering non-cSCC death as a competing event. Univariate competing risk regression was used to assess factors including

Table I. Baseline characteristics of the organ transplant recipients included in the study according to the later development of metastases of the index cutaneous squamous cell carcinomas and the later primary cutaneous squamous cell carcinomas developing after inclusion in the study, but before the end of the 2-year follow-up period

Characteristics	Total (*N* = 514) *n* (%)	No metastasis (*N* = 477) *n* (%)	Metastasis (*N* = 37) *n* (%)
Sex			
Women	120 (23.3)	111 (23.3)	9 (24.3)
Men	394 (76.7)	366 (76.7)	28 (75.7)
Age at transplantation (y)			
Median (IQR)	51.2 (36.4-60.3)	51.4 (36.5-60.3)	48.0 (34.0-67.1)
Age at inclusion study (y)			
Median (IQR)	66.4 (58.4-72.3)	66.4 (58.4-72.1)	67.5 (56.5-73.2)
Years after transplantation at inclusion study			
Median (IQR)	14.5 (6.5-25.1)	14.5 (6.7-25.1)	13.9 (5.1-25.3)
Skin type			
I	55 (10.9)	50 (10.7)	5 (13.5)
II	251 (49.6)	230 (49.0)	21 (56.8)
III	172 (34.0)	161 (34.3)	11 (29.7)
IV, V, or VI	28 (5.5)	28 (6.0)	0
Unknown or missing value	8	8	0
Type of transplantation			
Kidney	353 (68.7)	325 (68.1)	28 (75.7)
Kidney plus pancreas	22 (4.3)	20 (4.2)	2 (5.4)
Heart	43 (8.3)	41 (8.6)	2 (5.4)
Liver	54 (10.5)	53 (11.2)	1 (2.7)
Lung	40 (7.8)	36 (7.5)	4 (10.8)
Pancreas alone	2 (0.4)	2 (0.4)	0
No. of cSCC before index-cSCC			
0	212 (41.4)	202 (42.5)	10 (27.0)
1	81 (15.8)	71 (14.9)	10 (27.0)
2	45 (8.8)	43 (9.1)	2 (5.4)
3-9	117 (22.9)	110 (23.2)	7 (18.9)
≥10	57 (11.1)	49 (10.3)	8 (21.7)
Unknown or missing value	2	2	0

The *P* values of the categorical data were calculated with a χ^2 test and the continuous data with analyses of variance.
cSCC, cutaneous squamous cell carcinoma.

sex, age at transplantation and inclusion, and predefined risk factors. Variables with a *P* value of <.05 were considered statistically significant and included in the final model. Fine and Gray competing risk regression was used to evaluate risk factors for metastasis. Twenty-three patients were a part of the analysis in the Fine-Gray subdistribution hazard model tables. The number of patients included in the model and the number of patients excluded (censored because outside of analysis time or missing event time) were 75 and 336. Regression analysis excludes tumors with missing data; therefore, if there were missing data, that tumor would not contribute to data. Ordinal data were analyzed with χ^2 test and continuous data with analyses of variance. *P* values of ≤.05 were considered statistically significant. Statistical analyses were performed by using SPSS 25 and Stata 17.

RESULTS

Sixteen centers in 12 European countries and 3 centers from outside Europe contributed a total of 514 SOTRs with 621 (ranging from 1 to 7 tumors) index-cSCC.

Baseline characteristics of 514 SOTRs according to the later development of cSCC metastases are presented in Table I. In total, 76.7% were males and the mean age at transplantation was 51.2 years. Tumors were predominantly found in patients with Fitzpatrick skin type I to III and the most frequently transplanted organ was the kidney. The distribution of sex, age at inclusion, age at transplantation, skin type, and type of transplantation did not differ significantly between the patients with and without metastases, but those in whom metastases developed had significantly higher numbers of previous cSCC.

There were 38 different immunosuppressive regimens used at the time of inclusion. The most common regimen was triple therapy with prednisone, mycophenolate mofetil and tacrolimus (n = 90, 17.5%), followed by prednisone, mycophenolate mofetil, and cyclosporin (n = 61, 11.9%). In addition, many patients received dual therapy with prednisone and azathioprine (n = 51, 9.9%), prednisone and cyclosporin (n = 35, 6.8%), prednisone and tacrolimus (n = 38, 7.4%), or mycophenolate mofetil and tacrolimus (n = 38, 7.4%). Any combination with an mTOR inhibitor was given to 73 (14.2%) patients.

The median follow-up period after inclusion into the study was 2.3 years, with 75% of the SOTRs having a follow-up of at least 2 years (range: 0.05-6.5 years). During the follow-up period, 297 SOTRs had 860 (range: 1-36) additional cSCCs and 37 SOTRs (7.2%) had a cSCC metastasis: in 26 (4.2%) SOTRs, the metastasis was attributed to the index-cSCC and in 11 SOTRs, the metastasis developed from a subsequent nonindex-cSCC diagnosed during the follow-up period of the index-cSCC. Ninety-three (18.1%) SOTRs died during the follow-up period. Of the 37 SOTRs with cSCC metastases, 25 (67.6%) died before the end of the study, with 16 (64%) succumbing to metastatic disease, and 9 deaths due to other reasons. Five SOTRs with cSCC metastases were still alive and on treatment for metastases, and 7 were alive and disease-free at study end.

The person-based cumulative incidence from the 514 patients, based on 26 metastasized index-cSCCs and 11 other nonindex-cSCCs, diagnosed before the start of the study period and metastasized during the study period inclusion date of the index-cSCC, was 4.5% at 1 year and 6.2% at 2 years after inclusion in the study. The cSCC-based cumulative incidence of metastases from the 621 index-cSCCs was lower, with 3.1% and 4.2% at 1 and 2 years, respectively.

The most common location of metastasis was in the regional lymph nodes (in 19 cases, 73.1%). In-transit metastases were observed in 7 cases and distant organ metastases in 9 cases. Distant metastases were isolated in 4 of 9 cases and occurred in combination with lymph node metastases in 5 of 9 cases. In the latter group, distant metastases were identified after nodal disease in 3 of 5 cases and concurrent with nodal/in-transit disease in 2 of 5 cases.

Characteristics of all 621 index-cSCCs are shown in Table II. The time from transplantation to index-cSCC did not differ for those with/without metastasis. The 26 index-cSCCs that metastasized were more often sized >2 cm and located in the head and neck area. Also, these tumors were more often clinically ulcerated and less often hyperkeratotic compared with nonmetastasizing index-cSCCs. In 44% of metastatic cSCCs, surgical margins were not clear at first treatment and almost one-third of the metastasizing cSCCs were locally recurrent cSCCs. Metastatic cSCCs were more often poorly or undifferentiated tumors. Likewise, perineural invasion and invasion into the subcutaneous fat or deeper structures were significantly more frequent in metastasizing cSCCs. Using the BWH staging system, metastatic cSCCs were more often staged as T2b or T3 tumors compared with nonmetastasizing cSCCs. Similar results were found using the AJCC8 classification system.

Fine and Gray subdistribution hazard models are displayed in Tables III and IV. With univariate analysis (Table III), ulcerating cSCCs were associated with metastasis. Metastasized cSCCs were significantly more often staged as "high-stage" tumors using both the BWH and the AJCC8 staging systems. For the BWH and AJCC8 staging systems combined, a subdistribution hazard ratio (SHR) of 6.5 (95% CI: 2.9-14.2) was found.

Multivariable analysis (Table IV) shows a SHR of 6.6 (95% CI: 3.0-14.8) for combined BWH/AJCC8 high-stage tumors and a SHR of 3.6 (95% CI: 1.6-8.3) for ulcerated cSCCs compared with nonulcerated cSCCs.

Figure 1 shows that a high-stage clinically ulcerated tumor has the highest risk of metastasis, with a cumulative incidence of 46.2% (95% CI: 31.9-68.4). Low-stage ulcerated, high-stage nonulcerated, and low-stage nonulcerated tumors showed cumulative incidences of 7.7 (95% CI: 1.8-24.7), 6 (95% CI: 1.2-21.4), and 2.9 (95% CI: 1.7-5.9), respectively.

DISCUSSION

In this prospective, multicenter study the risk of a single index-cSCC to metastasize was 4.2%, but the person-based cumulative metastasis incidence measured at 2 years after inclusion was 6.2%. Since the lifetime risk of cSCC metastases in immunocompetent patients is between 2% and 4%,[8-11] this finding suggests that SOTRs not only have an increased risk of primary cSCC, but also an increased lifetime risk of cSCC metastases. It is known that Caucasian SOTRs have an increased risk of experiencing multiple cSCCs,[20] and that patients with multiple cSCCs, especially those with >10 cSCCs,[21,22] have an increased risk of metastasis. This suggests that the elevation in lifetime risk of cSCC metastases in this study is due to the formation of multiple cSCC in SOTRs. Prophylactic measures to

Table II. Characteristics of the index cutaneous squamous cell carcinomas according to the later development of metastasis

Characteristics	All index tumors (*N* = 621) *n* (%)	Tumors without metastasis (*N* = 595) *n* (%)	Tumors with metastasis (*N* = 26) *n* (%)
General characteristics			
Sex			
Women	137 (22.1)	129 (21.7)	8 (30.8)
Men	484 (77.9)	466 (78.3)	18 (69.2)
Age at transplantation (y), median (IQR)	51.1 (36.0-60.1)	51.0 (36.0-60.1)	51.3 (32.7-68.0)
Age at inclusion study (y), median (IQR)	66.4 (58.7-72.3)	66.4 (58.6-72.2)	66.1 (59.0-73.2)
Skin type			
I	71 (11.5)	67 (11.3)	4 (15.4)
II	299 (48.3)	287 (48.4)	12 (46.2)
III	204 (33.0)	194 (32.7)	10 (38.5)
IV	34 (5.5)	34 (5.7)	0
V	3 (0.5)	3 (0.5)	0
VI	1 (0.2)	1 (0.2)	0
Unknown or missing value	7 (1.1)	7 (1.2)	0
Type of transplantation			
Kidney	432 (69.6)	414 (69.6)	18 (69.2)
Kidney plus pancreas	27 (4.3)	25 (4.2)	2 (7.7)
Heart	51 (8.2)	49 (8.2)	2 (7.7)
Liver	62 (10.0)	62 (10.4)	0
Lung	49 (7.9)	45 (7.6)	4 (15.4)
Index-cSCC related clinical characteristics			
Painful lesion			
No	314 (51.1)	302 (51.3)	12 (46.2)
Spontaneous pain	89 (14.5)	84 (14.3)	5 (19.2)
Pain only by palpation	151 (24.6)	145 (24.6)	6 (23.1)
Unknown	61 (9.9)	58 (9.8)	3 (11.5)
Clinically ulcerated			
No	419 (68.1)	410 (69.6)	9 (34.6)
Yes	147 (23.7)	133 (22.4)	14 (53.8)
Unknown	49 (8.0)	46 (7.8)	3 (11.5)
Months from first transplant to index-cSCC, median (IQR)	176 (80-315)	178 (82-317)	160 (63-275)
Months from index-cSCC to censoring, median (IQR)	27.0 (23.4-33.2)	27.3 (24.2-33.6)	4.7 (0.8-13.9)
Index-cSCC related histologic characteristics			
Horizontal size			
$<$2 cm	425 (68.4)	411 (69.1)	14 (53.8)
$\geq$2 cm	82 (13.2)	73 (12.3)	9 (34.6)
Unknown	114 (18.4)	111 (18.7)	3 (11.5)
Differentiation grade			
Well	303 (48.9)	300 (50.5)	3 (11.5)
Moderate	215 (34.7)	203 (34.2)	12 (46.2)
Poor	61 (9.8)	54 (9.1)	7 (26.9)
Undifferentiated	12 (1.9)	8 (1.3)	4 (15.4)
Unknown	29 (4.7)	29 (4.9)	0
Desmoplastic lesion			
No	520 (83.9)	499 (84.0)	21 (80.8)
Yes	49 (7.9)	45 (7.6)	4 (15.4)
Unknown	51 (8.2)	50 (8.4)	1 (3.8)
Perineural invasion			
No	529 (85.3)	515 (86.7)	14 (53.8)
Yes	24 (3.9)	16 (2.7)	8 (30.8)
Unknown	67 (10.8)	63 (10.6)	4 (15.4)

Continued

Table II. Cont'd

Characteristics	All index tumors (*N* = 621) *n* (%)	Tumors without metastasis (*N* = 595) *n* (%)	Tumors with metastasis (*N* = 26) *n* (%)
Depth of invasion			
Dermis	458 (73.9)	453 (76.3)	5 (19.2)
Subcutaneous fat	63 (10.2)	53 (8.9)	10 (38.5)
Fascia	9 (1.5)	7 (1.2)	2 (7.7)
Muscle	15 (2.4)	9 (1.5)	6 (23.1)
Bone	2 (0.3)	1 (0.2)	1 (3.8)
Brain	1 (0.2)	1 (0.2)	0 (0.0)
Unknown	72 (11.6)	70 (11.8)	2 (7.7)
Index-cSCC staging characteristics			
BWH staging			
T1	293 (70.6)	287 (48.2)	6 (23.1)
T2a	96 (15.5)	90 (15.1)	6 (23.1)
T2b	21 (3.4)	17 (2.9)	4 (15.4)
T3	5 (0.8)	2 (0.3)	3 (11.5)
Unknown	206 (33.2)	199 (33.4)	7 (26.9)
BWH staging (low vs high)			
Low-stage	389 (93.7)	377 (95.2)	12 (63.2)
High-stage	26 (6.3)	19 (4.8)	7 (36.8)
Unknown	206 (33.2)	199 (33.4)	7 (26.9)
AJCC eighth edition			
T1	243 (39.1)	233 (39.2)	10 (38.5)
T2	28 (4.5)	25 (4.2)	3 (11.5)
T3	46 (7.4)	37 (6.2)	9 (34.6)
T4	1 (0.2)	1 (0.2)	0 (0.0)
Unknown	303 (48.8)	299 (50.3)	4 (15.4)
AJCC eighth edition (low vs high)			
Low-stage	271 (85.2)	258 (87.2)	13 (59.1)
High-stage	47 (14.8)	38 (12.8)	9 (40.9)
Unknown	303 (48.8)	299 (50.3)	4 (15.4)
Combined high-stage (BWH and AJCC high-stage)			
Low-stage	410 (88.2)	396 (90.0)	14 (56.0)
High-stage	55 (11.8)	44 (10.0)	11 (44.0)

AJCC, American Joint Committee on Cancer; *BWH*, Brigham and Women's Hospital; *cSCC*, cutaneous squamous cell carcinoma.

prevent cSCC formation may therefore minimize risk of cSCC metastasis and mortality in SOTRs.

Clinical and histologic risk factors for cSCC metastases were in concordance with previous studies, namely location at the head and neck area, local recurrence, clinical ulceration, large size, poor differentiation grade, perineural invasion, and invasion into deep structures.[16] This study furthermore showed that cSCCs which metastasized were significantly more often high-stage tumors compared with nonmetastasizing cSCCs using both the BWH and AJCC8 staging systems. High-stage clinically ulcerated cSCCs had the highest risk of metastasis, with a cumulative incidence of 46.2%. Previous literature states additional risk factors for metastasis such as male sex, increasing age, and age at transplantation, however in this study those risk factors were not statistically significant.[9,11,13,23,24] A possible explanation could be that in previous studies it was thought that male patients often seek dermatologic health care in a later phase which could lead to patient delay and worse outcomes. All SOTRs in our study, however, were already under routine surveillance by a dermatologist. Also, recent literature highlighted that the female immune system offers greater protection against cSCC than the male immune system, and that in the presence of immunosuppression, women are more likely to have high-risk and metastatic cSCCs.[25] The fact that we did not find significant differences in age at inclusion and age at transplantation between metastasized and nonmetastasized cSCC could also be related to the small number of metastatic cases.

Strengths of this study include the prospective and multicenter study design. Most epidemiologic studies on metastatic risk of cSCC in SOTRs is based

Table III. Fine-Gray subdistribution hazard model—univariate analysis

	Metastasis (combined)	
Factor	**HR (95% CI)**	***P* value**
Sex		
Women	1	
Men	0.62 (0.27-1.4)	.274
Age at transplantation (y)	1.00 (0.97-1.03)	.709
Age at inclusion study (y)	0.99 (0.94-1.03)	.673
Painful lesion		
No	1	
Yes	1.4 (0.63-3.2)	.385
Clinically ulcerated		
No	1	
Yes	4.6 (2.0-10.6)	.006
Size		
<2 cm	1	
≥2 cm	4.3 (1.9-9.8)	.001
Depth		
Dermis/subcutaneous fat	1	
Beyond subcutaneous fat	15.9 (7.2-35.6)	<.001
Perineural invasion		
No	1	
Yes	14.1 (6.0-33.0)	<.001
Differentiation		
Well/moderate	1	
Poor	5.3 (2.4-11.4)	<.001
BWH stage		
T1	1	
T2a	2.6 (0.77-8.4)	.122
T2b	12.6 (3.9-41.3)	<.001
T3	36.1 (10.9-118)	<.001
AJCC eighth edition		
T1	1	
T2	3.0 (0.81-11.2)	.098
T3	5.9 (2.3-14.7)	<.001
T4	0	
AJCC high-stage		
Low-stage (T1/T2)	1	
High-stage (T3/T4)	4.8 (2.0-11.3)	<.001
Combined high-stage		
Low-stage	1	
High-stage (high-stage BWH/high-stage AJCC)	6.5 (2.9-14.2)	<.001
No. of cSCC before index-cSCC		
<5	1	
5-9	0.78 (0.19-3.3)	.743
10-19	1.6 (0.56-4.8)	.366
≥20	0.76 (0.10-5.5)	.783

AJCC, American Joint Committee on Cancer; *BWH*, Brigham and Women's Hospital; *cSCC*, cutaneous squamous cell carcinoma; *HR*, hazard ratio.

Table IV. Fine-Gray subdistribution hazard model—multivariable analysis

	Metastasis (combined)	
Factor	**SHR (95% CI)**	***P* value**
Combined high-stage		
Low-stage	1	
High-stage (high-stage BWH/high-stage AJCC)	6.6 (3.0-14.8)	<.001
Clinically ulcerated		
No	1	
Yes	3.6 (1.6-8.3)	.002

AJCC, American Joint Committee on Cancer; *BWH*, Brigham and Women's Hospital; *SHR*, subdistribution hazard ratio.

on retrospective data.[9,10,14] Knowing that SOTRs having an increased risk of experiencing multiple cSCCs,[7] with some of them experiencing over 100 cSCCs, the prospective design of this study is important to help answer the question whether immunosuppression itself leads to a more aggressive behavior of cSCC in SOTRs or whether the multiplicity of cSCC is to blame for the increased risk of cSCC metastases. Another strength of this study is the adequate follow-up time of 2 years to detect metastasis. Nevertheless, several limitations need to be considered. The first concern is the diversity of SOTRs included in this study. Not only did we include a variety of transplanted organs in this study including a mixture of kidney, pancreas, heart, lung, and liver transplantations or a combination, due to the international multicenter design of the study, SOTRs often received different treatments for cSCCs (Mohs micrographic surgery, conventional excision, electrodessication, and curettage or radiotherapy). This study was also not designed to investigate the exact association of different immunosuppressive regimens on cSCC metastases relative to each other, which is important as each immunosuppressive drug has a different mechanism of action and risk of cSCC. A second limitation is that it was not possible to obtain clinical information for all cSCCs diagnosed before the start of the study for each of the 571 SOTRs: these data were only collected for the 26 patients with metastasized index-cSCCs. Third, histopathologic data, especially perineural invasion and depth of invasion, were often missing. Therefore, staging according to the BWH and AJCC8 staging system was only possible in 415 and 318 index-cSCCs, respectively. Lastly, many SOTRs had already >10 cSCCs before inclusion in the study, which may have influenced the outcome of this study. Nevertheless, we believe that this study contributes to a better understanding of metastatic behavior and risk factors for cSCC metastasis in SOTRs.

In conclusion, the person-based cumulative incidence of cSCC metastasis after a follow-up period of 2 years was 6.2%, which indicates an increased

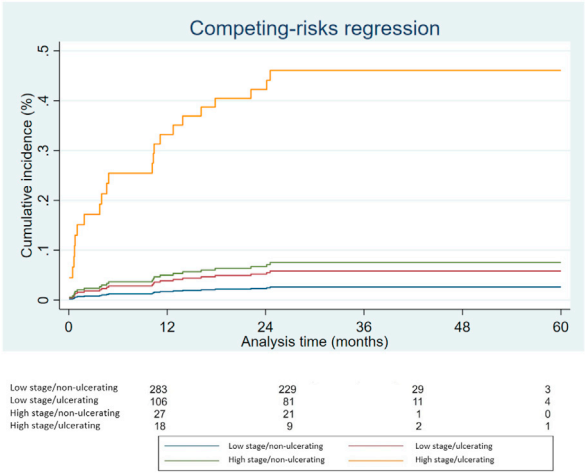

Fig 1. Competing-risks regression model showing the risk of metastases caused by cutaneous squamous cell carcinomas in combined low-stage nonulcerating tumors, low-stage ulcerating tumors, high-stage nonulcerating tumors, and high-stage ulcerating tumors.

risk of cSCC metastases in SOTRs compared with immunocompetent individuals. Well-established risk factors have been confirmed in this study, including location at the head and neck area, local recurrence, large size, clinical ulceration, poor differentiation grade, perineural invasion, and invasion into deep structures. High-stage clinically ulcerated tumors showed the highest risk of metastasis with a cumulative incidence of 46.2%. Because of the study design and complex nature of the different immunosuppressive regimens, it was not possible to draw firm conclusions on their risk of cSCC metastases, and future studies are necessary to investigate the association in more depth.

Finally, we demonstrate that at least part of the increased person-based cumulative risk of metastasis in SOTRs was the result of subsequent multiple cSCC development. This highlights the importance of efforts to prevent subsequent primary cSCC in these high-risk individuals as a key approach to reducing lifetime risk of cSCC metastasis.

Conflicts of interest

This study was partly sponsored by the European Academy of Dermatology and Venerology (EADV), however this did not affect the content of the manuscript. The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

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