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Painful skin lesions and squamous cell carcinoma predict overall mortality risk in organ transplant recipients: A cohort study

Running head: Pain, squamous cell carcinoma and overall mortality

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Key Words: squamous cell carcinoma, organ transplant recipients, epidemiology, death rate.

This study was not sponsored.

What's already known about this topic

Organ transplant recipients have a highly increased risk of cutaneous squamous cell carcinomas. Sensation of pain in cutaneous tumours is a powerful patient-reported warning signal for invasive cutaneous squamous cell carcinomas in organ transplant recipients. The question is whether painful lesions and the development of squamous cell carcinomas can predict the prognosis quoad vitam.

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What does this study add

Organ transplant recipients have an increased overall mortality risk if they develop painful skin lesions or are diagnosed with cutaneous squamous cell carcinomas. This finding highlights the need for close and long-term follow-up of organ transplant recipients who present with cutaneous squamous cell carcinomas or painful skin lesions in view of the higher overall mortality risk observed in these patients.

Abbreviations:

SCC: squamous cell carcinoma

BCC: basal cell carcinoma

KA: keratoacanthoma

OTR: organ transplant recipients

CI: confidence interval

SCOPE: Skin Care in Organ transplant Patients Europe

ITSCC: International Transplant Skin Cancer Collaborative

Abstract

Background: Organ transplant recipients have a highly increased risk of cutaneous squamous cell carcinomas. Sensation of pain in cutaneous tumours is a powerful patient-reported warning signal for invasive cutaneous squamous cell carcinomas in organ transplant recipients.

Objectives: The impact of painful compared to painless skin lesions and cutaneous squamous cell carcinoma (SCC) compared to other skin lesions on the overall mortality risk in organ transplant recipients (OTR) was investigated.

Methods: We followed 410 OTR from 10 different centres across Europe and North America during the period between 2008 and 2015. These patients had been enrolled in an earlier

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study to define clinically meaningful patient-reported warning signals predicting the presence of SCC and had been included if they had a lesion requiring histological diagnosis. Cumulative incidences of overall mortality were calculated using Kaplan-Meier survival analysis and risk factors were analysed with Cox proportional hazard analysis.

Results: There was an increased overall mortality risk in OTR who reported painful compared to painless skin lesions with a hazard ratio adjusted for age, sex, and other relevant factors of 1.6 (95% CI 0.97-2.7). There was also an increased overall mortality risk in OTR diagnosed with SCC compared to other skin lesions with an adjusted hazard ratio of 1.7 (95% CI 1.0-2.8). Mortality due to internal malignancies and systemic infections appeared to prevail in OTR with SCC.

Conclusions: We suggest that OTR have an increased overall mortality risk if they develop painful skin lesions or are diagnosed with cutaneous SCC.

Introduction

It has been well documented that organ transplant recipients (OTR) have a highly increased risk of cutaneous squamous cell carcinomas (SCC) compared to the general immunocompetent population, with reported increased risks of up to 50 to 100-fold.[1-3] In a previous study conducted by SCOPE (Skin Care in Organ transplant Patients Europe) and ITSCC (International Transplant Skin Cancer Collaborative) we reported that sensation of pain in cutaneous tumours is a powerful patient-reported warning signal for invasive cutaneous SCC in OTR.[4] Pain has, therefore, been identified as a key feature of SCC in OTR.[4;5] This important symptom helps to empower patients to seek treatment earlier.

Other skin conditions such as basal cell carcinoma (BCC) can present with pain as

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well,[5] but we could not confirm this in the SCOPE-ITSCC PAIN study.[4] Pain in general has also been reported to be associated with an increased risk of mortality, although the exact relationship is unclear and there is paucity of published data to date.[6-8] Earlier studies showed that OTR with cutaneous SCC have an increased risk of mortality from both malignancy and other causes.[9-11] Increased overall mortality after SCC may not be explained by the occurrence of intervening cancers alone, but perhaps reflects a more general predisposition to life-threatening illnesses.[12]

In the current study we intended to study the fate of OTR who presented with a painful compared to a painless skin lesion and with a cutaneous SCC compared to other skin lesions with regard to: 1) the development of subsequent SCC and/or BCC and 2) their risk of overall mortality. Improving our understanding of the fate of painful skin lesions and the burden of SCC in OTR is important, since these lesions can be found in a significant proportion of OTR, and are increasing with duration after transplantation.

Patients and Methods

The original SCOPE-ITSCC PAIN study was performed between July 2008 and February 2011 in 10 centres dedicated to surveillance of OTR with skin problems in Europe and the United States.[4] This investigator-sponsored study was designed by the principal investigators and emerged from a joint initiative between SCOPE, (http://www.scopenetwork.org/) and ITSCC (http://www. itscc.org/). Each site's independent ethics committee or institutional review board approved the protocol and participants gave informed consent in accordance with the Declaration of Helsinki.

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OTR could be included if they had a lesion requiring a histological diagnosis. Inclusion did not depend on the past clinical history. The study was designed to define clinically meaningful patient-reported warning signals predicting the presence of SCC. Painful lesions compared to painless lesions appeared to be the most powerful patient-reported warning signal for invasive SCC in OTR. The questions in the original study covered different aspects of pain: spontaneous pain (without touch or palpation); tenderness by touching or palpation (no spontaneous pain), intensity of pain on a visual-analog scale from 0 to 10 where 0 denotes no pain and 10 strongest pain, pain disturbing sleep as well as itching and bleeding of the lesion. For the current study spontaneous pain and tenderness by touching or palpation were combined as painful lesions and compared with painless lesions. In the original study, multiple biopsies could be taken during the first visit and additional biopsies could be taken during follow-up visits. This resulted in the inclusion of 410 patients with altogether 812 skin biopsies.

Data collection

In the current study, further clinical data in the period between 2007 and 2015 for patients enrolled in the initial SCOPE-ITSCC PAIN study cohort were collected. These additional data consisted of the dates of subsequent biopsies, the body location and the histological diagnosis (SCC/KA, BCC, Bowen's disease, or other skin tumours). The total numbers of tumours with different histologic subtypes for each patient were also captured. The occurrence of locally aggressive SCC, metastasis and death were recorded. Locally aggressive SCC were defined as SCC that were deeply invasive into the subcutaneous tissue or muscle and/or that locally recurred despite tumour-free excision margins at primary excision. Data about the cause of death were collected from the medical chart or the electronic system of the hospital.

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Statistical methods and analyses

In this cohort study, OTR who were included with painful skin lesions were compared with OTR with painless lesions and OTR with diagnoses of SCC/KA were compared with those with other histological diagnoses in relation to the endpoints of subsequent skin cancer, metastasis and/or death.

The p-values for categorical data were calculated by Pearson's 2-sided Chi-Square test and for continuous data by analyses of variance (ANOVA). Survival probabilities were estimated by the Kaplan-Meier method. The crude curves were used to depict survival in the different subgroups. We used Cox proportional hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CI) associated with mortality for painful compared to painless skin lesions and SCC/KA compared to other skin lesions. The primary outcome measurements were subsequent SCC/KA, BCC, metastasis and death. The starting date was the date of the first biopsy after the initiation of the original SCOPE-ITSCC PAIN study, and the end date was the end of the follow-up or the date of death of the patient. The HRs were adjusted for age, sex, time since transplant (i.e. time between transplant and the date of the first biopsy after the initiation of the original SCOPE-ITSCC PAIN study), number of SCC before the start of the study and, in the case of painful skin lesions, the HR was additionally adjusted for a histological diagnosis of SCC/KA, because these factors are potentially confounding factors for the associations tested. The proportional hazard assumption was tested by introducing an interaction term consisting of time and the group variable (i.e. SCC and/or KA vs. no SCC and/or KA) into the model. The hazard was supposed to be proportional if the interaction term was non-significant ($p > 0.05$). In all analyses the hazard was proportional.

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SCC and KA are often considered to be part of the same skin malignancy spectrum and are frequently treated similarly. Therefore, the histological diagnoses were grouped into invasive cutaneous SCC and/or KA and all other histological diagnoses. In sensitivity analyses SCC were also analysed without KA, but this did not lead to significantly different outcomes.

When analysing the association between painful lesions and overall mortality risk we followed two strategies: firstly, we only considered the first 410 biopsies taken during the original study without taking any further biopsies into consideration; secondly, we considered all 812 skin biopsies that were taken during the original study and we counted the number of painful lesions per patient.

When analysing the association between SCC/KA and overall mortality risk we considered the following categories of OTR with SCC: 1) OTR who were included in the original PAIN study with a biopsy of an SCC independent of their past medical history of SCC (Panel B in supplementary Figure 1); 2) OTR who were included in the original PAIN study with a biopsy of an SCC plus those OTR who had a previous medical history of SCC (Panel A in supplementary Figure 1); and 3) OTR who were included in the original PAIN study with a biopsy of an SCC plus those OTR who had a previous medical history of SCC plus those who developed an SCC during the follow-up period (Panel C in supplementary Figure 1),

For all analyses, we used the software package IBM SPSS Statistics, release 23.0 (2015; Armonk, NY).

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Results

The original SCOPE-ITSCC PAIN study included 122 OTR who presented with SCC/keratoacanthoma (KA) and 288 OTR who presented with other skin lesions at the time of inclusion (Table 1 and supplementary Figure 1). Of the 122 OTR with SCC/KA at inclusion, 88 (72.1%) already had between 1 and 100 (mean 12, median 5) SCC in their medical history and of the 288 OTR who presented with other skin lesions at the time of inclusion, 91 (31.6%) already had between 1 and 65 (mean 9, median 4) SCC in their medical history (Table 1 and supplementary Figure 1).

All 410 OTR were included in the current cohort study. From 3 patients the data regarding SCC/KA during the follow-up were not complete and from an additional 4 patients we could not determine whether they were still alive or had died.

Table 1 also shows the patient characteristics stratified by the presence of SCC/KA at inclusion in the SCOPE-ITSCC PAIN study. A total of 91 (74.6%) of the 122 patients with an SCC/KA at inclusion in the SCOPE-ITSCC PAIN study subsequently developed 1 to 125 SCC/KA (mean 9, median 5). Altogether 73 (80.2%) of the additional 91 patients with a medical history of SCC before inclusion subsequently developed 1 to 64 SCC/KA (mean 7, median 3), and 50 (24.9%) of the 201 patients without any SCC/KA developed their first SCC/KA during the follow-up period (range 1 to 12, mean 3, median 2 SCC/KA) (Table 1 and supplementary Figure 1).

Figure 1 demonstrates the development of subsequent skin cancers following an earlier skin cancer. The presence of SCC/KA was predictive for the development of a subsequent SCC/KA (Figure 1, panel A) and BCC predicted the development of a subsequent BCC (Figure 1, panel B). On the other hand, the presence of a BCC did not predict a new or

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subsequent SCC/KA (Figure 1, panel C) and SCC/KA did not predict a subsequent BCC (Figure 1, panel D).

Painful skin lesions predicted an increased mortality risk (Figure 2, panel A). Since pain predicts SCC/KA we expected that painful SCC/KA would lead to the highest death rate, but this was not the case since pain alone, SCC/KA alone and painful SCC/KA all led to the same increased mortality rate compared to lesions without pain and non- SCC/KA lesions (Figure 2, panel B). An OTR with a painful lesion had double the risk of overall mortality when the first biopsy per patient was analysed without taking the other biopsies into account (Table 2a). The majority of these painful lesions consisted of SCC, Bowen's disease and actinic keratoses as depicted in the legend of Table 2a. After adjustment for age, sex, SCC/KA as the histological diagnosis, number of SCC before inclusion in the study, and number of years after the transplantation there was still a 60% increased overall mortality risk in patients with a painful lesion (Table 2a). Taking all biopsies that were taken during the original study into account, we observed that the overall mortality risk increased even further where a patient had two or more painful lesions (Table 2b).

When analysing the impact of the development of SCC/KA on overall mortality risk one can distinguish two distinct clinical questions: 1) if a patient actually presents to a clinic with a (first or new) SCC/KA, what is his or her prognosis regarding overall mortality risk? or 2) if a patient is known with an SCC/KA at present or in the past or develops an SCC/KA during the follow-up period what is his or her prognosis regarding overall mortality risk? The analyses regarding the first question are depicted in Figure 3 and Table 3a and regarding the second question in Table 3b.

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A histological diagnosis of an SCC/KA, compared to a different histological diagnosis at the time of inclusion in the original SCOPE-ITSCC PAIN study, was associated with an increased overall mortality risk with a hazard ratio (adjusted for age, sex, time since transplant and number of SCC before the start of the study) of 1.7 (95% CI 1.0-2.8) (Figure 3 and Table 3a). Looking at the association between SCC at any time before, at or in the follow-up period after the original SCOPE-ITSCC PAIN study resulted in a higher hazard ratio, which was after adjustment for the same factors 3.9 (95% CI: 1.6 – 9.4) (Table 3b). The mean number of SCC in the patients with SCC was 7.1 in the OTR who were still alive and 7.8 in the OTR who had died (P = 0.717).

Among the 260 patients who had developed 1 or more SCC/KA, there were 9 patients with metastasis of which 5 originated from an aggressive SCC. Three of the 9 patients with metastasis were still alive at the end of the study. Five patients died of metastatic cutaneous SCC, 1 patient died of bone marrow cancer. Among 10 patients with aggressive SCC (5 of them also had metastatic disease), 4 were still alive at the end of the study. One patient died of aggressive SCC located on the face without metastasis, 3 died of metastatic cutaneous SCC, 1 died of gastrointestinal malignancy and one died of pneumonia. Table 4a shows the various causes of death in the OTR who had painful lesions or no painful lesions and in Table 4b the group with SCC/ KA is compared to the group with no SCC/KA with regard to causes of death. It is of interest that the mortality from systemic infection appeared to predominate in patients with SCC/KA, although, because of the small numbers statistical significance was not reached. Altogether 6 OTR died of SCC, in 5 cases because of metastatic SCC and once case due to an aggressive SCC without metastasis.

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Discussion

In our study, SCC/KA are frequently followed by new SCC/KA and similarly BCC increase the likelihood of the development of subsequent BCC. This trend has been reported in earlier papers, and our study further validated these findings.[13;14] Flohil et al. reported that patients with a BCC had a 17-fold increased risk of developing a subsequent BCC compared with the BCC risk in the general population, and SCC patients had a 4-fold risk of developing a subsequent SCC compared with the general population.[15] This type-specific predilection may be the consequence of particular genetic susceptibilities; e.g. for individuals in the BCC-only group, they may carry mutations of genes in the Hedgehog pathway or sporadic variants of Patched or other germ-line mutations.[13] In addition, the pattern of previous sun exposure, i.e. continuous sun exposure for SCC and intermittent sun exposure for BCC may be another explanatory factor.

We observed increased overall mortality in OTR with painful skin lesions which was independent of the histological diagnoses. There was also a positive association between the number of painful lesions and overall mortality. Our previous SCOPE-ITSCC PAIN study had excluded a significant association between perineural invasion and pain in SCC/KA and had not revealed a local factor for the pain recorded in skin lesions. Smith et al. have reported in a systematic review that chronic pain in general increased mortality,[7] Feeny et al. have also reported pain in general as a predictor for mortality.[16] However, the exact relationship is unclear. There is also a lack of published data on the relationship between acute pain and mortality. Potentially, skin lesions could be perceived as painful more often in people of lesser health with a lower threshold for the perception of pain. Alternatively, in persons with lesser health, SCC could behave more aggressively coupled with local induction of pain by as yet unknown mediators. Painful skin lesions, however, might be used as a clinical indicator to

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guide clinicians about the poorer prognosis of this group of individuals who might benefit from additional management, further investigation or more intensive follow-up.[8]

Our study shows that OTR who are under regular surveillance in centres dedicated to managing OTR-related skin problems have a very high burden of SCC/KA. Our study also supports the finding that OTR have an increased overall mortality risk if they are diagnosed with cutaneous SCC/KA. The most prevalent causes were internal malignancies and severe systemic infections. The contribution of metastatic cutaneous SCC to this increased mortality risk is limited, however, since only 10% of the mortality risk was attributable to metastatic SCC. Interestingly, part of the increased mortality risk compared to the OTR without SCC/KA could be attributed to severe systemic infections, which were observed more frequently in OTR with a history of SCC/KA. We do not have an explanation for this observation, but reduced immunity may possibly be a factor leading to more cutaneous SCC and at the same time an increased risk of severe systemic infections.

The strengths of our study include the large number of patients from multiple centres in Europe and North America. This is also the first paper to describe the mortality risk associated with painful skin lesions or SCC/KA. Limitations of this study include selection bias resulting from including OTR predominantly in specialist OTR referral centres, and potential inaccuracies and missing information on cause of death in 25% of the study group as well as possible confounding factors like past sun exposure, smoking and the presence of internal malignancies and/or cardiac disease before the diagnosis of cutaneous SCC.

In conclusion, OTR have an increased overall mortality risk if they develop painful skin lesions independent of the histological diagnoses or are diagnosed with cutaneous SCC/KA. The development of a cutaneous SCC should warn the clinician that the patient may have an increased risk of internal malignancies and/or serious infections with death as a

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possible end result. Our study highlights the need for close and long-term follow-up of OTR who present with SCC or painful skin lesions in view of the higher overall mortality risk observed in these patients.

Legend to the figures

Figure 1. The presence of squamous cell carcinoma or keratoacanthoma at enrolment predicts a subsequent squamous cell carcinoma or keratoacanthoma (Panel A); the presence of basal cell carcinoma at enrolment predicts a subsequent basal cell carcinoma (Panel B); the presence of basal cell carcinoma at enrolment does not predict a subsequent squamous cell carcinoma or keratoacanthoma (Panel C) and the presence of squamous cell carcinoma or keratoacanthoma at enrolment does not predict a subsequent basal cell carcinoma (Panel D).

Figure 2. Decreased survival after painful skin lesions compared to painless lesions (Panel A) and after the occurrence of squamous cell carcinoma or keratoacanthoma and/or painful skin lesions (Panel B).

Figure 3: A biopsy of squamous cell carcinoma or keratoacanthoma at the start of the study compared to a biopsy of another type of skin lesion (no SCC/KA) predicts an increased risk of death.

Supplementary Figure 1: Schematic representation of the original SCOPE-ITSCC PAIN study (Panel B), history of SCC before the SCOPE-ITSCC PAIN study (Panel A) and new or

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subsequent SCC/KA during the cohort study (Panel C). During the follow-up study 50 SCC/KA developed in the 197 patients who had never had SCC before; 73 SCC/KA developed in the 91 patients who had SCC before the PAIN study, but not when a biopsy was taken for the original PAIN study; 21 SCC/KA developed in the 34 patients who did not have a history of SCC prior to the original PAIN study but presented with an SCC/KA at the start of the original PAIN study and 70 SCC/KA developed in the 88 patients who had a history of SCC before and a new SCC/KA during the PAIN study (left side of Panel C).

The numbers indicate the number of patients in the different categories. SCC: squamous cell carcinoma; KA: keratoacanthoma.

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Table 1 Characteristics of the OTR at time of inclusion in the study and during the follow-up.

	All patients	OTR with other skin lesions at start of study*	OTR with diagnoses of SCC/KA at start of study
Number of OTR: (N)	410	288	122
Sex: (N (%))			
Women	125 (30.5)	89 (30.9)	36 (29.5)
Men	285 (69.5)	199 (69.1)	86 (70.5)
			P = 0.779
Age at start of study (years; N (%))			
Younger than 50	82 (20.1)	65 (22.6)	17 (14.0)
50 – 59	99 (24.3)	67 (23.3)	32 (26.4)
60 – 69	159 (39.0)	109 (38.1)	50 (41.3)
70 and older	68 (16.6)	46 (16.0)	22 (18.3)
(Missing values)	(2)	(1)	(1)
			P = 0.267
Age at start of study (years)			
(mean, SD)	59.3 (11.7)	58.6 (12.3)	61.0 (9.8)
			P = 0.054
Age at first transplantation (yrs.)			
(mean, SD)	44.3 (14.7)	45.9 (14.5)	40.6 (14.6)
			P = 0.001
Years since first transplantation			
(mean, SD)	14.9 (10.0)	12.6 (9.0)	20.5 (9.9)
			P < 0.001

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Painful lesions at start of study			
Painless	282 (68.8)	233 (80.9)	49 (40.2)
Painful	128 (31.2)	55 (19.1)	73 (59.8)
			P < 0.001
SCC before the start of the study			
No SCC	231 (56.3)	197 (68.4)	34 (27.9)
SCC	179 (43.7)	91 (31.6)	88 (72.1)
			P < 0.001
SCC/KA after the start of the study			
No SCC/KA	193 (47.4)	162 (56.8)	31 (25.4)
SCC/KA	214 (52.6)	123 (43.2)	91 (74.6)
(Missing values)	(3)	(3)	(0)
			P < 0.001
Death			
No	324 (80.4)	238 (84.1)	86 (71.7)
Yes	79 (19.6)	45 (15.9)	34 (28.3)
(Missing values)	(7)	(5)	(2)
			P = 0.004

OTR: Organ transplant recipients; SCC: squamous cell carcinoma; KA: keratoacanthoma.

*Other skin lesions consisted of 76 (26.4%) basal cell carcinoma; 37 (12.8%) Bowen's disease; 34 (11.8%) actinic keratoses; 19 (6.6%) seborrheic keratoses; 14 (4.9%) common warts; 9 (3.1%) hyperkeratotic papillomas; 7 (2.4%) other skin malignancies; 1 (0.3%) infection and 91 (31.6%) miscellaneous diagnoses (mainly all kind of nevi, dermatofibroma and epidermoid cysts).

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Table 2a Increased mortality risk in OTR with painful compared to painless lesions at the start of the study.

Patients (Missing values)	Patients still alive N (%)	Patients died N (%)	Hazard ratios
Patients with painless lesions (6)	234 (84.8)	42 (15.2)	1
Patients with painful lesions (1)*	90 (70.9)	37 (29.1)	2.0 (1.3;3.1)
	Adjusted for age at start of study and sex		2.1 (1.4;3.3)
Adjusted for age, sex, SCC/KA as the histological diagnosis, number of SCC before inclusion in the study, and number of years after the transplantation until inclusion in the study			1.6 (0.97;2.7)

*Painful lesions consisted of 73/122 (59.8%) SCC; 8/76 (10.5%) basal cell carcinoma; 12/37 (32.4%) Bowen's disease; 15/34 (44.1%) actinic keratoses; 2/19 (10.5%) seborrheic keratoses; 1/14 (7.1%) common warts; 2/9 (22.2%) hyperkeratotic papillomas; 0/7 (0%) other skin malignancies; 0/1 (0%) infection and 15/91 (16.5%) miscellaneous diagnoses.

OTR: Organ transplant recipients; SCC: squamous cell carcinoma; KA: keratoacanthoma.

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Table 2b Increased mortality risk in OTR with painful compared to painless lesions at any time during the study.

Patients	Patients still alive N (%)	Patients died N (%)	Hazard ratios
Patients with only painless lesions	210 (86.4)	33 (13.6)	1
Patients with 1 painful lesion	79 (73.8)	28 (26.2)	1.9 (1.2;3.2)
Pts. with 2 and more painful lesions	35 (66.0)	18 (34.0)	2.6 (1.4;4.6)
Adjusted for age at start of study and sex			1.9 (1.2;3.2)
			3.1 (1.7;5.5)
Adjusted for age, sex, SCC/KA as the histological diagnosis, number of SCC before inclusion in the study, and number of years after the transplantation until inclusion in the study			1.6 (0.90;2.8)
			2.5 (1.3;5.0)

OTR: Organ transplant recipients; SCC: squamous cell carcinoma; KA: keratoacanthoma.

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Table 3a Increased mortality risk in OTR with cutaneous squamous cell carcinoma and/or keratoacanthoma compared with other skin lesions at inclusion in the SCOPE-ITSCC PAIN study.

Patients (Missing values)	Patients still alive N (%)	Patients died N (%)	Hazard ratios
Patients with other skin lesions (5)	238 (84.1)	45 (15.9)	1
Patients with SCC/KA (2)	86 (71.7)	34 (28.3)	1.8 (1.1;2.8)
Adjusted for age at start of study and sex			1.7 (1.1;2.7)
Adjusted for age, sex, number of SCC before inclusion in the study, and number of years after the transplantation until inclusion in the study			1.7 (1.0;2.8)

OTR: Organ transplant recipients; SCC: squamous cell carcinoma; KA: keratoacanthoma.

Table 3b Increased mortality risk in OTR with cutaneous squamous cell carcinoma and/or keratoacanthoma when considering all SCC/KA developing at any time before, at the start or during the follow-up period of the cohort study.

Patients (Missing values)	Patients still alive N (%)	Patients died N (%)	Hazard ratios*
Patients with other skin lesions (4)	131 (91.6)	12 (8.4)	1
Patients with SCC/KA (3)	193 (74.2)	67 (25.8)	3.2 (1.7;5.9)
Adjusted for age at start of study and sex			2.7 (1.5;5.1)
Adjustedfor age, sex, number of SCC before inclusion in the study, and number of years after the transplantation until inclusion in the study			3.9 (1.6;9.4)

*The occurrence of SCC/KA during the cohort study was analysed as time-dependent variable.

OTR: Organ transplant recipients; SCC: squamous cell carcinoma; KA: keratoacanthoma.

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Table 4a. Causes of death stratified according to painful skin lesions during the original SCOPE-ITSCC PAIN study.

	OTR with painless lesions (N = 282) N (%)	OTR with painful lesions (N = 128) N (%)
No death by end of study	234 (84.8)	90 (70.9)
Total death	42 (15.2)	37 (29.1)
Cardiovascular	6 (14.3)	9 (24.4)
Cutaneous SCC	5 (11.9)	1 (2.7)
Other malignancy	14 (33.3)	12 (32.4)
Systemic infections	5 (11.9)	5 (13.5)
Other reasons of death*	5 (11.9)	2 (5.4)
Unknown reason	7 (16.7)	8 (21.6)
(Missing values)	(6)	(1)
		P = 0.015

*Renal failure, liver failure.

OTR: organ transplant recipients; SCC: squamous cell carcinoma.

Table 4b. Causes of death stratified according to cutaneous squamous cell carcinoma and/or keratoacanthoma at any time during the study.

	OTR with no SCC/KA at any time in the study (N = 147) N (%)	OTR with SCC/KA at any time in the study (N = 263) N (%)

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No death by end of study	131 (91.6)		193 (74.2)	
Total death	12 (8.4)		67 (25.8)	
Cardiovascular		4 (33.4)		11 (16.3)
Cutaneous SCC		0		6 (9.0)
Other malignancy		6 (50.0)		20 (29.9)
Systemic infections		0		10 (14.9)
Other reasons of death*		1 (8.3)		6 (9.0)
Unknown reason		1 (8.3)		14 (20.9)
(Missing values)	(4)		(3)	
			P = 0.002	

*Renal failure, liver failure.

OTR: organ transplant recipients; SCC: squamous cell carcinoma; KA: keratoacanthoma.

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Figures

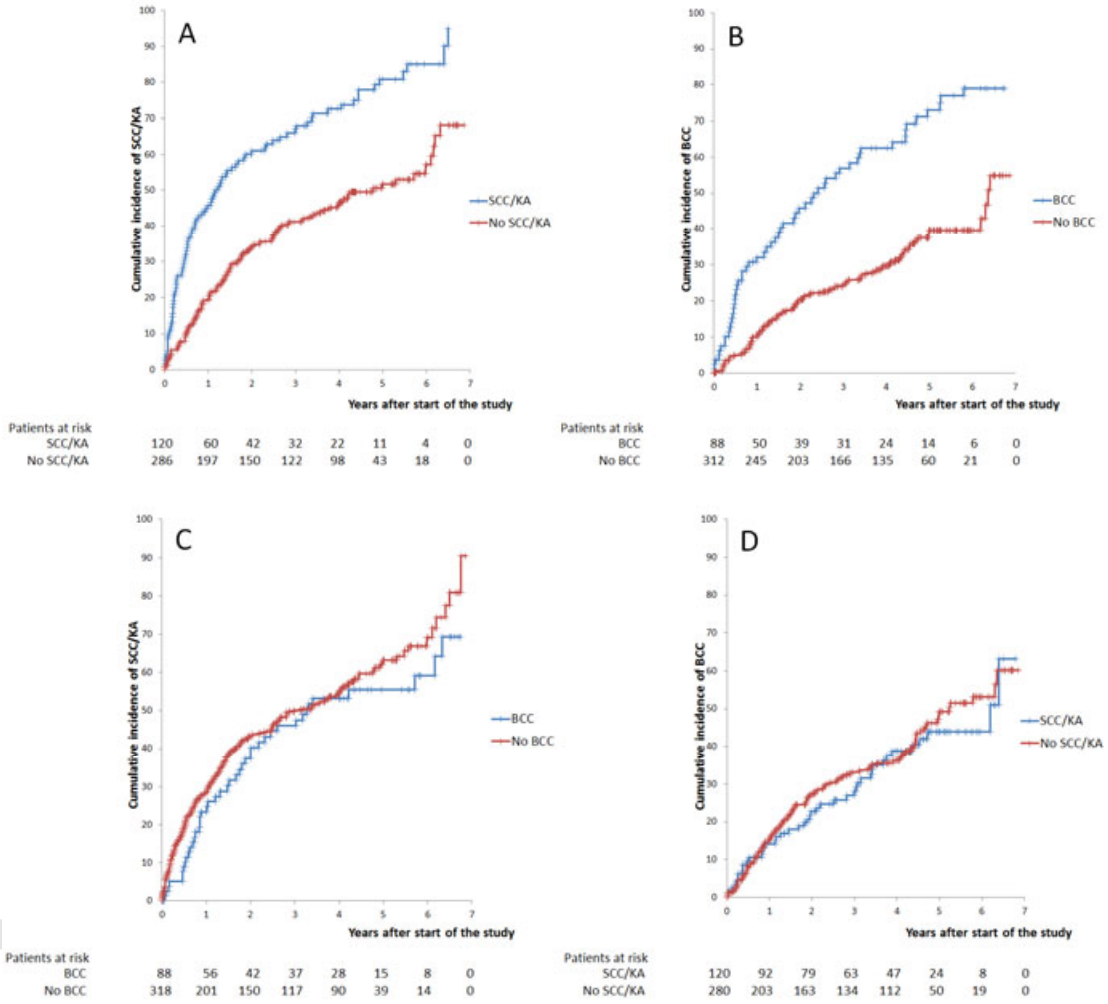

Figure 1. The presence of squamous cell carcinoma or keratoacanthoma at enrolment predicts a subsequent squamous cell carcinoma or keratoacanthoma (Panel A); the presence of basal cell carcinoma at enrolment predicts a subsequent basal cell carcinoma (Panel B); the presence of basal cell carcinoma at enrolment does not predict a subsequent squamous cell carcinoma or keratoacanthoma (Panel C) and the presence of squamous cell carcinoma or keratoacanthoma at enrolment does not predict a subsequent basal cell carcinoma (Panel D).

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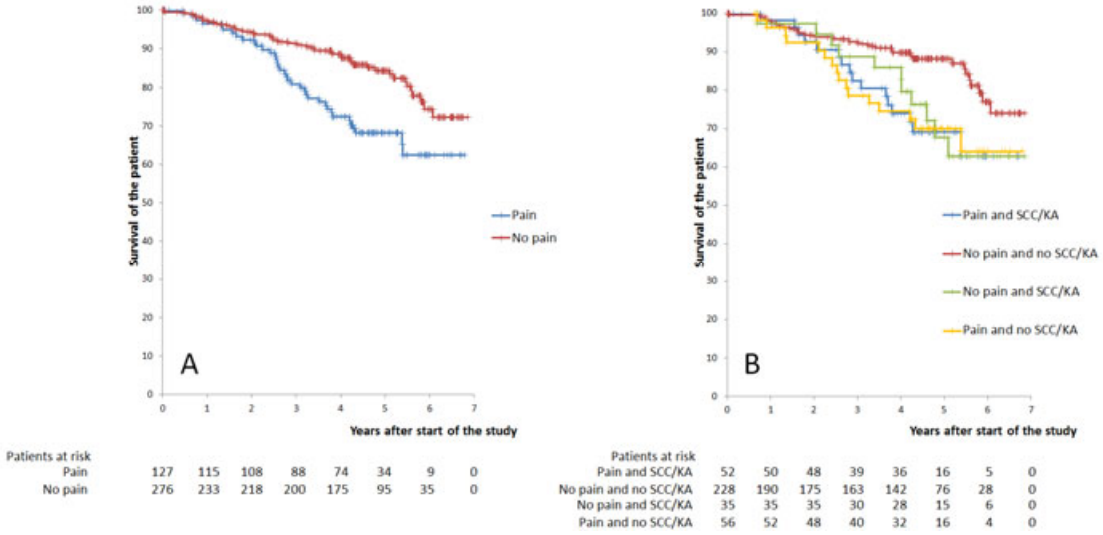

Figure 2. Decreased survival after painful skin lesions compared to painless lesions (Panel A) and after the occurrence of squamous cell carcinoma or keratoacanthoma and/or painful skin lesions (Panel B).

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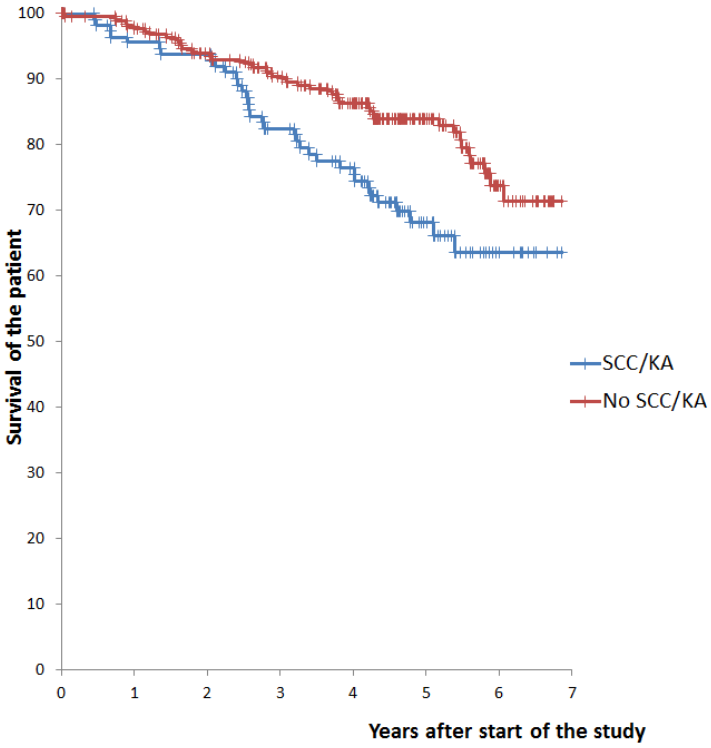

Patients at risk	0	1	2	3	4	5	6	7
SCC/KA	118	106	103	85	75	37	12	0
No SCC/KA	285	242	223	203	174	92	32	0

Figure 3: A biopsy of squamous cell carcinoma or keratoacanthoma at the start of the study compared to a biopsy of another type of skin lesion (no SCC/KA) predicts an increased risk of death.

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