Cumulative incidence and disease-specific survival of metastatic cutaneous squamous cell carcinoma: A nationwide cancer registry study

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Background: Cutaneous squamous cell carcinoma (cSCC) represents the most serious form of keratinocyte cancers because of its metastatic potential. Studies on nationwide incidence and disease-specific survival rates of metastatic cSCC (mcSCC) are lacking.

Objective: To investigate the cumulative incidence and disease-specific survival of patients with mcSCC in the Dutch population and assess patient-based risk factors.

Methods: We conducted a nationwide cancer registry study including all patients with the first cSCC in 2007 or 2008, using data from the Netherlands Cancer Registry, the nationwide network and registry of histopathology and cytopathology, and Statistics Netherlands. Cumulative incidence and Kaplan-Meier curves were calculated, and time-dependent Cox proportional hazards regression analyses were used.

Results: Of the 11,137 patients, metastases developed in 1.9% (n = 217). The median time to metastasis was 1.5 years (interquartile range 0.6-3.8 years). The risk factors were age (adjusted hazard ratio [aHR] 1.03, 95% CI 1.02-1.05), male sex (aHR 1.7, 95% CI 1.3-2.3), and immunosuppression (aHR [organ transplant recipient] 5.0, 95% CI 2.5-10.0; aHR [hematologic malignancy] 2.7, 95% CI 1.6-4.6). The 5-year disease-specific survival for patients with mcSCC was 79.1%.

Limitations: Only histopathologically confirmed mcSCCs were included.

Conclusion: About 2% of cSCCs metastasize, with higher risk for men, increasing age, and immunocompromised patients. Disease-specific survival for patients with mcSCC is high. (J Am Acad Dermatol 2022;86:331-8.)

Key words: cancer registry; cutaneous squamous cell carcinoma; epidemiology; hematologic malignancy; incidence; keratinocyte carcinoma; metastasis; organ transplantation; survival.

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Cutaneous squamous cell carcinoma (cSCC) is the second-most common cancer worldwide, and incidence rates are increasing rapidly.[1,2] Although the majority of patients with cSCC have excellent prognoses, metastasis may occur in 1.5%-5.2%.[3-9] Due to the high incidence rates, it has been estimated that cSCC accounted for similar death rates as various other cancers, including melanoma and leukemia, in the United States.[10]

Immunocompromised patients have a 65- to 250-fold increased risk of developing cSCC,[11,12] which are believed to behave more aggressively with a higher metastasis risk.[13,14] As cSCCs are not registered on a national level in most countries, the majority of studies retrieved cSCC incidence and corresponding metastatic rates from local hospital databases or regional registries, consequently including incomplete metastatic cSCC (mcSCC) data. Therefore, population-based studies are highly needed to obtain representative mcSCC incidence rates to correctly demonstrate the epidemiology of this disease on a nationwide level. In the Netherlands, cSCC is routinely registered by the Netherlands Cancer Registry (NCR), and all pathology reports are available via linkage with the nationwide network and registry of histopathology and cytopathology (PALGA). The aim of this study was to determine the Dutch cumulative incidence of mcSCC and describe disease-specific survival rates, stratified by patients' immune status, during a follow-up period of 10 years.

CAPSULE SUMMARY

- Cutaneous squamous cell carcinoma (cSCC) has metastatic potential. However, data on nationwide incidence and disease-specific survival rates of metastatic cSCC are lacking.
- About 2% of all cSCCs metastasize, three quarters within the first 4 years after diagnosis. Male, elderly, and immunocompromised patients are at increased risk and should, therefore, be specifically monitored.

METHODS

Patient population

Nationwide data from all patients with histopathologically confirmed first primary cSCCs in 2007 or 2008 were retrieved from the NCR, which registers all histopathologically confirmed incident cancers in the Netherlands since 1989. Completeness of registration of cutaneous malignancies (excluding basal cell carcinomas) is 92.9%.[15] Data for subsequent cSCCs and mcSCCs were retrieved through PALGA.[16]

The data obtained from the NCR contained information on sex, age at diagnosis and year of the first cSCC, cSCC topography, vital status, and follow-up duration (via nationwide linkage with the municipal records). PALGA data contained a complete history of pathology reports from all first and subsequent cSCCs and corresponding metastases with their dates of diagnosis. This nationwide cohort study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[17]

Data extraction

Potential mcSCCs were retrieved from pathology reports using a free-text search and PALGA codes confirming or suggestive of metastasis (Supplementary Table I, available via Mendeley at https://doi.org/10.17632/mkzknbhhn3.1). These records (n = 855) were manually read by 2 researchers (ST and WK), and uncertainties were discussed within the research team (MW, EN, and LH) to reach a consensus. The type of metastasis (lymph node, cutaneous, distant), its location, and the cSCC lesion accountable for metastasis were extracted from the pathology reports. The International Classification of Diseases for Oncology (ICD-O-3) with topography "skin" (C44) was used to determine the location of all primary cSCCs.[18] Metastasis reports with unknown primary origin and reports from which it was unclear whether it concerned a cSCC or cutaneous metastasis were excluded.

Data on nonmelanoma skin cancer (NMSC)-specific deaths were obtained through linkage with Statistics Netherlands (C44 of the International Classification of Diseases, 10th revision). To distinguish whether a patient died due to cSCC or another type of high-risk NMSC, we obtained data on all other types of NMSC per patient from the NCR. Consequently, only patients with cSCC who died due to NMSC with no other types of high-risk NMSCs were considered cSCC-specific deaths. Supplementary Table II (available via Mendeley at https://doi.org/10.17632/mkzknbhhn3.1) shows the morphology codes of each C44 tumor included in the disease-specific survival or overall survival analyses. In a sensitivity analysis, we considered all NMSC deaths as cSCC-specific deaths.

Data on organ transplant recipients (OTRs) were retrieved through linkage with the Netherlands Organ Transplant Registry (Dutch Transplant Foundation, Leiden, the Netherlands), a prospectively maintained national electronic database.[19] Data on hematologic malignancies were obtained from the NCR.

Abbreviations used:

aHR: adjusted hazard ratio
cSCC: cutaneous squamous cell carcinoma
mcSCC: metastatic cutaneous squamous cell carcinoma
IQR: interquartile range
NCR: Netherlands Cancer Registry
NMSC: nonmelanoma skin cancer
OTR: organ transplant recipient

Statistical analysis

Cumulative incidence curves were calculated to determine the mcSCC risk, taking into account the competing risk of death.[20] Follow-up time started on the day of the first cSCC diagnosis and ended on the day of mcSCC for cases and for the rest of the cohort, on the day of death or end of follow-up (December 31, 2018), whichever occurred first. Time to metastasis was defined as the time in years between the first primary cSCC diagnosis and metastasis diagnosis. Survival from mcSCC diagnosis until death or end of follow-up was calculated using the Kaplan-Meier method. Analyses were stratified by age (<70 vs ≥70 years old), sex, and immune status. Patients who received an organ transplantation or those in whom a hematologic malignancy developed after either baseline or mcSCC diagnosis were excluded from the cumulative incidence curve and survival analyses to only consider patients as immunocompromised if they were immunocompromised during the total follow-up duration of the analyses. Differences across subgroups were tested with Gray's test for equality of cumulative incidence functions and the log-rank test for the Kaplan-Meier survival curves.

Multivariable Cox proportional hazards regression analysis was performed to study mcSCC risk. The patient-based risk factors included were age, sex, and, as time-dependent variables, the presence of an organ transplant or hematologic malignancy. A potential nonlinear relationship between age and mcSCC risk was explored using a spline, but no evidence for nonlinearity was found.

This study was approved by the scientific committees of the NCR, PALGA, Dutch Transplant Foundation, Erasmus Medical Center (MEC-2020-0054), and Dutch Clinical Research Foundation (W20.048/NWMO20.02.007) and was granted a waiver of informed consent. Statistical analyses were performed using SPSS 25.0 statistical software (SPSS Inc) and R statistical software version 3.4.1 with the cmprsk and survival packages (R Core Team, 2017). Tests were 2-sided at a 5% statistical significance level.

RESULTS

Cumulative incidence of mcSCC

In total, 11,137 patients with the first cSCC in 2007 or 2008 were identified, with a median follow-up of 9.1 years (interquartile range [IQR], 3.9-10.0 years). Patient characteristics are shown in Table I.

From the pathology reports, 233 potential mcSCCs were identified. The exclusion of mcSCCs with unknown primary origin (n = 12) or where no distinction could be made between primary cSCC or cutaneous metastasis (n = 4) resulted in 217 patients with mcSCC in the final analyses. The majority of metastases occurred within the first 4 years after the first cSCC diagnosis (78%, n = 170), and these were often located in the parotid gland (33%, n = 72) (Table I). From all mcSCCs, 74% (n = 161) resulted from the first cSCC and 26% (n = 56) arose from subsequent cSCCs. Stratification by immune status showed that 89% of the mcSCCs in OTRs were caused by subsequent cSCCs and only 11% by the first cSCCs. In patients with hematologic malignancies, this ratio was reversed: about one third of mcSCCs (37%, n = 9) were caused by subsequent cSCCs and 63% (n = 15) resulted from first cSCCs. Supplementary Table III (available via Mendeley at https://doi.org/10.17632/mkzknbhhn3.1) shows the distribution of all types of organ transplants and hematologic malignancies along with their corresponding number of mcSCCs.

The overall cumulative incidence of mcSCC was 1.9% (95% CI 1.8-2.0) after 10 years' follow-up (Fig 1), with a median time to metastasis of 1.5 years (IQR 0.6-3.8 years) after the first cSCC. Men showed a higher mcSCC incidence rate than women: 2.3% (95% CI 2.2-2.4) versus 1.4% (95% CI 1.3-1.5) ($P < .001$) (Supplementary Fig 1, available via Mendeley at https://doi.org/10.17632/mkzknbhhn3.1). Stratification by age (<70 years old vs ≥70 years old) did not produce statistically significant differences ($P = .51$) (Supplementary Fig 2, available via Mendeley at https://doi.org/10.17632/mkzknbhhn3.1).

Risk of mcSCC by immune status

Stratification of the cumulative incidence functions across immune status showed an increased mcSCC risk in immunocompromised patients: 5.8% (95% CI 4.6-7.4) after 10 years in OTRs (1.3%) compared with non-OTRs ($P < .001$) (98.7%) and 4.0% (95% CI 3.4-4.8) in hematologic malignancy patients (3.2%) compared with patients without this disease (96.8%) ($P = .003$) (Supplementary Figs 3 and 4, available via Mendeley at https://doi.org/10.17632/mkzknbhhn3.1). The median time to

Table I. Descriptive characteristics of patients with a first primary cSCC in 2007 or 2008 stratified by metastasis outcome

Variable	Total (N = 11,137)	mcSCC (histopathologically confirmed) (n = 217)	Nonmetastatic cSCC (n = 10,920)
Follow-up since first cSCC until death or censoring, y, median (IQR)	9.1 (3.9-10.0)	4.3 (2.0-9.2)	9.1 (4.1-10.0)
Time to mcSCC since first cSCC, y, median (IQR)	NA	1.5 (0.6-3.8)	NA
Disease-specific death, n (%)	71 (0.7)	32 (15.0)	39 (0.4)
Sex, male (%)	6318 (56.7)	149 (68.7)	6169 (56.5)
Age at first cSCC diagnosis, y, median (IQR)	76.0 (67.0-82.0)	77.0 (68.0-83.0)	76.0 (67.0-82.0)
Organ transplantation, n (%)	155 (1.4)	9 (4.1)	146 (1.3)
Hematologic malignancy, n (%)	595 (5.3)	24 (11.1)	571 (5.2)
Site of first cSCC, n (%)			
Lip (cutaneous)	253 (2.3)	11 (5.1)	242 (2.2)
Eyelid	127 (1.1)	5 (2.3)	122 (1.1)
Ear	1147 (10.3)	44 (20.3)	1103 (10.1)
Face	4451 (40.0)	81 (37.3)	4370 (40.0)
Scalp or neck	1391 (12.5)	27 (12.4)	1364 (12.5)
Trunk	900 (8.1)	13 (6.0)	887 (8.1)
Upper extremity, including shoulder	1771 (15.9)	25 (11.5)	1746 (16.0)
Lower extremity, including hip	985 (8.8)	11 (5.1)	974 (8.9)
Overlapping	50 (0.4)	0 (0.0)	50 (0.5)
Skin NOS	62 (0.6)	0 (0.0)	62 (0.6)
Site of first metastasis (each patient counted once), n (%)			
Parotid gland		72 (33.2)	
Cervical glands		54 (24.9)	
Parotid & cervical glands		23 (10.6)	
Axilla		21 (9.7)	
Groin		10 (4.6)	
Other locations*		5 (2.3)	
Cutaneous metastasis		27 (12.4)	
Distant metastasis		5 (2.3)	

cSCC, Cutaneous squamous cell carcinoma; *IQR*, interquartile range; *mcSCC*, metastatic cutaneous squamous cell carcinoma; *NOS*, not otherwise specified.

*Includes lymph nodes located in the upper arm, retroauricular area, or unknown location.

metastasis was 5.7 years (IQR 1.8-8.4 years) and 2.5 years (IQR 0.6-3.9 years), respectively.

Multivariable Cox proportional hazards regression analyses confirmed the significantly increased mcSCC risk for both immunocompromised patient groups, resulting in a hazard ratio of 5.0 (95% CI 2.5-10.0) for OTRs and 2.7 (95% CI 1.6-4.6) for patients with hematologic malignancies after adjustment for age and sex (Table II). Male sex and increasing age showed significant but smaller effects on the mcSCC risk: men had a hazard ratio of 1.7 (95% CI 1.3-2.3), and each year increase in age yielded an adjusted hazard ratio of 1.03 (95% CI 1.02-1.05).

Survival of (m)cSCC patients

Linked cause-of-death data were available for 97% of all patients with primary cSCCs (n = 10,821) and for 98% of all patients with mcSCCs (n = 213). Seventy-six patients were identified with C44 death certificates. Of these patients, 5 had an additional high-risk NMSC besides their cSCC (eg, Merkel cell carcinoma) and were, therefore, regarded as uncertain cSCC-specific deaths, leaving 71 cSCC-specific deaths in the disease-specific survival analyses. As most cSCC patients died due to other causes, the 5-year disease-specific survival rate of the total population was very high (99.4%), whereas the overall survival was much lower (69.8%) (Supplementary Fig 5, available via Mendeley at https://doi.org/10.17632/mkzknbhhn3.1). Our sensitivity analysis including the 5 high-risk NMSC deaths did not change the 5-year disease-specific survival rates. Stratification by age resulted in a marginal difference in 5-year disease-specific survival rates: 99.8% for patients aged <70 years versus 99.2% for patients aged ≥70 years ($P < .001$). No differences across sex or immune status were observed for the total cSCC population (data not shown). Of the 213 mcSCC cases, 32 patients (15%) died of their (m)cSCC,

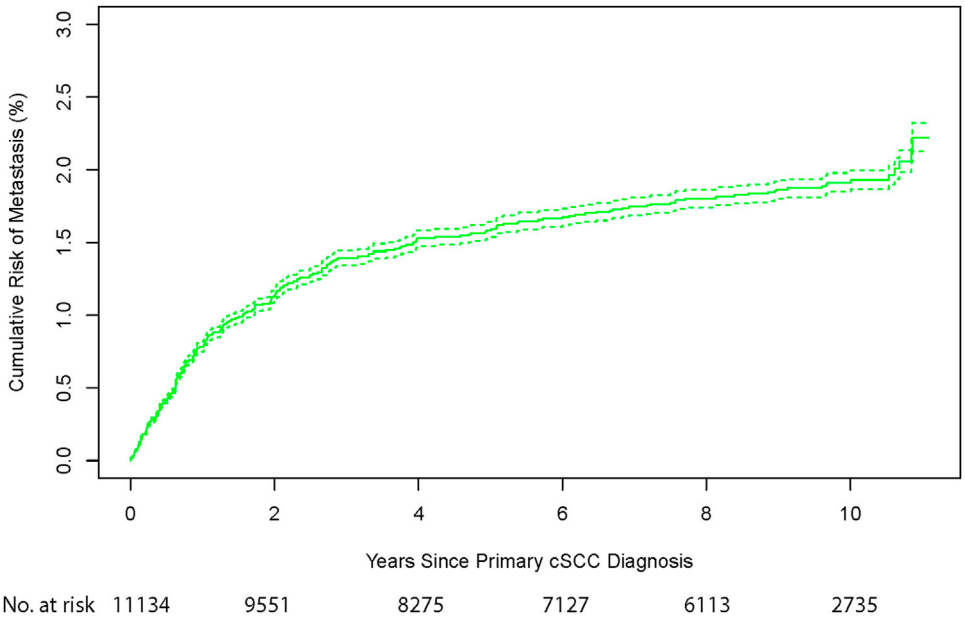

Fig 1. Cumulative incidence curves with 95% CIs for the risk of metastasis in 11,137 patients with first cSCCs in 2007 or 2008. *cSCC*, Cutaneous squamous cell carcinoma.

Table II. Hazard ratios for metastasis among cSCC patients based on time-dependent Cox proportional hazards regression analysis

Covariate	No. of events	Person-years*	Univariable HR (95% CI)	Multivariable HR (95% CI)	*P* value†
Age			1.03 (1.01-1.04)	1.03 (1.02-1.05)	<.001
Sex					
Female	68	35,091	REF	REF	
Male	149	43,448	1.7 (1.3-2.3)	1.7 (1.3-2.3)	<.001
OTR					
No	208	77,452	REF	REF	
Yes	9	1087	3.3 (1.7-6.4)	5.0 (2.5-10.0)	<.001
Hematologic malignancy					
No	193	76,297	REF	REF	
Yes	24	2243	2.8 (1.6-4.8)	2.7 (1.6-4.6)	<.001

cSCC, Cutaneous squamous cell carcinoma; *HR*, hazard ratio; *REF*, reference category; *OTR*, organ transplant recipient.
*Deviations in sum of person-years between covariates are a result of rounding off.
†*P* value corresponding with the multivariable HRs.

and the 5-year disease-specific survival was 79.1% (Fig 2). None of the patients with mcSCC had another type of high-risk NMSC. Disease-specific survival after mcSCC was stratified across sex, age at mcSCC diagnosis, OTR status, and the presence of hematologic malignancies, but no statistically significant differences were observed within the stratified groups (Supplementary Figs 6 to 9, available via Mendeley at https://doi.org/10.17632/mkzknbhhn3.1).

Of the 71 cSCC-specific deaths, 39 patients did not have histopathologically confirmed metastases. At least 31% of these patients had high-risk locally invasive cSCCs (n = 12, but possibly more, as >20 cSCCs had an unknown T-stage). Therefore, we additionally compared the disease-specific survival rates of metastatic patients with those of nonmetastatic patients, starting from their last registered cSCC (Fig 3). The median disease-specific survival durations of these groups (0.8 vs 0.9 years, respectively) did not differ significantly (P = .052).

DISCUSSION

This nationwide study comprising more than 10,000 patients with cSCC provides a national incidence and survival report of mcSCC in a Northern European population. With a follow-up duration of 10 years and linkage with a nationwide solid organ transplant registry, complemented by

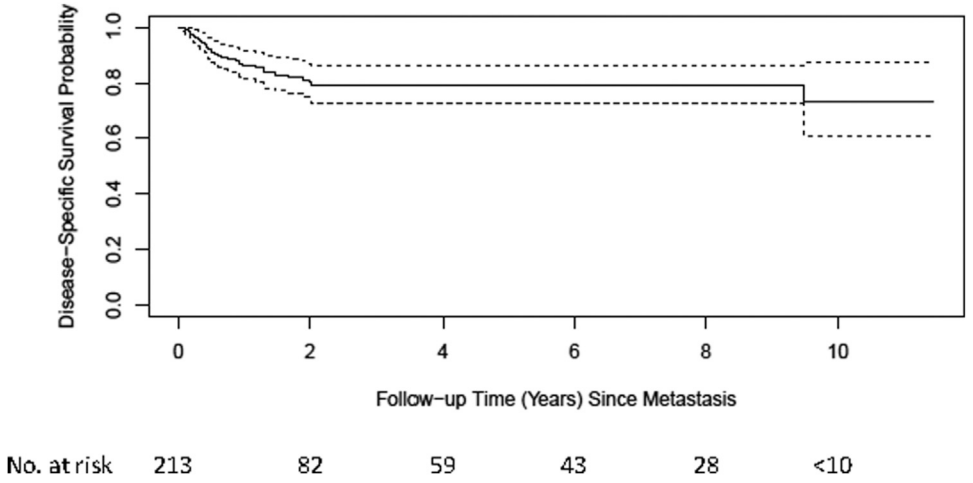

Fig 2. Disease-specific survival curves with 95% CIs for the 213 patients with metastatic cutaneous squamous cell carcinoma, starting from date of metastasis. Patients who died of other causes are censored, which means that the numbers at risk are the true numbers at risk.

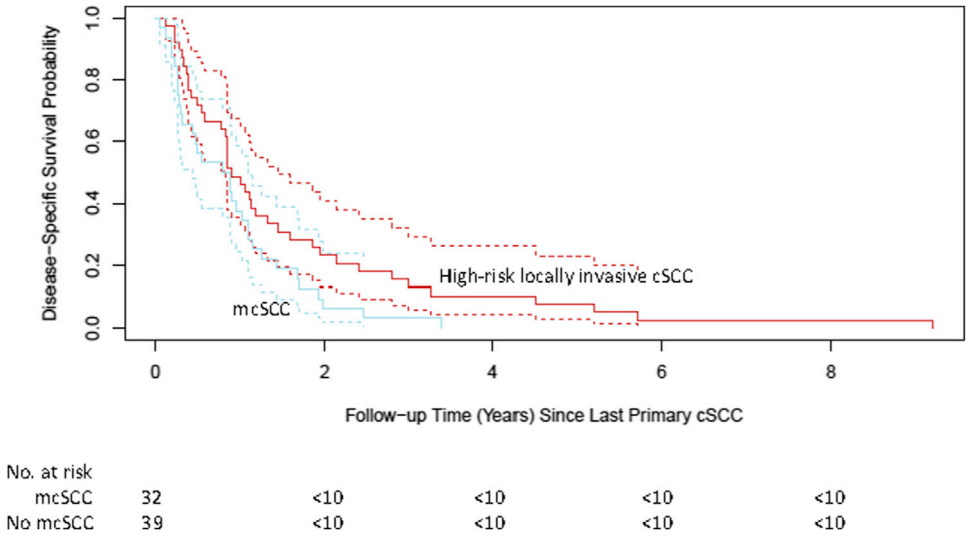

Fig 3. Disease-specific survival curves with 95% CIs for the 71 patients who died of cSCC: the *blue line* represents mcSCC patients, and the *brown line* represents high-risk locally invasive cSCC patients (P = .052). *cSCC*, Cutaneous squamous cell carcinoma; *mcSCC*, metastatic cutaneous squamous cell carcinoma.

nationwide data on hematologic malignancies, we were able to provide reliable incidence rates of mcSCC for the general population and 2 important immunocompromised patient groups.

Our findings for poor cSCC outcomes were within the lower range of previously published population-based studies.[3-9] A possible explanation for this is that we investigated the mcSCC incidence among patients with newly diagnosed cSCC. In other studies, mcSCCs were mostly detected retrospectively from registries/hospital databases, irrespective of the diagnosis dates of patients' first cSCCs.[6,9] Possibly, this led to a selection bias resulting in higher mcSCC incidence rates. Additionally, we may have underestimated the incidence of mcSCC because metastases without histopathologic confirmation were not included. However, we expect this proportion to be very small since histopathology is routinely obtained when mcSCC is suspected.

The significantly higher mcSCC incidence and risk in men than in women were also found by Venables et al[6] in the English population and could be caused by men seeking dermatologic health care in a later phase, resulting in patient delay, or a different immunologic tumor response in men, as is also seen in melanoma.[21] This theory is endorsed by the

higher proportions of advanced cSCCs in men compared with women, which are more likely to metastasize than the low-stage cSCCs mainly abundant in women.[2]

We confirmed a significantly higher mcSCC risk for immunocompromised patients.[13,14] Organ transplantation was the strongest independent risk factor for mcSCC, followed by the presence of a hematologic malignancy. The increased risk among OTRs is thought to be caused by the chronic use of immunosuppressive medication, impairing their immune surveillance and permitting tumor cells to proliferate uncontrollably.[22,23] The reason for worse cSCC outcomes in patients with hematologic malignancies is similarly believed to be related to an impaired immune system, where—dependent on the type of hematologic malignancy—immunosuppressive factors are produced and T cell interactions with antigen-presenting cells are hindered.[24,25] In contrast to other studies, the worse prognosis of immunocompromised patients was not reflected in the disease-specific survival rates.[26,27] The lack of significance in our study could be due to a lack of statistical power in this patient group.

Additionally, 39 patients died of cSCC without having had histologically confirmed metastases. These deaths might be explained by extensive local tumor growth (31% were T3/T4 tumors), which could have ended up fatally, or by fragile patients for whom histopathologic diagnosis and treatment of metastasis might have been ceased.

The majority of mcSCCs (78%) occurred in the first 4 years after patients' first cSCC diagnoses (85% nodal metastases, 13% cutaneous metastases, and 2% distant metastases). The median duration from the first cSCC until metastasis was the longest for OTRs, which is in line with a retrospective study among 593 cSCC patients showing a longer mean duration between cSCC diagnosis and metastasis detection in the OTR group than in immunocompetent patients because in most cases, a subsequent cSCC causes metastasis rather than the first cSCC.[28,29] On the other hand, fewer cSCCs develop in patients with hematologic malignancies than in OTRs, but their cSCCs tend to behave more aggressively,[14] which is supported by our findings that 63% of all mcSCCs in these patients resulted from first cSCCs. These findings may suggest a pivotal role for the total burden of cSCCs in the mcSCC pathogenesis among OTRs and, rather, for the individual cSCC lesion in patients with hematologic malignancies.

Strengths of our study include the availability of a nationwide cancer registry as well as nationwide pathology, OTR, and hematologic malignancy data over a long study period, which is generalizable to white-skinned populations worldwide. Also, all pathology records of potential mcSCCs were reviewed manually to have a capture rate as high as possible and, hence, were not dependent on physicians' diagnosis codes. Furthermore, we showed the first nationwide disease-specific survival rates for mcSCC, whereas the only other nationwide study on mcSCC only included data on overall survival rates.[6] Nevertheless, several limitations need to be considered, including the absence of data on immune status other than OTR/hematologic malignancies, such as human immunodeficiency virus, rheumatoid arthritis, or inflammatory bowel diseases. This might have caused misclassification of immunocompromised patients as immunocompetent patients, potentially leading to a dilution of the observed effects for immunosuppression. Lastly, we could not correct for potential coding errors of physicians on the death certificates, which is a general limitation of cause-of-death registry data.

In conclusion, the cumulative risk of the development of metastasis in a patient with cSCC is about 2%. This is low in terms of relative numbers, but as cSCC is the second-most common cancer worldwide, the absolute number of patients is substantial, with the total number of deaths estimated to be similar to that of melanoma and various other common cancers.[10] We showed that the majority of metastases occur within 4 years and that this risk is higher with male sex, increasing age, and immunosuppression. Although disease-specific survival rates after metastasis did not significantly differ across the subgroups, this could have been a power issue since relatively few immunocompromised mcSCC patients were included. Individual risk prediction models should include these high-risk patient characteristics to tailor follow-up care to the subgroups of patients with cSCC at increased risk of mcSCC among the large group of predominantly low-risk cSCC patients.

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Conflict of interest

Dr Wakkee participated as an advisory board member on advanced cSCC for Sanofi Genzyme, for which she received a financial reimbursement. Drs Venables,

Mooyaart, Louwman, Nijsten, and Hollestein and Authors Tokez and Kan have no conflicts of interest to declare.

REFERENCES

1. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. *Br J Dermatol*. 2012;166(5):1069-1080.
2. Tokez S, Hollestein L, Louwman M, Nijsten T, Wakkee M. Incidence of multiple vs first cutaneous squamous cell carcinoma on a nationwide scale and estimation of future incidences of cutaneous squamous cell carcinoma. *JAMA Dermatol*. 2020;156(12):1300-1306.
3. Brantsch KD, Meisner C, Schönfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. *Lancet Oncol*. 2008;9(8):713-720.
4. Brougham NDLS, Dennett ER, Cameron R, Tan ST. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. *J Surg Oncol*. 2012;106(7):811-815.
5. Mourouzis C, Boynton A, Grant J, et al. Cutaneous head and neck SCCs and risk of nodal metastasis—UK experience. *J Craniomaxillofac Surg*. 2009;37(80):443-447.
6. Venables ZC, Autier P, Nijsten T, et al. Nationwide incidence of metastatic cutaneous squamous cell carcinoma in England. *JAMA Dermatol*. 2019;155(3):298-306.
7. Knuutila JS, Riihilä P, Kurki S, Nissinen L, Kähäri VM. Risk factors and prognosis for metastatic cutaneous squamous cell carcinoma: a cohort study. *Acta Derm Venereol*. 2020;100(16):adv00266.
8. Nelson TG, Ashton RE. Low incidence of metastasis and recurrence from cutaneous squamous cell carcinoma found in a UK population: do we need to adjust our thinking on this rare but potentially fatal event? *J Surg Oncol*. 2017;116(6):783-788.
9. Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single-institution cohort study. *JAMA Dermatol*. 2013;149(5):541-547.
10. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. *J Am Acad Dermatol*. 2013;68(6):957-966.
11. Garrett GL, Blanc PD, Boscardin J, et al. Incidence of and risk factors for skin cancer in organ transplant recipients in the United States. *JAMA Dermatol*. 2017;153(3):296-303.
12. Moloney FJ, Comber H, O'Lorcain P, O'Kelly P, Conlon PJ, Murphy GM. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. *Br J Dermatol*. 2006;154(3):498-504.
13. Genders RE, Weijns ME, Dekkers OM, Plasmeijer EI. Metastasis of cutaneous squamous cell carcinoma in organ transplant recipients and the immunocompetent population: is there a difference? A systematic review and meta-analysis. *J Eur Acad Dermatol Venereol*. 2019;33(5):828-841.
14. Hartley BE, Searle AE, Breach NM, Rhys-Evans PH, Henk JM. Aggressive cutaneous squamous cell carcinoma of the head and neck in patients with chronic lymphocytic leukaemia. *J Laryngol Otol*. 1996;110(7):694-695.
15. Schouten LJ, Straatman H, Kiemeney LA, Gimbrere CH, Verbeek AL. The capture-recapture method for estimation of cancer registry completeness: a useful tool? *Int J Epidemiol*. 1994;23(6):1111-1116.
16. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in the Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cell Oncol*. 2007;29(1):19-24.
17. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;85(11):867-872.
18. Fritz A, Percy C, Jack A, et al. *International Classification of Diseases for Oncology (ICD-O)*. World Health Organization; 2002.
19. Nederlandse transplantatie stichting. Accessed April 20, 2021. https://www.transplantatiestichting.nl
20. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res*. 2007;13(2):559-565.
21. Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. *Hum Reprod Update*. 2005;11(4):411-423.
22. Muehleisen B, Jiang SB, Gladsjo JA, Gerber M, Hata T, Gallo RL. Distinct innate immune gene expression profiles in nonmelanoma skin cancer of immunocompetent and immunosuppressed patients. *PLoS One*. 2012;7(7):e40754.
23. Guba M, Graeb C, Jauch KW, Geissler EK. Pro- and anti-cancer effects of immunosuppressive agents used in organ transplantation. *Transplantation*. 2004;77(12):1777-1782.
24. Velez NF, Karia PS, Vartanov AR, Davids MS, Brown JR, Schmults CD. Association of advanced leukemic stage and skin cancer tumor stage with poor skin cancer outcomes in patients with chronic lymphocytic leukemia. *JAMA Dermatol*. 2014;150(3):280-287.
25. Aslakson CJ, Lee G, Boomer JS, Gilman-Sachs A, Kucuk O, Beaman KD. Expression of regeneration and tolerance factor on B cell chronic lymphocytic leukemias: a possible mechanism for escaping immune surveillance. *Am J Hematol*. 1999;61(1):46-52.
26. Lanz J, Bavinck JN, Westhuis M, et al. Aggressive squamous cell carcinoma in organ transplant recipients. *JAMA Dermatol*. 2019;155(1):66-71.
27. Garrett GL, Lowenstein SE, Singer JP, He SY, Arron ST. Trends of skin cancer mortality after transplantation in the United States: 1987 to 2013. *J Am Acad Dermatol*. 2016;75(1):106-112.
28. Genders RE, Osinga JA, Tromp EE, O'Rourke P, Bavinck JN, Plasmeijer EI. Metastasis risk of cutaneous squamous cell carcinoma in organ transplant recipients and immunocompetent patients. *Acta Derm Venereol*. 2018;98(5-6):551-555.
29. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol*. 2002;47(1):1-17.