Basic and clinical features of cutaneous squamous cell carcinoma in organ transplant recipients

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CHAPTER 7

Metastasis risk of cutaneous squamous cell carcinoma in organ transplant recipients and immunocompetent patients

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Abstract

Organ transplant recipients (OTR) have a high incidence of cutaneous squamous cell carcinoma (cSCC) and immunosuppression has been reported to be an important risk factor for metastasis.
This study aimed to identify the metastasis risk over a 10- year period for 593 cSCC patients of whom 134 were OTR and 459 were immunocompetent patients.
Metastasis incidence rate (IR) was 1046 (95%CI 524- 2096) per 100.000 person years in OTR and 656 (95%CI; 388-1107) in immunocompetent patients, yielding an IR ratio of 1.6 (95% CI 0.67-3.81). In OTR head/neck location, older age at transplantation and older age at the diagnosis of first cSCC were associated with metastatic risk and seven out of eight metastasized tumors were smaller than 2 centimetres. In immunocompetent patients tumor size and tumor depth were associated with metastasis.
In conclusion, we were not able to demonstrate an increased metastasis incidence rate in OTR compared to immunocompetent patients. However, OTR and immunocompetent patients differed in risk factors for metastasis.

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most frequent form of keratinocyte carcinoma (KC).[1,2] The incidence of cSCC varies globally, with a higher incidence closer to the equator. In Finland the incidence is reported to be 6 for men and 4 for women per 100.000 person years . In Australia, these numbers are reported to be 1035 and 472 per 100.000 person years.[3,4]
The incidence of cSCC metastasis varies, with higher incidence often reported from tertiary hospitals.[5-10] The risk of developing metastasis from low-risk cSCC in the general population is between 0.5 and 5% , but may be as high as 45% in high risk cSCC, i.e. tumors located on the lip and ear, large tumors and recurrent tumors.[5,11,12]

The risk of developing cSCC in organ transplant recipients (OTR) is 40-250 times increased compared to that in the general population.[13] In some reports, it has been suggested that cSCC in OTR frequently exhibit aggressive behaviour irrespective of size, that in transit metastases are more frequent and that cSCC in OTR have a worse prognosis than cSCC in immunocompetent patients.[14,15] Between 5 to 23 % of all patients with metastatic cSCC, have been reported to be immunosuppressed, many of whom were OTR and therefore immunosuppression has been reported to be a risk factor for metastasis.[16-18]
In clinical practice, it is difficult to identify high risk cSCC and to detect a metastasis at an early stage, both in immunosuppressed and immunocompetent patients.[19-21] Tumor size, Clark's level, Breslow's thickness, degree of differentiation, perineural invasion and location are associated with the development of metastasis.[22] Staging systems are developed to help determine high-risk tumors.[23-25] The American Joint Committee on Cancer (AJCC) classification is the most commonly used and subject to regular modifications. Since 2010 the AJCC classification is based on several high-risk features of cSCC.[23] Though immunosuppression is mentioned as a risk factor, it does not influence tumor stage in any of the staging systems.
OTR are subject to lifelong immunosuppressive therapy and therefore are an ideal population with regard to analysing the influence of immunosuppression on cSCC metastatic behaviour. Comparative studies between OTR and immunocompetent patients focusing on the metastasis risk of cSCC are scarce. We aimed to identify the risk of cSCC metastasis in a defined cohort of OTR and immunocompetent patients, calculated both per patients as well as per individual tumors.

Methods

For this retrospective study, all consecutive patients with primary cSCC who were diagnosed from January 2004 to December 2013 were identified from the institutional oncology database of the Leiden University Medical Centre. Each patient's medical record was cross-checked with pathology records of cSCC in the same period. Missing patients and/or tumors were added to the database manually. Each tumor was given its own record; one individual patient could have had more records in case of multiple primary cSCC. Detailed histopathological information on all tumors was extracted from the Dutch pathology registry (PALGA). Tumors were categorized by differentiation grade (good, moderate, poor, undifferentiated), presence of lymphovascular invasion, presence of perineural invasion, tumor depth, location and tumor size.[26] All tumors were classified using the TNM staging classification (AJCC 7th edition).

Patient data were extracted from the institutional oncology database. When missing, additional data were collected from patient files. Status and data of immunosuppression were retrieved from the institutional patient database and patient files. Patient files for all patients were checked for information on possible development of metastasis in December 2015, i.e. a minimum follow-up of 2 years. In case of metastasis, the cSCC that most probably was the index tumor was identified. Cases were defined as patients that developed a metastasis from a cSCC that was diagnosed during the study period. Follow-up time was defined as the time of cSCC diagnosis until time of diagnosis of metastasis, death or end of study or to censoring. In our institution OTR were examined at least every 3 months. Immunocompetent patients were followed clinically based on tumor stage according to national guidelines, i.e. twice a year first 1-2 years and once a year in year 3-5 for patients with low-risk cSCC and every three months first year, every 4, 6 and 12 months in year 2, 3 and 4-5, respectively for patients with high-risk cSCC. Screening for metastasis was routinely done by lymph node palpation, and on indication in high-risk tumors by radiologic imaging (ultrasound, X-ray, MRI, CT or PET-scan). Sentinel lymph node procedure was not performed. Descriptive statistics were used for patient and tumor characteristics at baseline. Frequencies, percentages, median, mean and range were calculated, when appropriate. Patients that were immunosuppressed for other reasons than organ transplantation were excluded. Univariable Cox regression analysis was used to identify risk factors for metastasis, excluding cases with missing values for each variable. Multivariable analyses were not carried out due to limited number of events.

Table 1. Baseline characteristics of 593 patients with cutaneous squamous cell carcinoma

	OTR N (%) N=134	**Immunocompetent N (%) N=459**
Sex		
Female	40 (30)	188 (41)
Male	94 (70)	271 (59)
Age first lifetime cSCC (years)		
<60	90 (67)	78 (17)
>=60	44 (33)	381 (83)
Number cSCC study period mean/patient	6.2	1.8
1	39 (29)	357 (78)
2-5	58 (43)	91 (20)
>5	37 (28)	11 (2)
Number lifetime cSCC mean/patient	8.6	2.4
1	32 (24)	313 (68)
2-5	52 (39)	130 (28)
>5	50 (37)	16 (4)
Type of transplantation		
Kidney	110 (82)	NA
Kidney-pancreas	17 (13)	NA
Liver	7 (5)	NA

Abbreviations: OTR: organ transplant recipient; cSCC: cutaneous squamous cell carcinoma; NA: not applicable

A p-value of <0.05 was set as statistically significant for all analyses. Statistical analysis was performed using SPSS version 23 (SPSS, Chicago, Illinois, USA). Incidence rate per person year of metastasis was calculated using STATA 13.1.

Results

During the follow-up time of median 4.0 years (range 1 month-10.8 years), 1792 cSCC were diagnosed in 665 patients, with up to 116 cSCC in one patient. After exclusion of one OTR who had developed a cSCC 1 year before transplantation, 66 patients that were immunosuppressed for other reasons than organ transplantation (inflammatory disease or hematologic malignancy) and six patients who had developed a metastasis from a cSCC diagnosed prior to the study period, the study cohort consisted of 134 OTR and 459 immunocompetent patients (Table 1).

Table 2. Patient and tumor characteristics in 23 patients with metastatic cutaneous squamous cell carcinoma

Sex	Age at cSCC diagnosis	OTR	Location	cSCC size in mm	Differentiation grade	Depth
F	43	kidney/pancreas	cheek	14	good	unknown
M	61	kidney	scalp	10	good	subcutis
M	62	kidney/pancreas	chest	14	undifferentiated	unknown
M	66	Kidney	frontal	15	good	unknown
M	68	kidney	peri-ocular	16	good	dermis
M	68	liver	neck	17	good	dermis
M	70	kidney/pancreas	ear	25	good	dermis
M	71	kidney	scalp	15	good	dermis
F	65	no	finger	10	poor	unknown
M	66	no	temporal	10	undifferentiated	muscle
F	72	no	cutaneous lip	16	good	muscle
M	74	no	temporal	unknown	moderate	dermis
M	75	no	ear	25	good	muscle
M	76	no	scalp	unknown	good	unknown
F	79	no	peri-ocular	38	undifferentiated	unknown
F	84	no	arm	unknown	poor	unknown
F	85	no	temporal	45	good	dermis
M	85	no	frontal	15	moderate	muscle
M	85	no	occipital	45	good	subcutis
M	86	no	neck	15	unclassifiable	dermis
M	88	no	temporal	32	good	subcutis
M	93	no	ear	19	good	cartilage
M	94	no	ear	30	moderate	subcutis

Abbreviations: cSCC = cutaneous squamous cell carcinoma, OTR = organ transplant recipient,

F = female, M = male, PNI = perineural invasion, meta = metastasis.

PNI	T-stage AJCC	Number of lifetime cSCC until metastasis	Type of metastasis	Time between cSCC and metastasis (months)	Death because of metastasis
no	1	8	nodal	27	no
no	1	3	nodal	14	no
no	unknown	8	nodal	3	yes
no	1	1	nodal	3	alive
no	1	3	distant	30	no
no	1	1	nodal	21	cause of death unknown
no	2	15	nodal	6	alive
no	1	15	nodal	38	alive
no	unknown	1	nodal	17	yes
no	3	1	distant	13	yes
no	3	1	nodal & distant	16	yes
no	unknown	1	nodal	7	yes
no	3	1	nodal	21	alive
no	unknown	1	distant	7	cause of death unknown
no	2	1	nodal	6	no
no	unknown	11	nodal	2	no
no	2	1	nodal	7	alive
no	3	1	nodal	39	cause of death unknown
no	2	5	nodal & distant	0	yes
no	1	1	nodal	15	no
yes	2	1	nodal & distant	1	yes
no	3	6	nodal	13	yes
no	2	1	nodal	8	cause of death unknown

Table 3. Univariate hazard ratios for patient characteristics as risk factors for metastasis in patients with cutaneous squamous cell carcinoma

	Organ transplant recipients			Immunocompetent patients		
	total	**with metastasis, n (%)**	**Hazard ratio (95%CI)**	**total**	**with metastasis, n (%)**	**Hazard ratio (95%CI)**
PATIENTS	**N=134**	**N=8**		**N=459**	**N=15**	
Sex						
Female	40	1 (2)	1	188	5 (3)	1
Male	94	7 (7)	4.4 (0.52-36.1)	271	10 (4)	
Age at 1st cSCC (years)						
<60	90	2 (2)	1	78	0	NA
>=60	44	6 (14)	8.3 (1.7-41.8)	381	15 (4)	NA
Number cSCC study period						
1	39	1 (3)	1	357	12 (3)	1
>1	95	7 (7)	1.5 (0.19-12.8)	102	3 (3)	0.75 (0.21-2.7)
Number lifetime cSCC						
1	33	2 (6)	1	314	12 (4)	1
>1	101	6 (6)	0.48 (0.09-2.6)	145	3 (2)	0.49 (0.14-1.7)
Age at TX (years)						
<60	113	5 (4)	1	NA	NA	NA
>=60	21	3 (14)	5.0 (1.2-21.7)	NA	NA	NA

Abbreviations: CI = confidence interval, cSCC = cutaneous squamous cell carcinoma, TX = transplantation, NA = not applicable

In all, 23 patients (3.9%; 95% CI 2.6-5.8) developed a metastasis from a cSCC diagnosed in the study period, eight (6.0; 95% CI 3.1-11.3) OTR and 15 (3.3%; 95% CI 2.0-5.3) immunocompetent patients. The incidence rate (IR) for metastasis was 1046 (95%CI 524-2096) per 100,000 person years in the OTR group and 656 (95%CI; 388-1107) in the immunocompetent patient group, yielding an incidence rate ratio (IRR) between OTR versus immunocompetent patients of 1.6 (95% CI 0.67-3.8). Median time between cSCC diagnosis and metastasis diagnosis was longer in the OTR group than in the immunocompetent group, 17.5 months and 10.5 months, respectively. Distant site metastasis was found in 1 OTR and in 5 immunocompetent patients, of whom 3 also had concomitant nodal metastasis.

Patient, tumor and metastasis characteristics are shown in Table 2, 3 and 4. Univariate hazard ratios for metastasis are listed in Tables 3 and 4. Having a first cSCC at an

Table 4. Univariate hazard ratio of tumor characteristics as risk factors for metastasis in patients with cutaneous squamous cell carcinoma

	Organ transplant recipients			Immunocompetent patients		
	total	**metastatic cSCC, n (%)**	**Hazard ratio (95%CI)**	**total**	**metastatic cSCC, n (%)**	**Hazard ratio (95%CI)**
TUMORS	**N=829**	**N=8**		**N=814**	**N=15**	
Location tumor						
Body	582	1 (1)	1	296	2 (1)	1
Head & neck	247	7 (3)	16.9 (2.1-138.5)	518	13 (3)	3.8 (0.85-16.9)
T-stage						
T1	657	6 (1)	1	584	1 (1)	1
T2-T4	73	1 (1)	1.5 (0.18-12.7)	105	10 (10)	61.4 (7.8-484.9)
Missing	99	1 (1)		125	4 (3)	
Tumor size (diameter)						
<=20mm	726	7 (1)	1	661	6 (1)	1
>20mm	59	1 (2)	1.8 (0.21-14.6)	71	6 (8)	10.1 (3.2-32.1)
Missing	44	0		82	3 (4)	
Differentiation						
Good-moderate	720	7 (1)	1	681	10 (1)	1
Poor-undifferentiated	94	1 (1)	1.1 (0.13-9.0)	120	4 (3)	2.3 (0.71-7.5)
Missing	15	0		13	1 (8)	
Depth/invasion						
Dermis	227	4 (2.0)	1	458	3 (1)	1
Hypodermis	27	1 (4)	1.4 (0.24-8.5)	46	8 (17)	6.5 (3.3-13.0)
Missing	575	3 (1)		310	4 (1)	

Abbreviations: cSCC = cutaneous squamous cell carcinoma, CI = confidence interval.

older age was significantly associated with an increased risk of metastasis in OTR (HR 8.3 95%CI:1.7-41.8). In the immunocompetent group, all patients (15) with metastasis developed their first cSCC after the age of 60 years. In OTR, being transplanted at 60 years or older (HR 5.0, 95%CI 1.2-21.7), increased the risk of metastasis. Having multiple cSCC was not associated with increased risk for metastasis in either group. cSCC located in the head and neck area was a risk factor for metastasis, both in the OTR group (HR 16.9, 95% CI 2.1-138.5) and in the immunocompetent group (HR 3.8, 95% CI 0.85-16.9), but statistically significant only in the OTR group. In the OTR group T stage, tumor size, differentiation grade and depth of invasion were not associated with increased metastasis risk. T stage of 2 or higher, tumor size and tumor depth beyond the dermis were associated with

increased risk of metastasis in the immunocompetent group. In the OTR group, perineural invasion was not found in any metastatic cSCC and in 3 non-metastatic cSCC, but was observed in one metastatic cSCC and in 9 non-metastatic cSCC in the immunocompetent population. Lymphovascular invasion was only seen in one non-metastatic cSCC in OTR and in 2 non-metastatic cSCC in immunocompetent patients.

Discussion

In this study we were not able to demonstrate a statistically significant increased risk for metastasis from cSCC in OTR compared to immunocompetent patients with cSCC. However, the risk factors seemed to be different between the two groups.
With cSCC metastases incidences of 6.0% in OTR and 3.3% in the immunocompetent patients, the incidence of metastasis in our study was lower than in other studies. In OTR metastasis incidences of 7-14% are reported for low-risk tumors and 10-20% for high-risk tumors.[1,9,18,27-30] In the general population, the overall incidence varies between 2.3-9.9%.[31] For low-risk tumors the risk is between 0.5-5% and may increase to more than 20% in high risk cSCC.[5,11,12]
The mean time between diagnosing the cSCC and detecting metastasis was longer in the OTR group than in the immunocompetent group. The OTR group had a median time of 17.5 months to develop metastasis, compared to 10.5 months in the immunocompetent group. This was a surprising finding, considering both the immunosuppressed state leading to decreased immunological tumor surveillance and the increased clinical surveillance of OTR. As the majority of tumors in OTR were not located in the head and neck area, in contrast to the immunocompetent group, this difference in tumor distribution could contribute to the relatively low risk of metastasis in OTR. In other studies, the median time to develop metastasis is reported from 4 to 12 months.[32,33]
In OTR, age over 60 years at transplantation and age over 60 years at time of first cSCC diagnosis were risk factors for metastasis. This is in line with previous studies.[34] As OTR developed their first cSCC at a younger age than immunocompetent patients, this could explain the relatively low number of metastases in OTR. Most OTR in our study were renal transplant recipients and have somewhat different immunosuppressive treatment regimens than other OTR , especially heart transplant recipients.[35-37] This could contribute to different incidence rates of cSCC metastasis across the literature.

In our immunocompetent patients, tumor size and depth, and subsequently T-stage, were significant risk factors for metastasis, as shown in other studies.[5,9,28,38,39] In our OTR we did not find these associations. Tumor size is a well-known risk factor for metastatic lesions with an association between increasing tumor thickness and lesion size.[5,9,18,19,40-43] In our study, seven out of eight cSCC that metastasised in OTR were smaller than 2 cm in diameter and most of the tumors were low risk T1 tumors.
This suggests that OTR with relatively small tumors (<2cm) are already at an increased risk of developing metastasis from cSCC, and are less dependent on specific tumor characteristics.[18,44] OTR have regular clinical follow-ups, and small tumors should therefore be diagnosed before they grow into large tumors. Although it is published that patients with multiple cSCC are at an increased risk of metastasis, we were unable to confirm that having multiple tumors led to a higher risk of metastasis.[45] Given the low number of metastases in our OTR group and with metastases mainly developing from relatively small tumors, frequent follow-up of OTR should continue.
This study has several limitations. First, we had only a small number of patients with metastasising cSCC in the OTR group. It was, therefore, difficult to estimate the effect size for risk factors. We acknowledge that statistical analysis should be considered insufficient and only indicative. We also had too few cases to perform multivariable analyses to control for possible confounders. Second, the Leiden University Medical Centre is a tertiary referral centre for selected cSCC patients. Due to this selection bias, extrapolation of our results is difficult, as one should expect a higher rate of metastases in immunocompetent patients with cSCC referred to the hospital. Finally, the cSCC in our cohort were diagnosed by several pathologists without a systematic re-evaluation of the histopathological slides. This might have introduced some error but probably not bias, as no differences are expected in how pathologists will evaluate tumors from OTR and immunocompetent patients.
To conclude, the metastatic rate of cSCC in OTR and immunocompetent patients in this study is lower than in most other studies. We were not able to demonstrate an increased risk of metastasis in OTR compared to immunocompetent patients. Most tumors that did metastasise in OTR were small tumors without high-risk features. Close and regular inspection of the skin with adequate and rapid diagnosis and treatment of cSCC is important to prevent metastasis.

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