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

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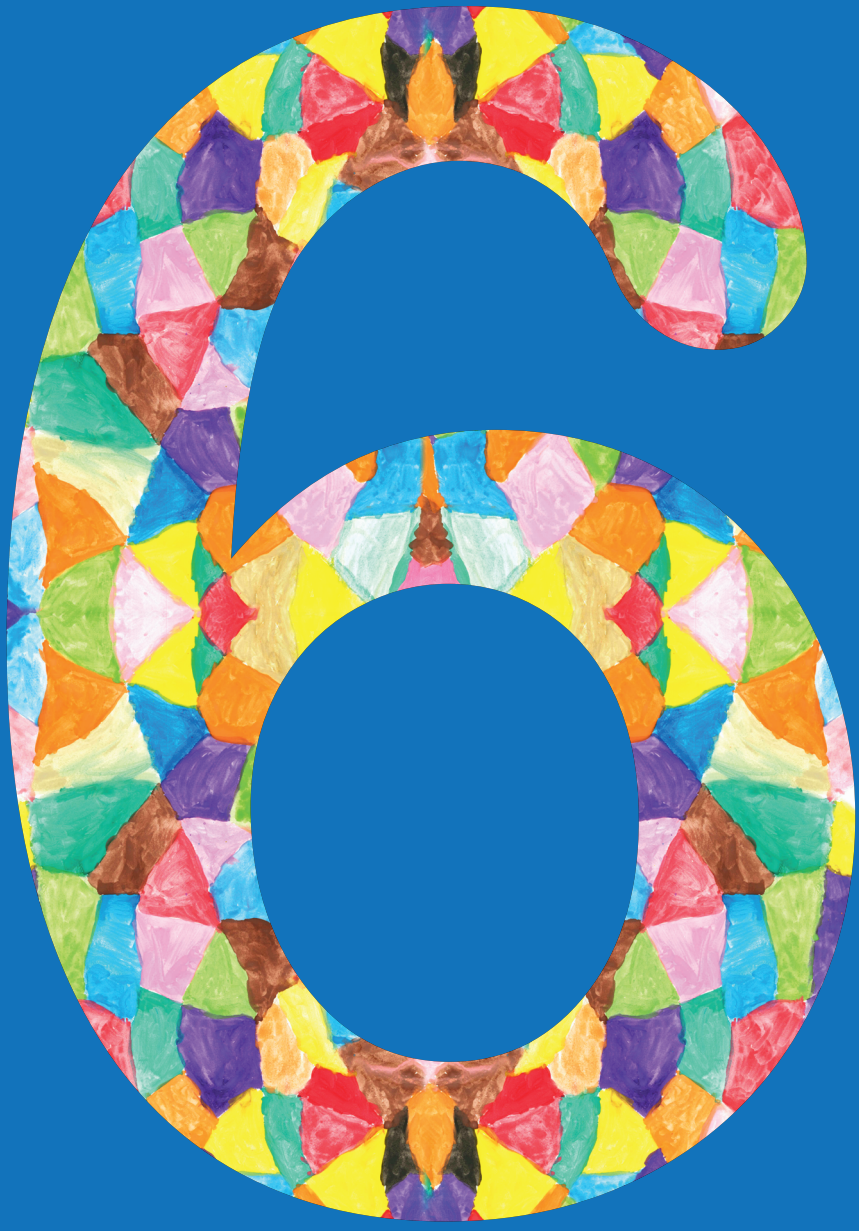

CHAPTER 6

Metastasis of cutaneous squamous cell carcinoma in organ transplant recipients and the immunocompetent population: is there a difference? A systematic review and meta-analysis

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Abstract

Organ transplant recipients (OTR) have a higher risk of developing cutaneous squamous cell carcinoma (cSCC) compared to the immunocompetent population. Immunosuppression is often stated as a risk factor for metastasis. However, evidence for this is scarce.

To investigate the cSCC metastasis risk in OTR and the immunocompetent population, a systematic review of the literature was performed up to January 2018 using: Medline; Embase; Web of Science and ISI Science Citation Index. Studies assessing cSCC metastasis risk in ORT or immunocompetent cohorts were considered. A pooled risk estimate for metastasis was calculated for the immunocompetent population and OTR separately.

The pooled metastasis risk estimate for OTR was respectively 7.3% (95% CI 6.2-8.4) for cSCC on total body, and 11.0% (95% CI 7.7-14.8) for cSCC of the head and neck area. For the immunocompetent population reported risk estimate analysis showed a pooled metastatic risk of 3.1% (95% CI 2.8-3.4) in total body cSCC and of 8.5% (95% CI 7.3-9.8) in cSCC of the head and neck area.

Pooled risk estimate per single cSCC in OTR were 1.3% (95% CI 1.0-1.7) in total body cSCC and 4.0% (95% CI 2.7-5.5) in cSCC of the head and neck area. In the immunocompetent population these pooled risk estimates were respectively 2.4% (95% CI 2.1-2.6) and 6.7% (95% CI 5.7-7.8).

OTR show a higher overall risk of cSCC metastasis compared to the immunocompetent population. Metastasis risks per single cSCC were substantially lower in both groups. However, due to heterogeneity and differences between studies, comparisons are difficult. Comprehensive follow-up studies with defined cohorts are necessary to adequately asses the risk for cSCC metastasis.

Introduction

Keratinocyte carcinoma (KC) is the most prevalent cancer worldwide, consisting of cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC).[1] Approximately 20-25% of the KCs are cSCC.[2,3] With a lifetime risk for cSCC between 7 to 14% and a rising incidence, cSCC is considered a major health problem in white populations, at substantial costs.[4-9] In high risk populations like solid organ transplant recipients (OTR) the reported cSCC risk is considerably higher, 60 to 250 times increased compared to the immunocompetent population.[10,11] The incidence of cSCC in OTR is directly related to the level and duration of immunosuppressive medication.[10,12-14] Important risk factors for both the immunocompetent and the transplant population are cumulative ultraviolet radiation, older age and male sex and probably human papillomavirus infection.[15-19]

Metastases occur in approximately 5% (range 0.1-9.9%) of cSCC, usually to regional lymph nodes.[15,16,18,20-25] Low risk cSCC (<2cm, depth not beyond dermis, good differentiation grade) metastasize only in 0-3%.[26-29] Presence of risk factors, like large tumor size (>2cm), deep infiltration, location on the lip or ear, poor differentiation grade and perineural and lymphovascular invasion increase the risk for metastasis up to 40%.[2,16,23,30,31] Currently, tumor depth is identified as the most important risk factor for metastasis.[32] For OTR patients a higher risk (13%) for metastatic disease has been described compared to immunocompetent patients with cSCC.[16] Furthermore, it seems that OTR present more commonly with aggressive cSCC (thicker tumors, poorly differentiated and infiltrative), irrespective of size, with a higher predilection for metastasis and worse outcome.[33-37] Furthermore, in studies reporting only on metastasized cSCC, around 5 to 23% of patients were immunosuppressed.[21,38,39]

However, data regarding the metastatic risk of cSCC in OTR is relatively scarce and mostly based on small studies. This current systematic review investigates whether the risk for cSCC metastasis is increased for OTR compared to immunocompetent patients.

Methods

Search strategy and Study selection

The Cochrane Database of Systematic Reviews was searched for a systematic review on this topic, but none was found. An electronic database search was performed up

to 01 January 2018 using the following data sources: Medline; Embase; Web of Science and the ISI Science Citation Index. No restrictions were applied with regards to language or calendar year.
The following search terms and equivalents were used: "squamous cell carcinoma, malignancy, non-melanoma, skin, immunosuppression, transplantation, metastasis". Detailed search strings for PubMed, Embase and Web of Science are shown in supplementary file 1. Relevant citations were checked by browsing the references of review articles and relevant publications of primary investigations were included. Titles and abstracts from retrieved articles were screened by 2 authors (RG and EP). Subsequently full-texts of potentially relevant articles were assessed for eligibility by the same 2 authors. Any discrepancy was resolved by consensus.

Eligibility criteria
Initially, a search was performed for studies that directly compared metastasis risk in OTR and in the immunocompetent population, but direct comparison of metastatic risk in both groups was scarce. Therefore, we broadened the eligibility criteria to include cohort studies and also single arm cohort studies of populations diagnosed with cSCC in: (1). a population of OTR or (2). the immunocompetent population, without immunosuppressed patients, and in which occurrence of metastasis was reported. Studies were included when they had 25 or more patients with a cSCC in any location in both immunocompetent patients and OTR. We excluded studies reporting on populations with solely metastasized cSCC. When more than one report was published on the same population or subpopulation, we included the report with the largest number of cSCC or with the longest follow-up.

Data collection process and risk of bias assessment
The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist was followed for reporting of the review.[40] Inclusion criteria and methods of data analysis were specified in advance. A data extraction sheet was developed and piloted. Two reviewers extracted data independently (RG and EP) and cross-checked each other's results and disagreements were resolved by discussion. The following information was extracted from each included study; (1) study characteristics (e.g. design, location, centre, years of data collection, aim), (2) population characteristics (including number of patients with a solid organ transplant and immunocompetent population patients, gender, age, transplantation characteristics) and tumor data (including

number of cSCC, length of follow-up) (3) type of outcome measure (metastasis; nodal, in-transit, systemic).
A component based approach to assess risk of bias based on the Newcastle-Ottawa Quality assessment scale was used.[41] Relevant items of this scale were used and adjusted for our cohort. Important items relevant to the topic of this review were added. The following design elements were assessed; (1) whether the outcome metastasis was noted in the study aim, (2) statement of absence of immunosuppressive patients in the immunocompetent population studies, (3) inclusion of all consecutive cSCC in patients (or a random sample) during a distinct study period, (4) adequacy of follow-up, (5) use of standardized diagnostic protocol for metastasis, (6) number of low and high risk tumors, (7) presence of high risk features of cSCC. Quality assessment was scored positive bullet for each item if it was mentioned in the article. For high risk features at least two features had to be present.

Statistical analysis
The risk of metastasis of cSCC was the primary outcome measure. We estimated a pooled risk of metastasis in the two populations separately: in studies reporting on the immunocompetent population and in studies of OTR. Descriptive statistics were used to calculate metastasis risk. A subdivision was made for cSCC studied on the total body and the head and neck area. Cohorts consisting of specific cSCC (e.g. only high risk or on specific anatomic locations) were excluded from analysis.
Summary estimates were calculated for the proportion of patients with metastasis and summary estimates were calculated for studies that reported the exact number of cSCC in their cohort.
Statistical analysis was performed using STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

Search results
Details of the selection process for eligible studies are shown in Figure 1. A total of 10396 publications were retrieved and 53 studies fulfilled the inclusion criteria. Two cohort studies described the metastasis risk in both OTR and immunocompetent population and will be described in more detail. Fourteen studies were performed solely in OTR and 37 solely in the immunocompetent population.

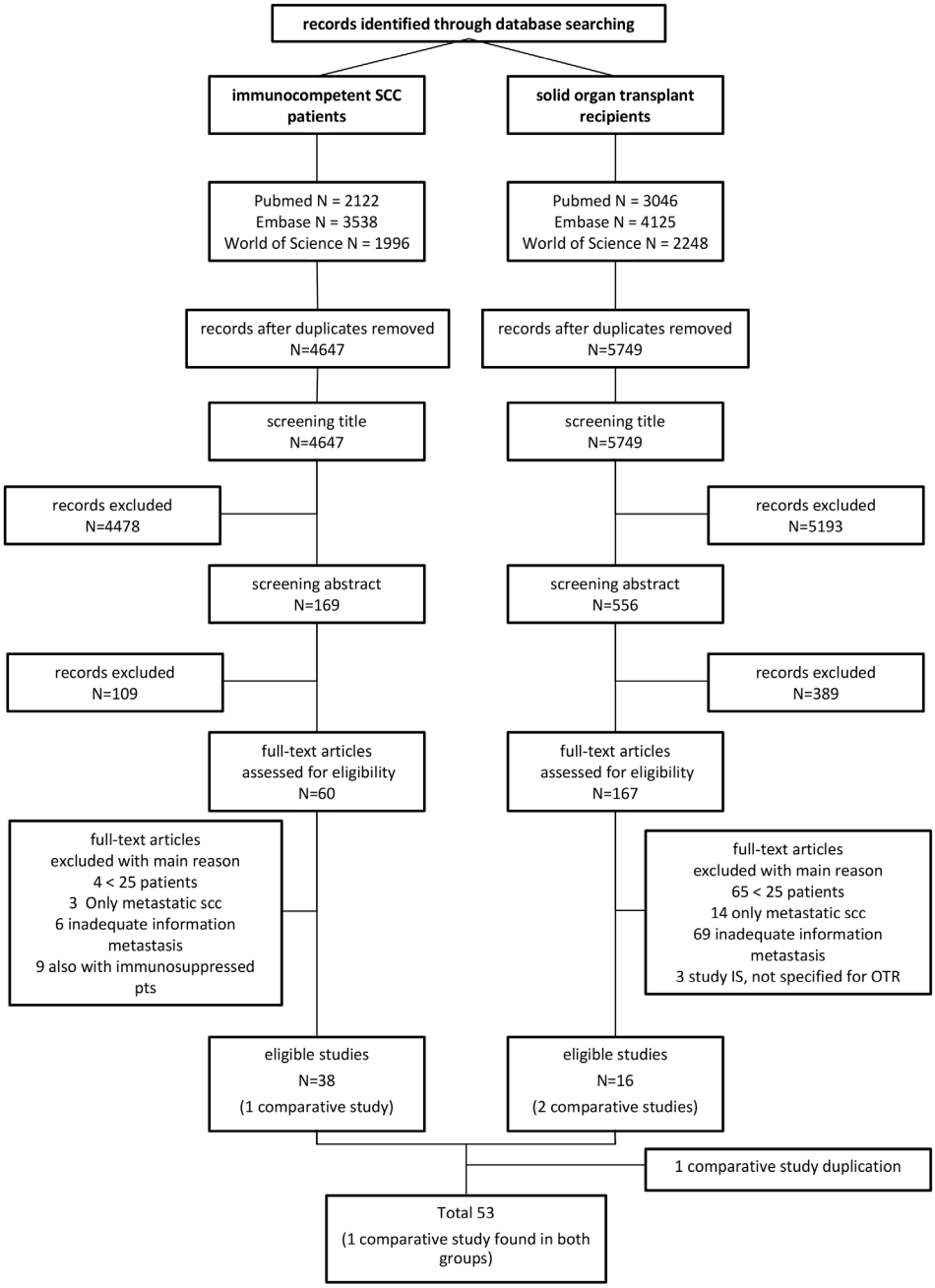

Figure 1. Flow chart. Details of the selection process for eligible studies.

Studies in OTR

Sixteen studies reported on the metastasis risk of cSCC in OTR. The included studies were published between 1980 and 2017; the number of included patients ranged from 34 to 796 (Table 1).[42-57] These studies were performed in the USA, New-Zealand, Australia, the Netherlands, France, Portugal and Israel. Follow-up in these studies was mainly calculated from time of transplantation instead of follow-up from cSCC development. Only 5 studies informed about follow-up time of cSCC. Thirteen studies included patients with cSCC on the total body,[42-49,51-53,56,57] three studies reported on patients with a cSCC in the head and neck area.[50,54,55]

Studies in the immunocompetent population

Thirty-nine studies reported on metastasis risk of cSCC in the immunocompetent population. Nineteen studies reported on special cohorts in the immunocompetent population, like specific anatomical locations or only reporting on specific high risk cSCC or cSCC derived in burns.[58-76] The results of these specific cohorts are not taken into account in the pooled metastasis risk analyses. The details of these studies are shown in Table 2.

Studies included for analyses were published between 1957 and 2017; the number of included patients ranged from 40 to 6164 (Table 1).[22-25,30,44,47,77-89] These studies were performed in the USA, New-Zealand, Australia, the Netherlands , Denmark, the UK, Greece, Turkey and Israel. Median follow-up time ranged from 24 to 81 months. Overall follow-up ranged from 0-312 months.

Fourteen studies included patients with cSCC on the total body [22-24,30,44,47,78-81,83,84,87,88], six studies with patients with cSCC in the head and neck area.[25,77,82,85,86,89] One study also included specified data on 10 OTR, that were excluded for this study as it were less than 25 patients.[88]

Two studies comparing immunocompetent population and OTR

Both studies were performed in the USA and studied total body cSCC.[44,47]

One study retrospectively compared 153 OTR with cSCC with 154 numerically matched cSCC patients in immunocompetent patient that were randomly chosen from a pool of patients.[47] Follow-up time was shorter in the control group (mean 37 months) compared to the OTR group (mean 65 months). The reported risk for metastasis in the OTR population was 4.6%, in the control population 1.3%. No significant differences between OTR and the control population were found for lymph node

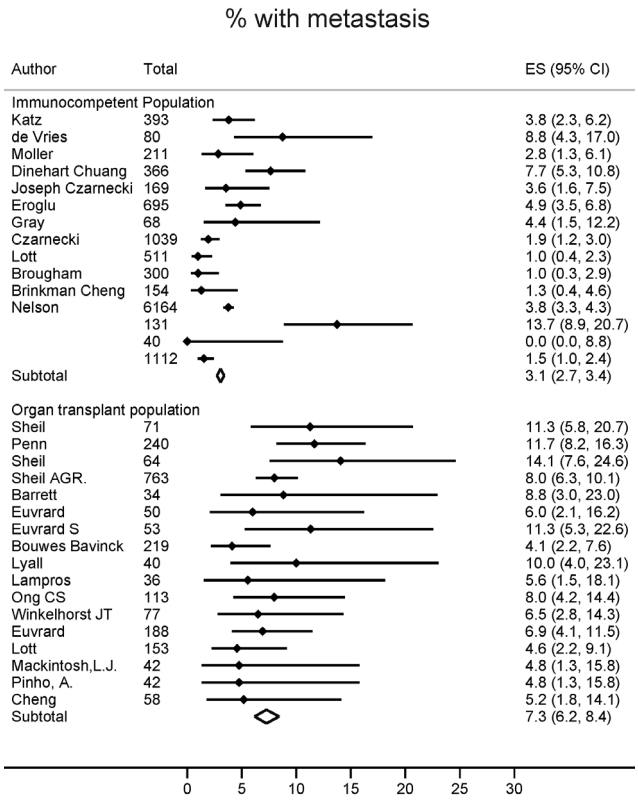

Figure 2.
Forest plot of metastasis risk of total body cutaneous squamous cell carcinoma per patient stratified by organ transplant population and immunocompetent population.

spread, although they stated that there was as a trend toward significance (p=0.10) and suggested that OTR are 3.5 times more likely to have lymph node spread.
The second retrospective cohort study compared 58 OTR and 40 high risk immunocompetent patients (defined as patients with more than 1 cSCC in the past).[44] The OTR and immunocompetent groups were comparable regarding race and sex, patient care, follow-up time, numbers of skin lesions, and field cancerization and chemo preventive therapies. This study included a total follow-up of 369 patient-years for both OTR and immunocompetent patients. Two OTR were diagnosed with regional lymph node metastases. No metastases were found in the control group.

Risk of bias assessment

Risk of bias assessment was based upon a component based approach for studies in OTR and normal population regarding total body and head and neck cSCC (Table 1).

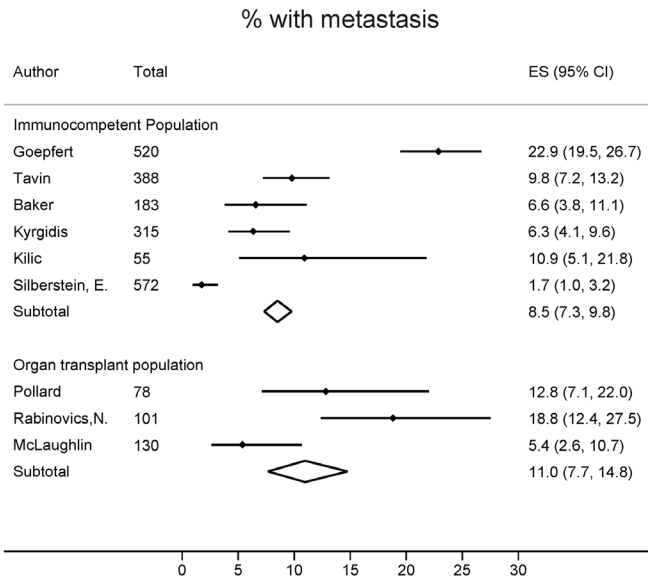

Figure 3.
Forest plot of metastasis risk of cutaneous squamous cell carcinoma of the head and neck area per patient stratified by organ transplant population and immunocompetent population.

6

The results were based upon the studies included in the pooled risk analysis and figures. In general, studies reporting on the immunocompetent population gave more details about the study population and the cSCC in the cohort.

The majority of studies reported on consecutive cSCC in their patients during the study period, but seven did not.[24,30,52,54,83,85] Seven studies reported on loss of follow-up [30,45,50,57,81,82,86] with a loss of follow-up of more than 5% in 6/7.[30,45,50,57,81,86] One study excluded patients with follow-up less than 6 months [50], and one study included only patients with a minimum follow-up of more than one year.[86] One study stated that a protocol was followed annually to detect metastasis with radiological imaging.[86] Four studies reported on clinical follow-up of patients.[42,44,50,55] In seven studies the distribution of T-stage among the cSCC was mentioned.[50,55,78,81,86,87,89] In 21 studies, one or more tumor related potential high risk features factors for metastasis, such as size, location, depth of invasion or perineural invasion, were taken into account. One study in the immunocompetent population specifically stated that no OTR were included in the cohort of the immunocompetent population.[30] One study reported separately on 10 OTR patients in their cohort.[88] Two studies compared OTR to the immunocompetent population.[44,47] In 14 studies, the outcome of metastasis was specifically noted in the study aim.[22,25,44,48,50,78-82,84,87-89]

Table 1. Details of studies included in the analyses.

STUDY CHARACTERISTICS														
Author, year, country	**Study period**	**N pt cSCC (%male)**	**N cSCC**	**Age pt median (mean) range in years**	**Treatment cSCC**	**FU cSCC median (mean) range in months**	**Total N pt metastasis**	**N in transit meta**	**N nodal meta**	**N distant meta**	**% meta per pt**	**% meta per cSCC**	**Meta risk factors**
TOTAL BODY cSCC														
OTR														
Barrett, 1993, USA	1968-1993	34 (nm)	nm	47	Surg	(27)	3	nm	3	1	8,8	-	nm	
Bouwes Bavinck, 1996, AU	1969-1994	219 (66)	2042	(50), 15-72	nm	nm	9	nm	nm	nm	4,1	0,4	nm	
Cheng,, 2017, US,	2008-2015	58 (76)	167	(70)	nm	46	3	2	1	nm	5,2	1,8	nm	
Euvrard, 2006, FR	1966-2004	188 (nm)	476	nm	nm	(21)	13	nm	nm	nm	6,9	2,1	nm	
Lampros, 1998, US	1985-1996	36 (nm)	172	(55)	nm	nm	2	nm	nm	nm	5,6	1,2	nm	
Lott, 2010, US	1997-2008	153 (73)	978	nm	nm	36	7	nm	7	nm	4,6	0,7	nm	
Lyall, 1998, NA	1972-1997	40 (nm)	nm	nm	nm	nm	4	nm	4	nm	10,0	-	nm	
Mackintosh, 2012, UK	2005-2008	42 (nm)	151	nm	nm	nm	2	nm	2	nm	4,8	1,3	nm	
Ong, 1999, AU	1984-1998	113 (nm)	849	54	nm	nm	9	nm	nm	nm	8,0	1,1	nm	
Penn, 1980, US	1968-1993	240 (nm)	nm	nm	nm	nm	28	nm	24	4	11,7	-	nm	
Pinho, 2016, PT	2004-2013	42 (nm)	43	nm	nm	nm	2	nm	2	nm	4,8	4,7	nm	
Sheil, 1992, AU/NZ	1963-1992	796 (nm)	nm	nm	nm	nm	61	nm	nm	nm	8,0	-	nm	
Winkelhorst, 2001, NL	1968-1998	77 (nm)	nm	(53), 29-72	nm	nm	5	nm	nm	nm	6,5	-	nm	
Immunocompetent population														
Brinkman, 2013, NL	2001-2008	131 (66)	155	(73), 19-96	Surg	81, 27-125	18	0	12	6	13,7	11,6	nm	
Brougham, 2012, NZ	1997-2007	6164 (57)	8997	(74), 21–108	Surg	71, 31-121	232	8	251	23	3,8	2,6	location, size, diff , PNI	
Cheng, 2017, US	2008-2015	40 (60)	111	(70)	nm	46	0	nm	nm	nm	0,0	0,0	nm	
Chuang, 1990, US	1976-1984	169 (60)	169	72 (71)	Surg	46	6	1	5	0	3,6	3,6	nm	
Czarnecki, 1994, AU	1988-1989	68 (75)	68	(72)	nm	> 36	3	0	1	2	4,4	4,4	nm	

	RISK OF BIAS / QUALITY ASSESSMENT							
	Metastasis noted in study aim	Statement IS present	Consecutive cSCC	Loss to FU in %	Diagnostic protocol meta	% T stage	cSCC features	Score
	no	OTR cohort	yes	nm	yes	nm	nm	●●●○○○○
	no	OTR cohort	yes	nm	nm	nm	nm	●●○○○○○
	no	OTR cohort	yes	nm	yes	nm	11% > 2mm depth, 1% PNI	●●●●○○○
	no	OTR cohort	yes	6	nm	nm	nm	●●●○○○○
	no	OTR cohort	yes	nm	nm	nm	70% Head and neck	●●○○○○○
	no	OTR cohort	yes	nm	nm	nm	9% > subdermal, 8% PNI, 3% LVSI	●●●○○○○
	yes	OTR cohort	yes	nm	nm	nm	nm	●●●○○○○
	no	OTR cohort	yes	nm	nm	nm	nm	●●○○○○○
	no	OTR cohort	yes	nm	nm	nm	nm	●●○○○○○
	no	OTR cohort	no	nm	nm	nm	nm	●○○○○○○
	no	OTR cohort	yes	nm	nm	nm	7% > 2cm, 16% poor diff, 30% > 4mm depth, 30% ear/lip/ anogenital, 2% PNI	●●●○○○○
	no	OTR cohort	yes	nm	nm	nm	nm	●●○○○○○
	no	OTR cohort	yes	8	nm	nm	nm	●●●○○○○
	yes	nm	yes	nm	nm	1:46, 2:25, 3:6, NS: 24 (AJCC 6th)	13% poor diff, 68% HN	●●●●○○○
	yes	nm	yes	nm	nm	nm	10% >2cm, 8% poor diff, 49% HN, 1% PNI, 1% LVSI	●●●○○○○
	no	yes, present	yes	nm	yes	nm	0% PNI	●●●○○○○
	no	nm	no	nm	nm	nm	79% HN	○○○○○○○
	yes	yes, not present	no	13	nm	nm	nm	●●○○○○○

Table 1. Continued

Author, year, country	Study period	N pt cSCC (%male)	N cSCC	Age pt median (mean) range in years	Treatment cSCC	FU cSCC median (mean) range in months	Total N pt metastasis	N in transit meta	N nodal meta	N distant meta	% meta per pt	% meta per cSCC	Meta risk factors
STUDY CHARACTERISTICS													
Czarnecki, 2000, AU	1988-1998	300 (67)	nm	nm	Surg	6-120	3	nm	nm	nm	1,0		nm
Dinehart, 1989, US	1979-1988	366 (77)	366	(67)	Surg	(20) 2-94	27	nm	23	4	7,7	7,7	nm
Eroglu, 1996, TR	1980-1989	1039 (nm)	nm	65, 15-97	Surg/ RT/CT	28, 6-149	20	nm	20	nm	1,9		nm
Gray, 1997, US	1984-1992	511 (54)	511	(74), 10-101		52	5	nm	nm	nm	1,0	1,0	nm
Katz, 1957, US	1946-1950	393 (70)	577	nm	Surg/ RT	60	15	nm	nm	nm	3,8	2,6	nm
Lott, 2010, US	1997-2008	154 (66)	256	nm	nm	36	2	nm	2	nm	1,3	0,8	nm
Moller, 1979, DK	1950-1959	211 (73)	211	(65)	Surg/ RT	204-312	11	0	9	4	5,2	5,2	nm
Nelson, 2017, UK	2005-2014	1122 (64)	1495	78, 44-102	Surg	79, 24-143	18	nm	nm	nm	1,6	1,2	size, depth
de Vries, 1969, NL	1962-1967	80 (nm)	80	nm	Surg/ RT	6-60	7	nm	7	nm	8,8	8,8	nm
cSCC OF THE HEAD AND NECK AREA													
OTR													
McLaughlin, 2017, USA	2005-2015	130	383	(62)	Surg	(40)	7	nm	7	n nm	5.4	1.8	Scalp, subdermal growth
Pollard, 2000, US	1968-1998	78 (nm)	214	nm	nm	nm	10	nm	nm	nm	12,8	4,7	nm
Rabinovics, 2013, IL	1992-2010	101 (84)	198	nm	nm	nm	19	nm	17	2	18,8	9,6	nm
Immunocompetent population													
Baker, 2001, UK	1990-1995	183 (73)	227	78	Surg	24	12	nm	12	nm	6,6	5,3	nm
Goepfert, 1984, USA	1970-1979	520	967	64	nm	24	119	nm	93	26	22.9	12.3	nm
Kilic, 2014, TR	2010-2012	55	55	56, 29-89	Surg	24	6	nm	6	nm	10,9	10,9	nm
Kyrgidis, 2010, GR	1996-2006	315 (46)	nm	72. 26–95	Surg/ RT/CT	47, 12-124	20	nm	nm	5	6,3		nm
Silberstein, 2015, IL	1998-2005	572 (59)	725	(72)	Surg	72, 24-x	10	nm	10	0	1,7	1,4	T stage
Tavin, 1996, US	1961-1992	388	388	nm	Surg/ RT		38	nm	40	8	9,8	9,8	nm

Abbreviations: N; number, pt; patients, cSCC; cutaneous squamous cell carcinoma, FU; follow-up, meta; metastasis, IS; immunosuppression, OTR; organ transplant recipients, nm; not mentioned, Surg; surgery, RT; radiotherapy, CT; chemotherapy, diff; differentiation grade, USA; United states of America, AU; Australia, FR; France, NZ; New Zealand, UK; United Kingdom, PT; Portugal, NL; the Netherlands, TR; Turkey, DK; Denmark, IL; Israel, GR; Greece

RISK OF BIAS / QUALITY ASSESSMENT							
Metastasis noted in study aim	Statement IS present	Consecutive cSCC	Loss to FU in %	Diagnostic protocol meta	% T stage	cSCC features	Score
no	nm	yes	nm	nm	nm	nm	●○○○○○○
yes	nm	no	nm	nm	nm	85% HN, 2% PNI	●●○○○○○
yes	nm	yes	> 10	nm	1:10, 2:21, 3:32, 4:28 (AJCC 5th)	9% poor diff	●●●●○○○
no	nm	no	nm	nm	nm	78% HN	○○○○○○○
yes	nm	yes	nm	nm	nm	58% HN	●●○○○○○
no	yes, present	yes	nm	nm	nm	2% subdermal. 1% PNI	●●●○○○○
yes	nm	yes	nm	nm	1:2, 2:38, 3:8, 4:1 (AJCC 3rd)	75% HN	●●●○○○○
yes	yes, present	yes	nm	nm	nm	11% poor diff, mean size 15mm, mean depth 4.5mm, 65% HN	●●●●○○○
yes	nm	yes	nm	nm	nm	85% HN	●●○○○○○
yes	OTR cohort	yes	10.3	Clinical FU protocol	1:73, 2: 27 (AJCC), 1 69, 2a 24, 2b: 7 (BWH)	12% subdermal,	●●●●●○○
no	OTR cohort	no	nm	nm	nm	nm	●○○○○○○
no	OTR cohort	yes	nm	yes	1:69, 2:27, 3+4: 4, Other: 3% (AJCC)	69% stage 1+2	●●●●○○○
no	nm	yes	nm	nm	nm	26% ear, 6% lip	●○○○○○○
yes	no	yes	2	nm	nm	14% PNI	●●●○○○○
no	nm	no	nm	nm	nm	36% ear, 1% periocular, 3% lip	○○○○○○○
no	nm	yes	8	yes	1:51, 2:20, 3:29 (AJCC 7th)	mean size 2.2 cm, mean depth 5mm, 18% poor diff, 13% periocular, 24% ear, 20% PNI	●●●●●○○
yes	nm	yes	nm	nm	0:3, 1:89. 2:8, 3:1, 4:1 (nm)	17% ear, 6.3% peri-ocular	●●●○○○○
yes	nm	yes	nm	nm	nm	26% ear, 6% lip	●●○○○○○

Table 2. Details of studies regarding special locations or high risk tumors

STUDY CHARACTERISTICS													
Author, year, country	**Study period**	**N pt cSCC (%male)**	**N cSCC**	**Age pt median (mean) range in years**	**Treatment cSCC**	**FU cSCC median (mean) range in months**	**Total N pt metastasis**	**N in transit meta**	**N nodal meta**	**N distant meta**	**% meta per pt**	**% meta per cSCC**	**Meta risk factors**
Auricle													
Mayo, 2017, UK[66]	2007-2012	192 (100)	192	(81), 41-98	SURG/ RT	24-60	4	nm	4	nm	2,1	2,1	diff, PNI
Shiffman, 1975, CA[72]	1952-1973	52 (96)	nm	(73), 28-96	SURG/ RT	(23)	7	1	5	3	13,5	nm	nm
Eyelid													
Faustina, 2004, USA[62]	1952-2000	111 (80)	nm	64, 31-91	SURG/ RT	77, 6-484	33	nm	27	7	29,7	nm	nm
Nasser, 2014, USA[69]	1999-2011	65 (62)	nm	67, 41-89	SURG/ RT	27, 1-150	6	nm	6	0	9,2	nm	T stage, size
Soysal, 2007, TR[73]	1997-2006	76 (54)	76	67, 11-93	SURG/ RT	nm	5	nm	5	nm	6,6	6,6	nm
Lip													
Boddie, 1977, USA[58]	1943-1973	56 (nm)	56	9-39	SURG/ RT	60	18	nm	18	nm	32,1	32,1	nm
Cerezo, 1993, ES[59]	1976-1985	117 (87)	nm	68, 31-93	SURG/ RT	65, 11-160	8	nm	8	nm	6,8	nm	T stage
McCombe, 2000, AU[67]	1979-1988	323 (87)	nm	65, 18-94	SURG/ RT	94	16	nm	16	nm	5,0	nm	T stage, RT, age
Unsal, 2017, USA[74]	1973-2013	14901 (82)	14901	68	SURG/ RT	nm	131	nm	119	12	0,9	0,9	nm
de Visscher, 1998, NL[61]	1979-1992	184 (90)	nm	(66)	SURG	(56), 24-x	12	nm	12	1	6,5	nm	depth, PNI
Scalp													
Jenkins, 2014, UK[64]	2005-2009	101 (78)	nm	(82)	SURG	nm	7	nm	7	nm	6,9	6,9	no
Hand													
Bean, 1984, USA[57]	1963-1983	51 (80)	64	(72), 41-92	SURG/ RT	nm	5	nm	4	1	9,8	7,8	nm
Trunk and extremities													
Friedman, 1985, USA[63]	1965-1975	63 (73)	71	(65), 33-97	nm	100, 2-215	5	nm	5	1	7,9	7,0	nm
Joseph, 1992, AU[65]	1977-1987	695 (90)	695	(68), 51-84	SURG	48, 12-216	34	0	33	1	4,9	4,9	nm
de Lima Vasquez, 2008, BR[60]	1987-2005	57 (60)	57	nm	SURG/ RT	23	22	nm	22	4	38,6	38,6	nm
Ribeiro, 2006 BR[70]	1995-1999	36(16)	43	(74), 50-95	nm	nm	0	nm	nm	nm	0,0	0,0	nm

	RISK OF BIAS / QUALITY ASSESSMENT							
	Metastasis noted in study aim	Statement IS present	Consecutive cSCC	Loss to FU in %	Diagnostic protocol meta	% T stage	cSCC features	Score
	yes	yes, absent	no	1%	nm	nm	17% poor diff, 21% subdermal, 5% PNI, 2% LVSI	●●●●●○○
	no	nm	yes	nm	nm	nm	31%> 2cm, 21% catillage,	●●○○○○○
	yes	nm	yes	nm	nm	nm	8% PNI	●●○○○○○
	yes	nm	yes	nm	yes	1:9, 2:46, 3:38, 4:6 (AJCC 7th)	25% PNI	●●●○○○○
	no	nm	yes	nm	nm	nm	size mean 24mm, 12% poor diff, 24% PNI	●●○○○○○
	no	nm	yes	1	nm	1:53, 2:21, 3:7, 4:5% 52.6% UK:15 (nm)	3% PNI	●●●○○○○
	no	nm	yes	7%	nm	1:86, 2:13, 3:1 (UICC 1987)	size mean 10mm	●●●○○○○
	no	nm	yes	nm	nm	1:85, 2:10, 3-4:1 (AJCC 4th)	size mean 12mm, 4% poor diff	●●●○○○○
	no	nm	yes	nm	nm	1:80, 2:12, 3:4, 4:4 (AJCC 8th)	7% poor diff	●●○○○○○
	yes	nm	yes	nm	nm	1:93, 2:5, 3:2, 4:1 (AJCC, 4th)	size 7%>20mm, 5% poor diff, 5% PNI, 1% LVSI	●●●●○○○
	yes	nm	yes	nm	nm	nm	size mean 30mm, 25% poor diff, 41% > 10mm depth,	●●●○○○○
	no	yes, present	yes	nm	nm	nm	size mean 16mm,	●●○○○○○
	yes	nm	no	nm	nm	nm	10% poor diff, 12% subdermal	●●○○○○○
	yes	nm	yes	nm	nm	nm	nm	●●○○○○○
	no	nm	yes	18%	nm	1:-, 2:-, 3:63, 4:37 (AJCC, 6th)	nm	●●●○○○○
	no	nm	yes	12%	nm	nm	nm	●●○○○○○

Table 2. Continued

STUDY CHARACTERISTICS													
Author, year, country	**Study period**	**N pt cSCC (%male)**	**N cSCC**	**Age pt median (mean) range in years**	**Treatment cSCC**	**FU cSCC median (mean) range in months**	**Total N pt metastasis**	**N in transit meta**	**N nodal meta**	**N distant meta**	**% meta per pt**	**% meta per cSCC**	**Meta risk factors**
High risk SCC only													
Salmon, 2011,USA/ NZ[71]	1988-2008	72 (64)	73	76, 45-91	SURG/ RT	36	0	nm	nm	nm	0,0	0,0	nm
Burns													
Ames, 1982, USA[56]	1944-1976	1118 (nm)	1118	nm	nm	nm	106	0	75	15	1,4	1,4	nm
Metwally, 2017, EG[68]	2004-2015	26 (61)	26	(47)	SURG	> 12	6	nm	6	3	23,1	23,1	diff

Abbreviations: N; number, pt; patients, cSCC; cutaneous squamous cell carcinoma, FU; follow-up, meta; metastasis, IS; immunosuppression, OTR; organ transplant recipients, nm; not mentioned, Surg; surgery, RT; radiotherapy, CT; chemotherapy, diff; differentiation grade, UK; United Kingdom, CA; Canada, USA; United states of America, , TR; Turkey, ES; Spain, AU; Australia, NL; the Netherlands, BR; Brazil, NZ; New Zealand, EG; Egypte

Metastasis risk: pooled analysis

Summary estimates were calculated for the proportion of patients with metastasis in the studies reporting on total body (Figure 2) and cSCC of the head and neck area (Figure 3).

For cSCC on total body, the pooled metastasis risk estimate for OTR was 7.3% (95% CI 6.2-8.4), with a range of 4.1 to 14.1% reported in these studies. For the immunocompetent population reported risk estimates in individual studies ranged from 0 to 13.7% and analysis showed a pooled risk of 3.1% (95% CI 2.7-3.4).

For studies reporting on cSCC of the head and neck area, the pooled metastasis risk estimate for OTR was 11.0% (95% CI 7.7-14.8), with a range of 5.4 to 18.8% reported in these studies. For the immunocompetent population reported risk estimates in individual studies ranged from 1.7 to 22.9% and analysis showed a pooled risk of 8.5% (95% CI 7.3-9.8).

In addition, estimates were calculated for studies that reported the exact number of cSCC with metastasis as patients can have multiple primary cSCC.

	RISK OF BIAS / QUALITY ASSESSMENT							
	Metastasis noted in study aim	Statement IS present	Consecutive cSCC	Loss to FU in %	Diagnostic protocol meta	% T stage	cSCC features	Score
	no	nm	yes	nm	nm	nm	6% poor diff, depth mean 3.6mm, 90% HN, 73% PNI, 0% LVSI	●●○○○○
	yes	nm	yes	nm	nm	nm	nm	●●○○○○
	no	nm	yes	nm	yes	nm	0% poor diff	●●○○○○

Eight studies in the immunocompetent population reported the same number of cSCC as patients. Five of those were excluded from the risk analysis of metastasis per cSCC because the cSCC were not included consecutively.

For cSCC on total body, the pooled metastasis risk estimate for a single cSCC in OTR was 1.3% (95% CI 1.0-1.7), with a range of 0.4 to 7.7% reported in these studies. For the immunocompetent population analysis showed a pooled risk of 2.4% (95% CI 2.1-2.6) and reported risk estimates in individual studies ranged from 0 to 11.6% (Figure 4).

For studies reporting on cSCC of the head and neck area, the pooled metastasis risk estimate for a single cSCC in OTR was 4.0% (95% CI 2.7-5.5), with a range of 1.8 to 9.6% reported in these studies. For the immunocompetent population analysis showed a pooled risk of 6.7% (95% CI 5.7-7.8) and reported risk estimates in individual studies ranging from 1.4 to 12.3% (Figure 5).

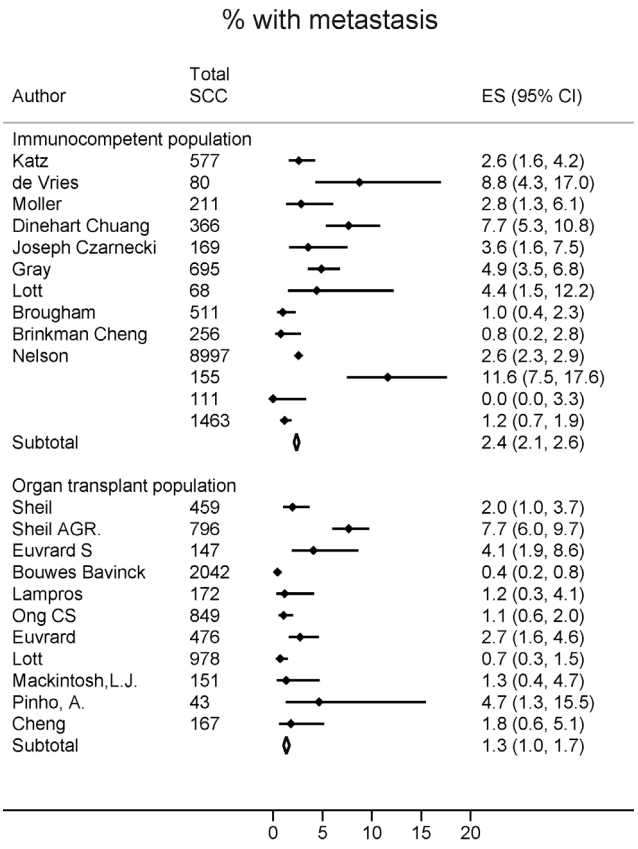

Figure 4.
Forest plot of metastasis risk of total body cutaneous squamous cell carcinoma per tumor stratified by organ transplant population and immunocompetent population.

Discussion

The aim of this study was to estimate the overall risk for cSCC to develop metastasis in OTR versus the immunocompetent population. This review suggests a low overall metastasis risk in cSCC, in both the immunosuppressed organ transplant population and the immunocompetent population, and a higher overall metastasis risk in OTR.

We found a risk of metastasis of cSCC on total body skin per patient in OTR patients of 7.3%, versus a pooled risk of 3.1% in the immunocompetent population. For cSCC of the head and neck area these estimates were higher, 11.0% in OTR and 8.5% in the immunocompetent population. These findings are in line with the hypothesis that OTR are at higher risk of metastasis.[16,33-37] The chronic use of immunosuppressive

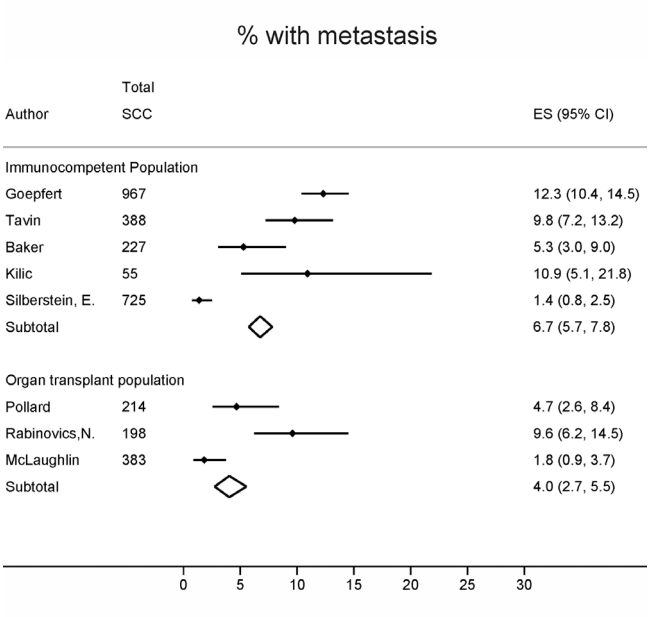

Figure 5.
Forest plot of metastasis risk of cutaneous squamous cell carcinoma of the head and neck area per tumor stratified by organ transplant population and immunocompetent population.

medication is thought to be a driver of this increased risk, earlier studies reported that patients on immunosuppression tend to have more cSCC and a higher proportion of aggressive cSCC that are less differentiated and thicker tumors.[18,37] Immunosuppressive drugs (e.g. azathioprine, calcineurin inhibitors) are linked to aberrant production of cytokines that promote tumor growth, angiogenesis and metastasis.[90] Immunosuppressive drugs have a potential oncogenic action in cells or by facilitating tumor cell escape from immunosurveillance.[91] Immunosuppression is not included as a risk factor for upgrading tumor stage in the tumor TNM classification system. Instead, it is described as a prognostic factor to take into account for clinical practice.[92-94]

However, the pooled risk of metastasis per cSCC was lower, as patients often develop multiple lesions, especially OTR. In this analyses, the risk for a single cSCC to metastasize in OTR is lower compared to the immunocompetent population. Therefore, immunosuppressive state in OTR does not seem to increase the risk of metastasis in a single cSCC, but could be an overall risk factor for metastasis due to the multiplicity of cSCC in OTR. A possible explanation for the lower metastatic risk of a single cSCC in the OTR group might be due to the frequent skin checks in OTR. Those skin checks enable the detection of cSCC in OTR in an earlier stage compared to some cSCC in the immunocompetent population. However, since OTR patients develop more cSCC compared to immunocompetent patients, the cumulative risk for the total number of cSCC per patient is higher in the OTR group.

The definition of an immunosuppressed patient is often not clear and in studies regarding risk factors for metastasis different criteria are used. Ideally, immunosuppression should be defined more precise in studies. OTR are subject to lifelong immunosuppressive therapy and therefore an ideal population for studying the influence of immunosuppression on cSCC behaviour. Nevertheless, also patients with hematologic malignancies, HIV or chronic diseases on immunosuppressive drugs are to a certain extent immunosuppressed.[95-100]

The presence of cSCC high risk features was taken into account for our risk of bias assessment. High risk features mentioned in literature are size, depth of invasion, location on head and neck, differentiation grade and perineural invasion.[101] Not all studies report on these items. In addition, most studies do not mention proportion of high risk cSCC in their cohort. The proportion of high risk tumors obviously influences the metastasis rate in a cohort. Another important factor to take into account is age, as older age is a risk factor for metastasis.[102] In the OTR, the age of cSCC patients is lower compared to the immunocompetent population and therefore could contribute to the lower metastasis risk per cSCC in these group.

This systematic review has some limitations. The quality of evidence is limited due to diversity in study design, types of patients studied and data reporting. Because of this considerable heterogeneity between studies, limiting both the interpretation and scope of this review, the outcomes have to be interpreted with caution. Second, the studies reporting on the immunocompetent population could include some non-reported OTR, diluting the effect. Lastly, but most importantly, follow-up time is variable. Although most cSCC metastasize within the first two years, longer follow-up allows more cSCC to metastasize and might therefore influence the results of

studies with a longer follow up.[103] Unfortunately the majority of studies in OTR did not provide adequate follow up time per cSCC. Follow-up time started at time of transplantation, and not at time of cSCC diagnosis. Also differences in study periods influence the rate of cSCC, especially the risk of metastasis per cSCC
Concluding, we found a difference in metastasis risk for OTR and immunocompetent cSCC patients. Prospective follow-up studies, with distinct cohorts of risk groups are necessary to adequately assess the risk for metastasis rate of cSCC, mainly in organ transplant patients and other immunosuppressed patients.

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Supplementary files can be found in the online version of the article

References

1. Almahroos M, Kurban AK. Ultraviolet carcinogenesis in nonmelanoma skin cancer. Part I: incidence rates in relation to geographic locations and in migrant populations. Skinmed. 2004;3(1):29-35.
2. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. NEnglJMed. 2001;344(13): 975-83.
3. Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. Lancet. 2010;375(9715): 673-85.
4. Deady S, Sharp L, Comber H. Increasing skin cancer incidence in young, affluent, urban populations: a challenge for prevention. BrJDermatol. 2014;171(2):324-31.
5. Hollestein LM, de VE, Nijsten T. Trends of cutaneous squamous cell carcinoma in the Netherlands: increased incidence rates, but stable relative survival and mortality 1989-2008. EurJCancer. 2012;48(13):2046-53.
6. 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. JAmAcadDermatol. 2013;68(6):957-66.
7. Robsahm TE, Helsing P, Veierod MB. Cutaneous squamous cell carcinoma in Norway 1963-2011: increasing incidence and stable mortality. Cancer Med. 2015.
8. Yoong C, De'Ambrosis B. Cutaneous invasive squamous cell carcinoma: 10-year experience and recommendations for follow up. AustralasJDermatol. 2009;50(4):261-5.
9. Green AC, Olsen CM. Cutaneous squamous cell carcinoma: an epidemiological review. Br J Dermatol. 2017;177(2):373-81.
10. 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. BrJDermatol. 2006;154(3):498-504.
11. Tessari G, Naldi L, Boschiero L, Nacchia F, Fior F, Forni A,... Girolomoni G. Incidence and clinical predictors of a subsequent nonmelanoma skin cancer in solid organ transplant recipients with a first nonmelanoma skin cancer: a multicenter cohort study. ArchDermatol. 2010;146(3):294-9.
12. Bordea C, Wojnarowska F, Millard PR, Doll H, Welsh K, Morris PJ. Skin cancers in renal-transplant recipients occur more frequently than previously recognized in a temperate climate. Transplantation. 2004;77(4):574-9.
13. Hartevelt MM, Bouwes Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in the Netherlands. Transplantation. 1990;49(3):506-9.
14. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part I. Epidemiology of skin cancer in solid organ transplant recipients. JAmAcadDermatol. 2011;65(2):253-61.
15. Brantsch KD, Meisner C, Schonfisch B, Trilling B, Wehner-Caroli J, Rocken M, Breuninger H. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9(8):713-20.
16. Rowe DE, Carroll RJ, Day CL, Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. JAmAcadDermatol. 1992;26(6):976-90.
17. Terhorst D, Drecoll U, Stockfleth E, Ulrich C. Organ transplant recipients and skin cancer: assessment of risk factors with focus on sun exposure. BrJDermatol. 2009;161 Suppl 3:85-9.
18. Weinberg AS, Ogle CA, Shim EK. Metastatic cutaneous squamous cell carcinoma: an update. DermatolSurg. 2007;33(8):885-99.
19. Quint KD, Genders RE, de Koning MN, Borgogna C, Gariglio M, Bouwes Bavinck JN,... Feltkamp MC. Human Beta-papillomavirus infection and keratinocyte carcinomas. J Pathol. 2015;235(2):342-54.
20. Farasat S, Yu SS, Neel VA, Nehal KS, Lardaro T, Mihm MC,... Liegeois NJ. A new American Joint Committee on Cancer staging system for cutaneous squamous cell carcinoma: creation and rationale for inclusion of tumor (T) characteristics. JAmAcadDermatol. 2011;64(6):1051-9.
21. Veness MJ, Palme CE, Morgan GJ. High-risk cutaneous squamous cell carcinoma of the head and neck: results from 266 treated patients with metastatic lymph node disease. Cancer. 2006;106(11):2389-96.
22. Brougham ND, Dennett ER, Cameron R, Tan ST. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. JSurgOncol.

2012;106(7):811-5.
23. Chuang TY, Popescu NA, Su WP, Chute CG. Squamous cell carcinoma. A population-based incidence study in Rochester, Minn. ArchDermatol. 1990;126(2):185-8.
24. Dinehart SM, Pollack SV. Metastases from squamous cell carcinoma of the skin and lip. An analysis of twenty-seven cases. JAmAcadDermatol. 1989;21(2 Pt 1):241-8.
25. Tavin E, Persky M. Metastatic cutaneous squamous cell carcinoma of the head and neck region. Laryngoscope. 1996;106(2 Pt 1):156-8.
26. Baum CL, Wright AC, Martinez JC, Arpey CJ, Brewer JD, Roenigk RK, Otley CC. A new evidence-based risk stratification system for cutaneous squamous cell carcinoma into low, intermediate, and high risk groups with implications for management. J Am Acad Dermatol. 2018;78(1):141-7.
27. Rose AM, Nicoll KJ, Moinie A, Jordan DJ, Evans AT, Proby CM, Naasan A. Patients with low-risk cutaneous squamous cell carcinoma do not require extended out-patient follow-up. J Plast Reconstr Aesthet Surg. 2017;70(6):852-5.
28. Veness MJ. Defining patients with high-risk cutaneous squamous cell carcinoma. AustralasJDermatol. 2006;47(1):28-33.
29. Veness MJ, Porceddu S, Palme CE, Morgan GJ. Cutaneous head and neck squamous cell carcinoma metastatic to parotid and cervical lymph nodes. Head Neck. 2007;29(7):621-31.
30. Czarnecki D, Staples M, Mar A, Giles G, Meehan C. Metastases from squamous cell carcinoma of the skin in southern Australia. Dermatology. 1994;189(1):52-4.
31. Breuninger H, Schaumburg-Lever G, Holzschuh J, Horny HP. Desmoplastic squamous cell carcinoma of skin and vermilion surface: a highly malignant subtype of skin cancer. Cancer. 1997;79(5):915-9.
32. Thompson AK, Kelley BF, Prokop LJ, Murad MH, Baum CL. Risk Factors for Cutaneous Squamous Cell Carcinoma Recurrence, Metastasis, and Disease-Specific Death: A Systematic Review and Meta-analysis. JAMA Dermatol. 2016;152(4):419-28.
33. Carucci JA. Squamous cell carcinoma in organ transplant recipients: approach to management. Skin therapy letter. 2004;9 (4):5-7.
34. Veness MJ, Quinn DI, Ong CS, Keogh AM, Macdonald PS, Cooper SG, Morgan GW. Aggressive cutaneous malignancies following cardiothoracic transplantation: the Australian experience. Cancer. 1999;85(8):1758-64.
35. Carucci JA, Martinez JC, Zeitouni NC, Christenson L, Coldiron B, Zweibel S, Otley CC. In-transit metastasis from primary cutaneous squamous cell carcinoma in organ transplant recipients and nonimmunosuppressed patients: clinical characteristics, management, and outcome in a series of 21 patients. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]. 2004;30(4 Pt 2):651-5.
36. Martinez JC, Otley CC, Stasko T, Euvrard S, Brown C, Schanbacher CF, Weaver AL. Defining the clinical course of metastatic skin cancer in organ transplant recipients: a multicenter collaborative study. ArchDermatol. 2003;139(3):301-6.
37. Smith KJ, Hamza S, Skelton H. Histologic features in primary cutaneous squamous cell carcinomas in immunocompromised patients focusing on organ transplant patients. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]. 2004;30(4 Pt 2):634-41.
38. Dinehart SM, Chu DZ, Maners AW, Pollack SV. Immunosuppression in patients with metastatic squamous cell carcinoma from the skin. JDermatolSurgOncol. 1990;16(3):271-4.
39. Khurana VG, Mentis DH, O'Brien CJ, Hurst TL, Stevens GN, Packham NA. Parotid and neck metastases from cutaneous squamous cell carcinoma of the head and neck. AmJSurg. 1995;170(5):446-50.
40. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D,... Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.
41. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [Available from: www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

42. Barrett WL, First MR, Aron BS, Penn I. Clinical course of malignancies in renal transplant recipients. Cancer. 1993;72(7):2186-9.
43. Bouwes Bavinck JN, Hardie DR, Green A, Cutmore S, MacNaught A, O'Sullivan B,... Hardie IR. The risk of skin cancer in renal transplant recipients in Queensland, Australia. A follow-up study. Transplantation. 1996;61(5):715-21.
44. Cheng JY, Li FY, Ko CJ, Colegio OR. Cutaneous Squamous Cell Carcinomas in Solid Organ Transplant Recipients Compared With Immunocompetent Patients. JAMA Dermatol. 2017.
45. Euvrard S, Kanitakis J, Decullier E, Butnaru AC, Lefrancois N, Boissonnat P,... Chapuis F. Subsequent skin cancers in kidney and heart transplant recipients after the first squamous cell carcinoma. Transplantation. 2006;81(8):1093-100.
46. Lampros TD, Cobanoglu A, Parker F, Ratkovec R, Norman DJ, Hershberger R. Squamous and basal cell carcinoma in heart transplant recipients. JHeart Lung Transplant. 1998;17(6):586-91.
47. Lott DG, Manz R, Koch C, Lorenz RR. Aggressive behavior of nonmelanotic skin cancers in solid organ transplant recipients. Transplantation. 2010;90(6):683-7.
48. Lyall P, Lynn KL. Metastatic squamous cell carcinoma of skin following renal transplantation. Nephrology. 1998;4(5-6):423-6.
49. Mackintosh LJ, Geddes CC, Herd RM. Skin tumours in the West of Scotland renal transplant population. BrJDermatol. 2012.
50. McLaughlin EJ, Miller L, Shin TM, Sobanko JF, Cannady SB, Miller CJ, Newman JG. Rate of regional nodal metastases of cutaneous squamous cell carcinoma in the immunosuppressed patient. American journal of otolaryngology. 2017;38(3):325-8.
51. Ong CS, Keogh AM, Kossard S, Macdonald PS, Spratt PM. Skin cancer in Australian heart transplant recipients. JAmAcadDermatol. 1999;40(1):27-34.
52. Penn I. Immunosuppression and skin cancer. ClinPlastSurg. 1980;7(3):361-8.
53. Pinho A, Gouveia M, Cardoso JC, Xavier MM, Vieira R, Alves R. Non-melanoma skin cancer in Portuguese kidney transplant recipients - incidence and risk factors. An Bras Dermatol. 2016;91(4):455-62.
54. Pollard JD, Hanasono MM, Mikulec AA, Le QT, Terris DJ. Head and neck cancer in cardiothoracic transplant recipients. Laryngoscope. 2000;110(8):1257-61.
55. Rabinovics N, Mizrachi A, Hadar T, Ad-El D, Feinmesser R, Guttman D,... Bachar G. Cancer of the head and neck region in solid organ transplant recipients. Head Neck. 2013.
56. Sheil AGR. Development of Malignancy Following Renal-Transplantation in Australia and New-Zealand. Transplantation Proceedings. 1992;24(4):1275-9.
57. Winkelhorst JT, Brokelman WJ, Tiggeler RG, Wobbes T. Incidence and clinical course of de-novo malignancies in renal allograft recipients. EurJSurgOncol. 2001;27(4):409-13.
58. Ames FC, Hickey RC. Metastasis from squamous cell skin cancer of the extremities. SouthMedJ. 1982;75(8):920-3, 32.
59. Bean DJ, Rees RS, O'Leary JP, Lynch JB. Carcinoma of the hand: a 20-year experience. South MedJ. 1984;77(8):998-1000.
60. Boddie AW, Jr., Fischer EP, Byers RM. Squamous carcinoma of the lower lip in patients under 40 years of age. South MedJ. 1977;70(6):711-2, 5.
61. Cerezo L, Liu FF, Tsang R, Payne D. Squamous-Cell Carcinoma of the Lip - Analysis of the Princess-Margaret-Hospital Experience. Radiotherapy and Oncology. 1993;28(2):142-7.
62. de LV, V, Sachetto T, Perpetuo NM, Carvalho AL. Prognostic factors for lymph node metastasis from advanced squamous cell carcinoma of the skin of the trunk and extremities. World J SurgOncol. 2008;6:73.
63. de Visscher JGAM, van den Elsaker K, Grond AJK, van der Wal JE, van der Waal I. Surgical treatment of squamous cell carcinoma of the lower lip: Evaluation of long-term results and prognostic factors - A retrospective analysis of 184 patients. Journal of Oral and Maxillofacial Surgery. 1998;56(7):814-20.
64. Faustina M, Diba R, Ahmadi MA, Esmaeli B. Patterns of regional and distant metastasis in patients with eyelid and periocular squamous cell carcinoma. Ophthalmology. 2004;111(10):1930-2.
65. Friedman HI, Cooper PH, Wanebo HJ. Prognostic and therapeutic use of microstaging of cutaneous squamous cell carcinoma of

the trunk and extremities. Cancer. 1985;56(5):1099-105.
66. Jenkins G, Smith AB, Kanatas AN, Houghton DR, Telfer MR. Anatomical restrictions in the surgical excision of scalp squamous cell carcinomas: does this affect local recurrence and regional nodal metastases? IntJ Oral MaxillofacSurg. 2014;43(2):142-6.
67. Joseph MG, Zulueta WP, Kennedy PJ. Squamous cell carcinoma of the skin of the trunk and limbs: the incidence of metastases and their outcome. AustNZJSurg. 1992;62(9):697-701.
68. Mayo E, Sharma S, Horne J, Yuen HM, Lee A, Gulati A. Squamous cell carcinoma of the pinna: which histological features could be used to predict prognosis? The British journal of oral & maxillofacial surgery. 2017;55(5):524-9.
69. McCombe D, MacGill K, Ainslie J, Beresford J, Matthews J. Squamous cell carcinoma of the lip: A retrospective review of the Peter MacCallum Cancer Institute experience 1979-88. Australian and New Zealand Journal of Surgery. 2000;70(5):358-61.
70. Metwally IH, Roshdy A, Saleh SS, Ezzat M. Epidemiology and predictors of recurrence of Marjolin's ulcer: experience from Mansoura Universityxs. Ann R Coll Surg Engl. 2017;99(3):245-9.
71. Nasser QJ, Roth KG, Warneke CL, Yin VT, El Sawy T, Esmaeli B. Impact of AJCC 'T' designation on risk of regional lymph node metastasis in patients with squamous carcinoma of the eyelid. British Journal of Ophthalmology. 2014;98(4):498-501.
72. Ribeiro AM, Curado MP, Filho JB. Cutaneous squamous cell carcinoma of the lower limbs in Goiania, Goias, Brazil. Int J Dermatol. 2006;45(9):1039-42.
73. Salmon PJ, Hussain W, Geisse JK, Grekin RC, Mortimer NJ. Sclerosing squamous cell carcinoma of the skin, an underemphasized locally aggressive variant: a 20-year experience. DermatolSurg. 2011;37(5):664-70.
74. Shiffman NJ. Squamous cell carcinomas of the skin of the pinna. CanJ Surg. 1975;18(3):279-83.
75. Soysal HG, Markoc F. Invasive squamous cell carcinoma of the eyelids and periorbital region. BrJ Ophthalmol. 2007;91(3):325-9.
76. Unsal AA, Unsal AB, Henn TE, Baredes S, Eloy JA. Cutaneous squamous cell carcinoma of the lip: A population-based analysis. Laryngoscope. 2017.
77. Baker NJ, Webb AA, Macpherson D. Surgical management of cutaneous squamous cell carcinoma of the head and neck. BrJ Oral MaxillofacSurg. 2001;39(2):87-90.
78. Brinkman JN, Hajder E, van der Holt B, Den Bakker MA, Hovius SE, Mureau MA. The Effect of Differentiation Grade of Cutaneous Squamous Cell Carcinoma on Excision Margins, Local Recurrence, Metastasis, and Patient Survival: A Retrospective Follow-up Study. AnnPlastSurg. 2014.
79. Czarnecki D, Sutton T, Czarnecki C, Culjak G. A 10-year prospective study of patients with skin cancer. JCutanMedSurg. 2002;6(5):427-9.
80. de Vries NC. Metastases of squamous cell carcinoma of the skin and lip. Dermatologica. 1969;138(4):333-9.
81. Eroglu A, Berberoglu U, Berreroglu S. Risk factors related to locoregional recurrence in squamous cell carcinoma of the skin. Journal of Surgical Oncology. 1996; 61(2):124-30.
82. Goepfert H, Dichtel WJ, Medina JE. Perineural invasion in squamous cell skin carcinoma of the head and neck. American Journal of Surgery. 1984;148(4):642-7.
83. Gray DT, Suman VJ, Su WPD, Clay RP, Harmsen WS, Roenigk RK. Trends in the population-based incidence of squamous cell carcinoma of the skin first diagnosed between 1984 and 1992. Archives of Dermatology. 1997;133(6):735-40.
84. KATZ AD, URBACH F, LILIENFELD AM. The frequency and risk of metastases in squamous-cell carcinoma of the skin. Cancer. 1957;10(6):1162-6.
85. Kilic C, Tuncel U, Comert E, Polat I. Nonmelanoma facial skin carcinomas: methods of treatment. J CraniofacSurg. 2014;25(2): e113-e6.
86. Kyrgidis A, Tzellos TG, Kechagias N, Patrikidou A, Xirou P, Kitikidou K,... Antoniades K. Cutaneous squamous cell carcinoma (SCC) of the head and neck: Risk factors of overall and recurrence-free survival. European Journal of Cancer. 2010;46(9): 1563-72.
87. Moller R, Reymann F, Hou-Jensen K. Metastases in dermatological patients with squamous cell carcinoma. ArchDermatol.

1979;115(6):703-5.
88. 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? Journal of surgical oncology. 2017;116(6): 783-8.
89. Silberstein E, Sofrin E, Bogdanov-Berezovsky A, Nash M, Segal N. Lymph Node Metastasis in Cutaneous Head and Neck Squamous Cell Carcinoma. Dermatol Surg. 2015;41(10):1126-9.
90. Guba M, Graeb C, Jauch KW, Geissler EK. Pro- and anti-cancer effects of immunosuppressive agents used in organ transplantation. Transplantation. 2004;77(12):1777-82.
91. Gutierrez-Dalmau A, Campistol JM. Immunosuppressive therapy and malignancy in organ transplant recipients - A systematic review. Drugs. 2007;67(8):1167-98.
92. In: Amin MB ES, Greene F, et al, eds., editor. AJCC Cancer Staging Manual. 8th ed. ed. New York, NY: Springer; 2017.
93. Karia PS, Morgan FC, Califano JA, Schmults CD. Comparison of Tumor Classifications for Cutaneous Squamous Cell Carcinoma of the Head and Neck in the 7th vs 8th Edition of the AJCC Cancer Staging Manual. JAMA Dermatol. 2018;154(2):175-81.
94. Karia PS, Jambusaria-Pahlajani A, Harrington DP, Murphy GF, Qureshi AA, Schmults CD. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32 (4):327-34.
95. Frierson HF, Jr., Deutsch BD, Levine PA. Clinicopathologic features of cutaneous squamous cell carcinomas of the head and neck in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. Human pathology. 1988;19(12):1397-402.
96. Mehrany K, Weenig RH, Lee KK, Pittelkow MR, Otley CC. Increased metastasis and mortality from cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. JAmAcadDermatol. 2005;53(6):1067-71.
97. Nguyen P, Vin-Christian K, Ming ME, Berger T. Aggressive squamous cell carcinomas in persons infected with the human immunodeficiency virus. Arch Dermatol. 2002;138(6):758-63.
98. Jennings L, Schmults CD. Management of high-risk cutaneous squamous cell carcinoma. Journal of Clinical and Aesthetic Dermatology. 2010;3(4).
99. Fine JD, Johnson LB, Weiner M, Li KP, Suchindran C. Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986-2006. J Am Acad Dermatol. 2009;60(2):203-11.
100. Kinlen LJ. Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. The American journal of medicine. 1985;78(1A):44-9.
101. Nehal KS, Bichakjian CK. Update on Keratinocyte Carcinomas. N Engl J Med. 2018;379(4):363-74.
102. Genders RE, Osinga JAJ, Tromp EE, O'Rourke P, Bouwes Bavinck JN, Plasmeijer EI. Metastasis Risk of Cutaneous Squamous Cell Carcinoma in Organ Transplant Recipients and Immunocompetent Patients. Acta Derm Venereol. 2018;98(6):551-5.
103. Haisma MS, Plaat BE, Bijl HP, Roodenburg JL, Diercks GF, Romeijn TR, Terra JB. Multivariate analysis of potential risk factors for lymph node metastasis in patients with cutaneous squamous cell carcinoma of the head and neck. J Am Acad Dermatol. 2016;75(4):722-30.