View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by University of Dundee Online Publications

University of Dundee

Aggressive Squamous Cell Carcinoma in Organ Transplant Recipients

Lanz, Joana; Bouwes Bavinck, Jan Nico; Westhuis, Marlies; Quint, Koen D.; Harwood, Catherine A.; Nasir, Shaaira

Published in:
JAMA Dermatology

DOI:
10.1001/jamadermatol.2018.4406

Publication date:
2019

Document Version
Peer reviewed version

Link to publication in Discovery Research Portal

Citation for published version (APA):
Lanz, J., Bouwes Bavinck, J. N., Westhuis, M., Quint, K. D., Harwood, C. A., Nasir, S., ... Vital, D. G. (2019). Aggressive Squamous Cell Carcinoma in Organ Transplant Recipients. *JAMA Dermatology*, *155*(1), 66-71. https://doi.org/10.1001/jamadermatol.2018.4406

General rights
Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 24. Dec. 2019

Lanz, J, Bouwes Bavinck, JN, Westhuis, M, Quint, KD, Harwood, CA, Nasir, S, Van-de-Velde, V, Proby, CM, Ferrándiz, C, Genders, RE, Del Marmol, V, Forchetti, G, Hafner, J, Vital, DG & Vital, DG 2019, 'Aggressive Squamous Cell Carcinoma in Organ Transplant Recipients', JAMA Dermatology, vol. 155, no. 1, pp. 66-71. https://doi.org/10.1001/jamadermatol.2018.4406

Aggressive squamous cell carcinoma in organ transplant recipients: A retrospective multicenter case series form SCOPE (Skin care in organ transplant patients Europe)

Joana Lanz[1]; Jan Nico Bouwes Bavinck[2]; Marlies Westhuis[2]; Koen D. Quint[8]; Catherine A. Harwood[3]; Shaaira Nasir[3]; Vanessa Van-de-Velde[3]; Charlotte M. Proby[4]; Carlos Ferrándiz[5]; Roel E. Genders[8]; Véronique del Marmol[6]; Giulia Forchetti[6]; Jürg Hafner[1]; Domenic G. Vital[7]; Guenther F.L. Hofbauer[1]

[1]Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

[2]Department of Dermatology, Leiden University Medical Center, Leiden, The Netherlands

[3]Centre for Cell Biology and Cutaneous Research, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, U.K.

[4]Division of Cancer Research, School of Medicine, University of Dundee, Dundee, U.K.

[5]Department of Dermatology, Hospital Germans Trias i Pujol, Badalona, Universitat Autònoma de Barcelona, Spain

[6]Dermatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

[7]Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital of Zurich, Zurich, Switzerland

[8]Department of Dermatology, Roosevelt Clinics, Leiden, the Netherlands

Date of revision: 26.09.2018. Word count: 1679.

Corresponding Author: Joana Lanz, University Hospital Zurich, Department of Dermatology, Rämistrasse 100, 8091 Zurich, Switzerland, 079 645 35 66, lanz.joana@outlook.com

KEY POINTS

Question: Which factors are associated with aggressive SCC in OTR?

Findings: Aggressive SCC were preferentially localized on the face (66.7%). 41.2% of the tumors were poorly-differentiated with a median tumor diameter of 18mm and tumor depth of 6.2mm.

Meaning: Anatomical site, differentiation, tumor diameter, tumor depth and perineural invasion are important risk factors in aggressive SCC in OTR.

ABSTRACT

Importance: Squamous cell carcinoma (SCC) is the most frequent malignancy found in solid organ transplant recipients (OTR) and is associated with a more aggressive behavior and a higher risk of metastasis and death than in the general population.

Objective: We aimed to report clinicopathological features and to identify factors associated with aggressive SCC in OTR.

Methods: This retrospective multicentric case series included 51 patients after solid organ transplantation with aggressive SCC defined by nodal or distant metastasis or death by local progression of primary SCC.

Results: 84.3% of the 51 solid organ transplant recipients who developed an aggressive SCC were men, with a median age of 51 years at time of transplantation and 62 years at time of diagnosis of aggressive SCC. The distribution of aggressive SCC was preferentially on the face (66.7%) and scalp (11.8%), followed by the upper extremities (11.8%). 41.2% of the tumors were poorly-differentiated with a median tumor diameter of 18 mm and tumor depth of 6.2 mm. Perineural invasion was present in 39.2%, while 45.1% showed a local recurrence. 5-year overall survival rate was 23%, while 5-year disease-specific survival was 30.5%.

Conclusion: Taken together, our case series confirms anatomical site, differentiation, tumor diameter, tumor depth and perineural invasion as important risk factors in aggressive SCC in OTR. **Trial registration**: clinicalTrials.gov, ID Number NCT02095912.

INTRODUCTION

Cutaneous squamous cell carcinoma (SCC) is a malignant neoplasm deriving from epidermal keratinocytes. In the general population it is the second most common form of keratinoyte carcinoma (KC) after basal cell basal cell carcinoma **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}** and in organ transplant recipients (OTR) it is the most common skin cancer **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Previous studies report a risk for nodal metastasis of 1.9-4% and for disease-specific death (DSD) of 1.5-2.1% in the general population **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**.

The number of solid organ transplants and the long-term survival in organ transplant recipients have increased over the last decades as a result of progress in both surgical techniques and drug-induced immunosuppression **{** ADDIN EN.CITE <EndNote><Cite><Author>Lechler</Author><Year>2005</Year><IDText>Organ transplantation--how much of the promise has been realized?</IDText><DisplayText>(16)</DisplayText><record><dates><pub-dates><date>Jun</date></pub-dates><year>2005</year></dates><keywords><keyword>Animals</keyword><keyword>B-Lymphocytes</keyword><keyword>Graft Rejection/immunology</keyword><keyword>Graft Survival</keyword><keyword>Humans</keyword><keyword>Immunologic Memory</keyword><keyword>Immunosuppressive Agents/therapeutic use</keyword><keyword>*Organ Transplantation</keyword><keyword>T-Lymphocytes</keyword><keyword>Transplants/supply & distribution</keyword></keywords><isbn>1078-8956 (Print)
1078-8956</isbn><titles><title>Organ transplantation--how much of the promise has been realized?</title><secondary-title>Nat Med</secondary-title><alt-title>Nature medicine</alt-title></titles><pages>605-13</pages><number>6</number><contributors><authors><author>Lechler, R.

I.</author><author>Sykes, M.</author><author>Thomson, A. W.</author><author>Turka, L. A.</author></authors></contributors><edition>2005/06/07</edition><language>eng</language><added-date format="utc">1455269548</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Guy's King's and St. Thomas's Medical School, King's College London, Hodgkin Building, Guy's Campus, London SE1 9RT, UK.</auth-address><remote-database-provider>NLM</remote-database-provider><rec-number>153</rec-number><last-updated-date format="utc">1455269548</last-updated-date><accession-num>15937473</accession-num><electronic-resource-num>10.1038/nm1251</electronic-resource-num><volume>11</volume></record></Cite></EndNote>**}**. Notwithstanding the clear benefits of successful allograft transplantation, organ transplant recipients experience important side effects from the long term immunosuppressive medication, including a 10-fold increased risk for malignancies overall **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. In particular, OTR have a 65-250 -fold higher incidence of SCC compared to the non-transplanted population. After transplantation, 20 to 75 percent of OTR are affected by at least one SCC within 20 years. After a first invasive SCC, multiple subsequent SCC will develop in 60-80% of these patients within 3 years **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. The risk of SCC increases over time, with the incidence increasing to 40-60% at 20 years post-transplant **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Cutaneous SCC is also associated with a more aggressive behavior and a higher risk of metastasis and death in OTR than in the general population **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. The metastaric rate in OTR is reported to be 5-8% **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**.

In addition to immunosuppression and time from transplantation, the factors for the development of SCC in OTRs are similar to those found in the general population, namely male gender, age, cumulative ultraviolet radiation exposure and fair skin **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**.

While the majority of SCC will be successfully treated, some show a very aggressive clinical course. Currently, the distinction between the many SCC cured without sequelae and the few SCC with an aggressive course can be hard to make at diagnosis. The objective of the present study based on a European OTR case series is to report clinicopathological features of behavior aggressive SCC and to identify factors which are associated with an aggressive development of SCC in OTR

METHODS

Clinical and histological data were retrospectively collected from 5 centers: Brussels (Belgium), Barcelona (Spain), Leiden (Netherlands), London (United Kingdom) and Zurich (Switzerland) within the Skin Care in Organ Transplant Patients, Europe (SCOPE) Network. The study protocol was approved by the Ethics Committee of Zurich, Switzerland.

Inclusion criteria were patients who underwent a solid organ transplantation and developed an aggressive SCC including nodal or distant metastasis or death by local progression of primary SCC. All patient identifiers were coded to assure patient anonymity. Exclusion criteria were the absence of an aggressive SCC, mucosal head and neck SCC or missing data. All participating centres were able to identify and retrieve organ transplant recipients with aggressive SCC from their archives. Standard questionnaires were completed between July 2005 and January 2015. Patients were followed up from the data of first transplantation to date of death or the last dermatologist visit. Skin photo type classification was not recorded because of incomplete data at the time of inclusion. Data were obtained from the hospital database including patient's charts and pathology reports.

Disease-specific death was considered to have occurred if the treatment team documented that the patient died of a specific SCC or of complications that directly arose from SCC. Non-disease-specific death was considered to have occurred in patients who developed nodal or

distant metastasis or a local, treatment-refractory tumor but died because of other causes (for example cardiac arrest).

STATISTICAL ANALYSIS

Clinical characteristics were summarized with the use of descriptive statistics and frequency tabulation. Overall survival, disease-specific survival, progression-free survival and time from metastasis to death were analyzed by the Kaplan-Meier method. IBM SPSS statistic software (version 23.0.) was used for statistical analysis.

RESULTS

The majority of the 51 solid organ transplant recipients who developed an aggressive SCC were male (84.3%) and kidney transplanted (78.4%). Median age at diagnosis was 62 years (range 36-77y). Three patients (5.8%) underwent combined kidney/pancreas transplantation and 1 patient had a liver and lung transplant. Ten patients (19.6%) underwent 2 transplantations because of organ failure. Full characteristics of the study population are summarized in Table 1.

The most common primary site for SCC was the face. The median diameter of aggressive SCC was 18.0 mm (range 4-64 mm) with a median depth of invasion of 6.2 mm (range 1-20 mm). 21 (41.2%) of the tumors were histologically classified as poorly-differentiated and perineural invasion was identified in 39.2% of the SCC. The local recurrence rate was 45.1%. Tumour characteristics are listed in detail in Table 2. Figure 1a - d show overall survival, disease-specific survival, progression-free survival and time from metastasis to death overall by Kaplan Meier analysis. Briefly summarized, the graphs show that mortality was mostly

due to aggressive SCC. Almost all SCC showed progression within two years from diagnosis.

DISCUSSION

Patient characteristics

The majority of our OTR were male with a median age of 51 years at time of transplantation and median 62 years old at diagnosis of aggressive SCC. This is in agreement with the findings of Pinho et al, who reported KC with a median age of 54.5 years at transplantation and 61.9 years at diagnosis of aggressive SCC. In contrast to our data, there was no difference in terms of gender in their study **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. In a study by Lott et al, SCC in OTR occurred earlier at the age of 57 years compared to the immunocompetent patients who developed SCC at a median age of 67 years **{** ADDIN EN.CITE <EndNote><Cite><Author>Lott</Author><Year>2010</Year><IDText>Aggressive behavior of nonmelanotic skin cancers in solid organ transplant recipients</IDText><DisplayText>(22)</DisplayText><record><dates><pub-dates><date>Sep 27</date></pub-dates><year>2010</year></dates><keywords><keyword>Adolescent</keyword><keyword>Adult</keyword><keyword>Age Factors</keyword><keyword>Aged</keyword><keyword>Aggression/*psychology</keyword><keyword>Carcinoma, Basal Cell/epidemiology/psychology</keyword><keyword>Carcinoma, Squamous Cell/epidemiology/psychology</keyword><keyword>Child</keyword><keyword>Humans</keyword><keyword>Intensive Care Units/statistics & numerical data</keyword><keyword>Middle Aged</keyword><keyword>Organ Transplantation/adverse effects/*psychology</keyword><keyword>Skin Neoplasms/epidemiology/*psychology</keyword></keywords><isbn>0041-1337</isbn><titles><title>Aggressive behavior of nonmelanotic skin cancers in solid organ

transplant recipients</title><secondary-title>Transplantation</secondary-title><alt-title>Transplantation</alt-title></titles><pages>683-7</pages><number>6</number><contributors><authors><author>Lott, D. G.</author><author>Manz, R.</author><author>Koch, C.</author><author>Lorenz, R. R.</author></authors></contributors><edition>2010/09/03</edition><language>eng</language><added-date format="utc">1421242615</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Cleveland Clinic Head and Neck Institute, Cleveland, OH 44195, USA. lottd@ccf.org</auth-address><remote-database-provider>NLM</remote-database-provider><rec-number>129</rec-number><last-updated-date format="utc">1421242615</last-updated-date><accession-num>20808266</accession-num><electronic-resource-num>10.1097/TP.0b013e3181ec7228</electronic-resource-num><volume>90</volume></record></Cite></EndNote>**}**.

In summary, while our case series was not selected in a randomized fashion, our patient characteristics suggest our series to be quite typical for OTR.

Tumor characteristics

The body site for aggressive SCC in our study was preferentially on the face and scalp, followed by the upper extremities. Rabinovics et al similarly report a high number of SCC in the head and neck region with a 24% incidence of aggressive (local recurrence, nodal or distant metastasis) head and neck SCC in OTR, compared to other aggressive malignancies occurring on the head and neck **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Pinho et al found NMSC on UV-exposed sites for 83% of SCC and 87% of BCC **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**.

Most tumors in our series were poorly or moderately differentiated. The presence of poor differentiation indicates a poorer prognosis: Brantsch et al shows a 3-fold higher risk for local recurrence and a 2-fold higher risk for metastasis compared with well-differentiated SCC **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Mullen et al show a 2.9-fold higher risk of

metastasis or death in poorly differentiated tumors compared to well or moderately differentiated tumors **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**.

Our median tumor diameter was 18 mm (range 4-64 mm). This is slightly less than the Swedish cohort in which aggressive SCC were 20 mm in diameter or greater **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Based on a meta-analysis by Thompson et al tumor diameter > 2 cm is the risk factor most highly associated with disease-specific death and a 19-fold higher risk of death from SCC compared to tumors < 2 cm **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**.

The median tumor thickness in our study population was 6.2 mm. This risk factor is highly associated with recurrence and metastasis, with tumor thickness > 2 mm having a 10-fold higher risk of local recurrence and 11-fold higher risk of metastasis **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. In a prospective study of Breuninger et al, depth greater than 4 mm was linked to a metastasis rate of 9%, increasing to a metastasis rate of 16% for a tumor thickness of 6 mm and more **{** ADDIN EN.CITE <EndNote><Cite><Author>Breuninger</Author><Year>2012</Year><IDText>Comparison and evaluation of the current staging of cutaneous carcinomas</IDText><DisplayText>(34)</DisplayText><record><dates><pub-dates><date>Aug</date></pub-dates><year>2012</year></dates><keywords><keyword>Carcinoma/*classification/*pathology</keyword><keyword>Germany</keyword><keyword>Humans</keyword><keyword>Internationality</keyword><keyword>Neoplasm Staging/*methods/*standards</keyword><keyword>*Practice Guidelines as Topic</keyword><keyword>Reproducibility of Results</keyword><keyword>Sensitivity and Specificity</keyword><keyword>Skin Neoplasms/*classification/*pathology</keyword></keywords><isbn>1610-0379</isbn><titles><title>Comparison and evaluation of the current staging of cutaneous carcinomas</title><secondary-title>J Dtsch Dermatol Ges</secondary-title><alt-title>Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of

Dermatology : JDDG</alt-title></titles><pages>579-86</pages><number>8</number><contributors><authors><author>Breuninger, H.</author><author>Brantsch, K.</author><author>Eigentler, T.</author><author>Hafner, H. M.</author></authors></contributors><edition>2012/03/13</edition><language>eng
ger</language><added-date format="utc">1515337485</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Department of Dermatology, Tubingen University Hospital, Germany. helmut.breuninger@med.uni-tuebingen.de</auth-address><remote-database-provider>NLM</remote-database-provider><rec-number>189</rec-number><last-updated-date format="utc">1515337485</last-updated-date><accession-num>22405579</accession-num><electronic-resource-num>10.1111/j.1610-0387.2012.07896.x</electronic-resource-num><volume>10</volume></record></Cite></EndNote>**}**.

Perineural invasion (39%) and local recurrence (45%) were frequent, but will have been selected for in a cohort of aggressive SCC. In the general population, perineural invasion is rather rare with an incidence of 2.5-5% for primary SCCs and is associated with a 4- to 5-fold increased risk of nodal metastasis and death due to SCC **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Local recurrence is reported to occur in 7-16% of all SCC and is more frequent when there is perineural invasion **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**.

The most common location of metastasis in our OTR were lymph nodes including parotid gland and skin. Lindelöf et al demonstrated that all lethal SCC (7 of 544 SCC in a cohort of 5931 OTR) were located on the head, and that the parotid gland was the principal site for metastasis **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. A retrospective study by Lott et al found a 3.5 higher risk for OTR to develop lymph node metastasis compared to the tumors in the immunocompetent control group **{** ADDIN EN.CITE <EndNote><Cite><Author>Lott</Author><Year>2010</Year><IDText>Aggressive behavior of nonmelanotic skin cancers in solid organ transplant recipients</IDText><DisplayText>(22)</DisplayText><record><dates><pub-

dates><date>Sep 27</date></pub-dates><year>2010</year></dates><keywords><keyword>Adolescent</keyword><keyword>Adult</keyword><keyword>Age Factors</keyword><keyword>Aged</keyword><keyword>Aggression/*psychology</keyword><keyword>Carcinoma, Basal Cell/epidemiology/psychology</keyword><keyword>Carcinoma, Squamous Cell/epidemiology/psychology</keyword><keyword>Child</keyword><keyword>Humans</keyword><keyword>Intensive Care Units/statistics & numerical data</keyword><keyword>Middle Aged</keyword><keyword>Organ Transplantation/adverse effects/*psychology</keyword><keyword>Skin Neoplasms/epidemiology/*psychology</keyword></keywords><isbn>0041-1337</isbn><titles><title>Aggressive behavior of nonmelanotic skin cancers in solid organ transplant recipients</title><secondary-title>Transplantation</secondary-title><alt-title>Transplantation</alt-title></titles><pages>683-7</pages><number>6</number><contributors><authors><author>Lott, D. G.</author><author>Manz, R.</author><author>Koch, C.</author><author>Lorenz, R. R.</author></authors></contributors><edition>2010/09/03</edition><language>eng</language><added-date format="utc">1421242615</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Cleveland Clinic Head and Neck Institute, Cleveland, OH 44195, USA. lottd@ccf.org</auth-address><remote-database-provider>NLM</remote-database-provider><rec-number>129</rec-number><last-updated-date format="utc">1421242615</last-updated-date><accession-num>20808266</accession-num><electronic-resource-num>10.1097/TP.0b013e3181ec7228</electronic-resource-num><volume>90</volume></record></Cite></EndNote>**}**.

In summary, our case series confirms anatomical site, differentiation, tumor diameter, thickness and perineural invasion as important risk factors in aggressive SCC in OTR.

Survival

Our study demonstrated a poor prognosis of aggressive SCC with a 5-year overall survival rate of 23% and a 5-year disease-specific survival of 30.5%. Rabinovics et al showed a 5-year survival of 67.7% and 10-year survival of 40% in patients with SCC, including however non-aggressive SCC **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. Lott et al reported a 3-year disease-specific survival of 56% for metastatic SCC in OTR **{** ADDIN EN.CITE <EndNote><Cite><Author>Lott</Author><Year>2010</Year><IDText>Aggressive behavior of nonmelanotic skin cancers in solid organ transplant recipients</IDText><DisplayText>(22)</DisplayText><record><dates><pub-dates><date>Sep 27</date></pub-dates><year>2010</year></dates><keywords><keyword>Adolescent</keyword><keyword>Adult</keyword><keyword>Age Factors</keyword><keyword>Aged</keyword><keyword>Aggression/*psychology</keyword><keyword>Carcinoma, Basal Cell/epidemiology/psychology</keyword><keyword>Carcinoma, Squamous Cell/epidemiology/psychology</keyword><keyword>Child</keyword><keyword>Humans</keyword><keyword>Intensive Care Units/statistics & numerical data</keyword><keyword>Middle Aged</keyword><keyword>Organ Transplantation/adverse effects/*psychology</keyword><keyword>Skin Neoplasms/epidemiology/*psychology</keyword></keywords><isbn>0041-1337</isbn><titles><title>Aggressive behavior of nonmelanotic skin cancers in solid organ transplant recipients</title><secondary-title>Transplantation</secondary-title><alt-title>Transplantation</alt-title></titles><pages>683-7</pages><number>6</number><contributors><authors><author>Lott, D. G.</author><author>Manz, R.</author><author>Koch, C.</author><author>Lorenz, R. R.</author></authors></contributors><edition>2010/09/03</edition><language>eng</language><added-date format="utc">1421242615</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Cleveland Clinic Head and Neck Institute, Cleveland, OH 44195, USA. lottd@ccf.org</auth-address><remote-database-provider>NLM</remote-

database-provider><rec-number>129</rec-number><last-updated-date format="utc">1421242615</last-updated-date><accession-num>20808266</accession-num><electronic-resource-num>10.1097/TP.0b013e3181ec7228</electronic-resource-num><volume>90</volume></record></Cite></EndNote>**}**. A Texan study by Mullen et al showed a 5-year overall survival rate of 35% and a 5-year disease-specific survival of 50% in patients with aggressive SCC of the trunk or extremities **{** ADDIN EN.CITE **{** ADDIN EN.CITE.DATA **}}**. In summary, our case series in OTR shows an unfavorable survival of primary SCC with aggressive features, comparable to other reports.

Limitations

This study is limited by its retrospective design, the limited number of cases and number of contributing centers. There is an implict bias in selecting tumors with a poor outcome (recurrence, metastasis, death) towards clinical and pathological factors known to be associated with poor outcomes, such as perineural invasion. Another limitation is the lack of a control group (OTR without development of aggressive SCC). Data on ethnicity, skin type and sun exposure were not available.

Conclusion

Taken together, our case series confirms anatomical site, differentiation, tumor diameter, tumor depth and perineural invasion as important risk factors in aggressive SCC in OTR. We demonstrated a poor prognosis of aggressive SCC.

REFERENCES

{ ADDIN EN.REFLIST }

	n = 51
Sex	n (%)
Female	8 (15.7)
Male	43 (84.3)
Age	Median (Range), [years]
At time of transplantation	51 (19-71)
At diagnosis of aggressive SCC	62 (36-77)
Transplanted organ	n (%)
Kidney	40 (78.4)
Heart	2 (3.9)
Liver	1 (2.0)
Lung	4 (7.8)
Kidney and pancreas	3 (5.9)
Liver and lung	1 (2.0)
Survival status at last follow-up	n (%)
Alive	7 (13.7)
Death due to SCC	32 (62.7)
Death due to other causes	12 (23.5)

Table 1: **Patient characteristics**

	n (%), total 51	
Location of aggressive SCC		
Scalp	6 (11.8)	
Face	34 (66.7)	
Neck	1 (2.0)	
Trunk	2 (3.9)	
Arm or hand	6 (11.8)	
Genitalia	2 (3.9)	
Histological Classification of SCC		
Well-differentiated	10 (19.6)	
Moderately-differentiated	15 (29.4)	
Poorly-differentiated	21 (41.2)	
Spindle cell morphology	2 (3.9)	
Desmoplastic	3 (5.9)	
Primary tumor	Median (Range), [mm]	Total (Missing)
Diameter of SCC	18.0 (4-64)	50 (1)
Depth of invasion	6.2 (1-20)	48 (3)
Tumor-free margins on histology	2.0 (0-15)	38 (13)
Clark level of Invasion		
Level I	1 (2.0)	
Level II	1 (2.0)	
Level III	0 (0)	
Level IV	14 (27.5)	
Level V	33 (64.7)	
Missing data	2 (3.9)	
Perineural Invasion		
Absent	30 (58.8)	
Present	20 (39.2)	
Missing data	1 (2.0)	
Local recurrence		
Absent	21 (41.2)	
Present	23 (45.1)	
Missing data	7 (13.7)	
Metastasis site		
No Metastasis	6 (11.8)	
Lymph Nodes	30 (58.8)	
Parotid Gland	10 (19.6)	
Liver	2 (3.9)	
Lung	6 (11.8)	
Brain	4 (7.8)	
Bone	7 (13.7)	
Skin	11 (21.6)	
Muscle	1 (1.9)	
Intraorbital	1 (1.9)	

Table 2: **Tumor characteristics**

An aggressive SCC was defined by regional metastasis (lymph nodes, parotid gland), distant metastasis including liver, lung, brain, bone etc., or a local, therapy-resistant progression of primary SCC.
Clark level I (confined to epidermis), level II (penetrating papillary dermis), level III (filling the papillary dermis), level IV (extending into reticular dermis), level V (invasion of subcutis).
Metastasis location was counted for every patient, while some had multiple organ metastasis.

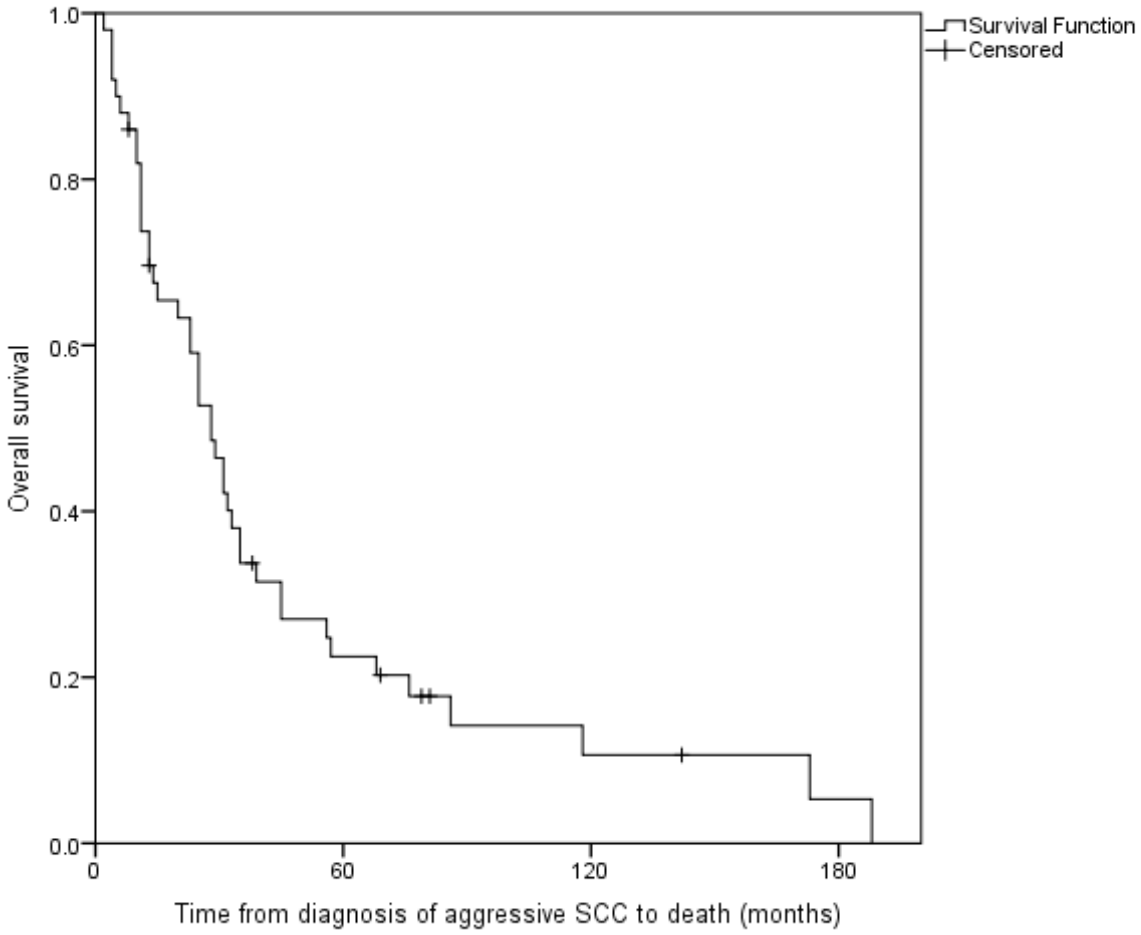

Figure 1a: **Overall survival**

The graph shows overall survival by Kaplan Meier analysis. 50% overall survival was reached at 28 months with an 95 % confidence interval from 21.3 to 34.7. 5-year overall survival was 23 % (SD ± 6.4 %), while 10-year survival was 11.3% (SD ± 5.5 %).
SD: standard deviation.

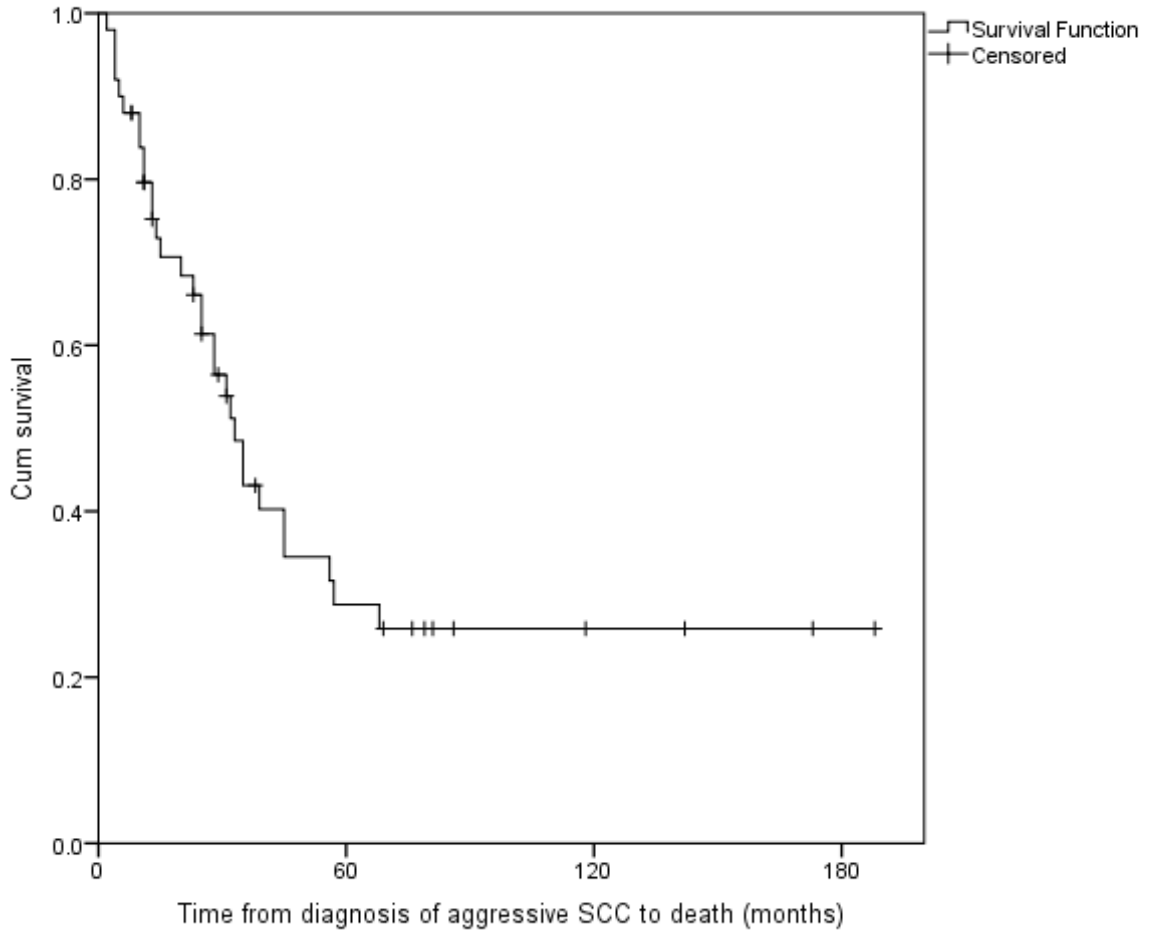

Figure 1b: **Disease-specific survival**

The graph shows disease-specific survival by Kaplan Meier analysis. 50% disease-specific survival was reached at 33 months with an 95 % confidence interval from 0.9 to 45.1.
5-year disease-specific survival was 30.5 % (SD ± 7.6 %) and 10-year survival was 25.9% (SD ± 7.1 %).
SD: standard deviation.

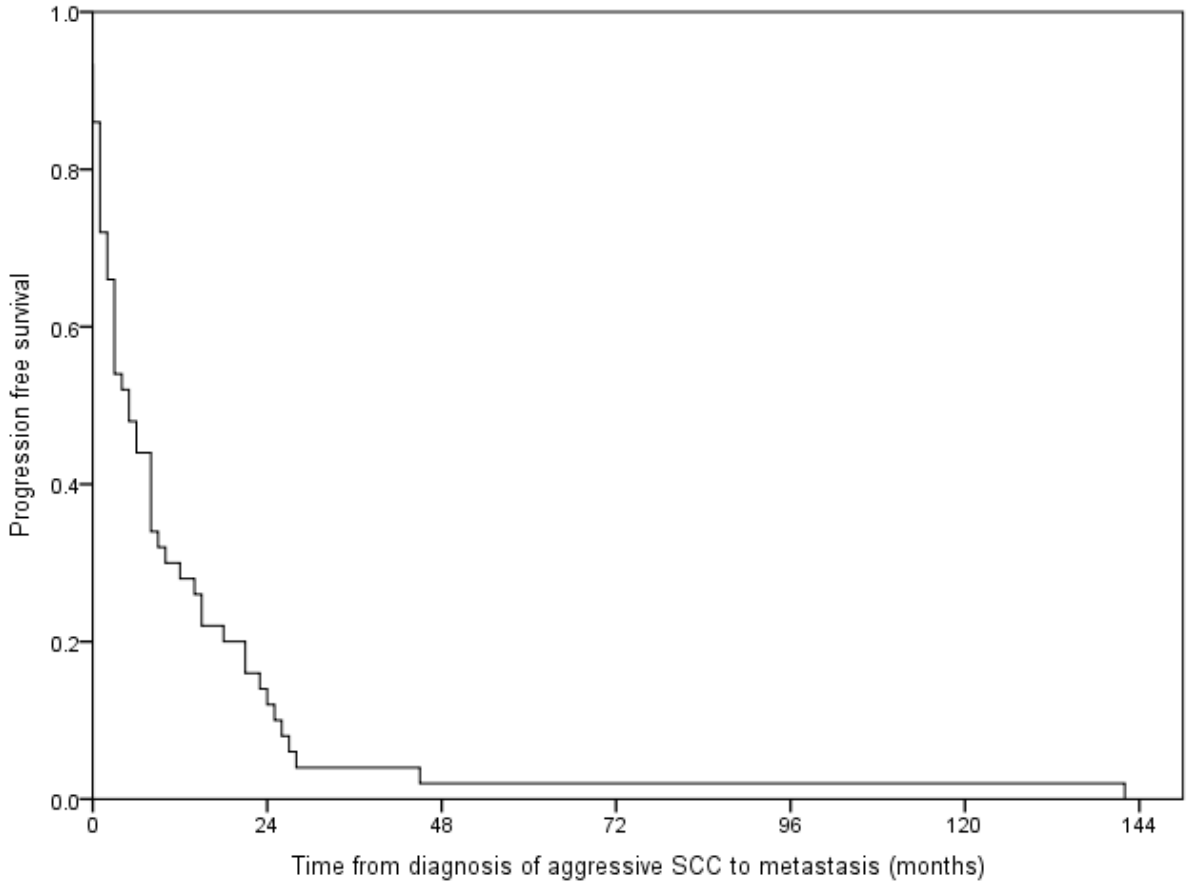

Figure 1c: **Progression-free survival**

The graph shows progression-free survival by Kaplan Meier analysis. 5- and 10-year overall survival were 5 % with a 95 % confidence interval of 2.5 to 7.25 years (SD ± 1.3 %).
SD: standard deviation.

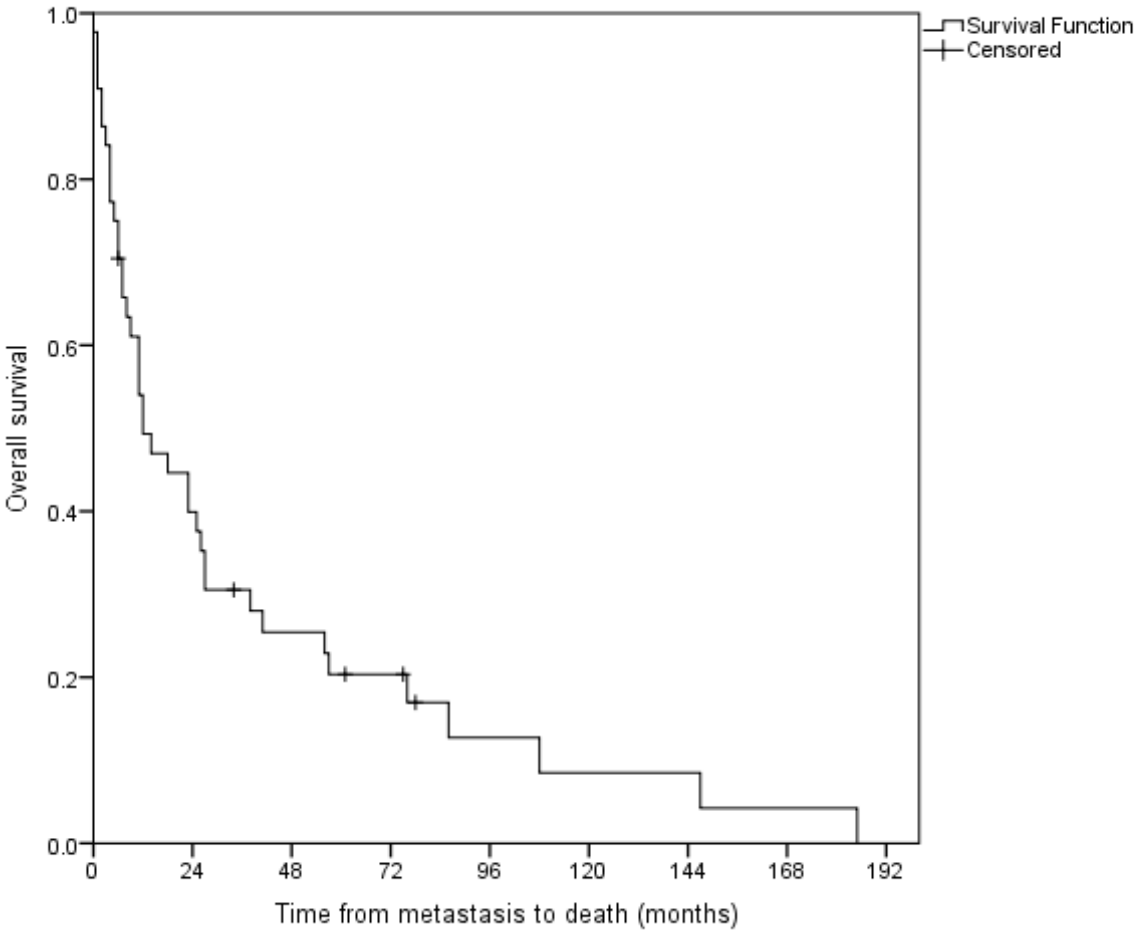

Figure 1d: **Time from metastasis to death overall**

The graph shows overall time from metastasis to death by Kaplan Meier analysis. The median time from metastasis to death was 12 months with a 95 % confidence interval from 3.8 to 20.2.