Risk factors for metastasis of cutaneous squamous cell carcinoma: a single-institution cohort study

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BACKGROUND

Cutaneous squamous cell carcinoma (cSCC) is a keratinocyte carcinoma with increasing incidence. It is the most common metastatic skin cancer and accounts for at least 20% of all skin cancer-related mortality. It has been suggested that invasion depth and horizontal diameter of the primary tumor are main factors associated with the risk of metastasis.

METHODS

In order to provide more insight regarding risk factors associated with metastasis and poor prognosis, we created a cohort of metastatic cSCCs (mcSCC) and a control cohort of non-metastatic cSCCs (non-mcSCC), which were evaluated both on patient and tumor levels.

Three sequential automated screenings were executed utilizing keywords and topographical codes in order to uncover mcSCCs diagnosed during 1993–2018 in the study region comprehending 4 hospital districts.

Clinical and histopathological variables were manually collected from patient records and pathology reports and cohorts analyzed in comparison using descriptive statistics and eventually binary logistic regression.

Research material	Cohorts combined	Non-metastatic patient cohort	Metastatic patient cohort
Patients, n	207	125	82
Number of cSCCs in total, n	337	184	153
Metastatic primary cSCCs, n	85	0	85
Non-metastatic cSCCs, n	252	184	68
Number of cSCCs included into tumor analysis, n	303	173	130
Metastatic tumor cohort, n	85	0	85
Non-metastatic tumor cohort, n	218	173	45

Table 1: Research material; Altogether 207 patients were included in the study and divided into a metastatic patient cohort comprising 82 patients with at least one mcSCC and a non-metastatic patient cohort consisting of 125 patients with solely non-mcSCC(s). Out of aforesaid patients with in total 337 primary cSCCs, 303 tumors comprehending 85 individual mcSCCs and 218 non-mcSCCs regardless patient cohort were eligible for the analysis of tumor-related characteristics and formed the tumor cohorts.

RESULTS

Figure 1: Metastatic rate in the study region; During a 10-year period, between 2004 and 2013 there were 2097 cSCCs diagnosed in the study region based on the statistics of Finnish Cancer Registry and 46 primary mcSCCs based on our study. During this study period the rate of metastasis varied between 0.82% and 4.46% with mean metastatic rate of 2.28%.

Figure 2: Time to metastasis detection; Median time between the initial diagnosis of primary mcSCC and its metastasis was 198 days (interquartile range (IQR) 62–527 days). First metastasis was detected within six months in 42 (49.4%) cases and within 2 years in 72 (84.7%) cases.

Figure 3: Kaplan-Meier overall survival estimates; One-, 2-, 3- and 5-year overall survival estimate from the initial diagnosis of first metastasis was 68.0%, 43.4%, 31.6% and 31.6% respectively. Concerning 43 (71.2% of dead) patients in metastatic cohort the underlying cause of death was deduced to be cSCC.

Binary logistic regression analysis of patient-level characteristics	Included into logistic regression analysis (positive/total) Patients with mcSCC	Patients without mcSCC	Missing	Risk of metastasis by variable Unadjusted OR (95% CI)	P value
Gender					
Male	55/82	71/125	0	1.55 (0.87–2.77)	0.140
Female	27/82	54/125	0	1 (ref)	
Immunocompromised					
SOTR	16/82	26/125	0	0.92 (0.46–1.85)	0.822
	2/82	6/125	0	0.50 (0.10–2.52)	0.398
5α-reductase inhibitor	9/82	4/125	0	3.73 (1.11–12.55)	0.033
In males	9/85	4/71	0	3.28 (0.95–11.28)	0.060
Alpha-1 blocker	10/82	7/125	0	2.34 (0.85–6.42)	0.099
Thiazide	29/82	30/125	0	1.73 (0.94–3.19)	0.078
Aspirin	20/82	52/125	0	0.45 (0.24–0.84)	0.012
Isosorbide mono-/ dinitrate	7/82	26/125	0	0.32 (0.13–0.78)	0.012
Isosorbide mono-/ dinitrate and aspirin	1/82	17/125	0	0.08 (0.01–0.60)	0.014
AK diagnosed	30/82	67/125	0	0.50 (0.28–0.88)	0.017
cSCCs diagnosed	17/82	36/125	0	0.65 (0.33–1.25)	0.195
BCC diagnosed	17/82	53/125	0	0.36 (0.19–0.67)	0.002

Table 2: Patient-level factors associated with the risk of metastasis; SOTR = solid organ transplant recipient; AK = actinic keratosis; cSCCIS = cSCC in situ; BCC = basal cell carcinoma

Binary logistic regression analysis of tumor-level characteristics	Included into logistic regression analysis (positive/total) mcSCC	non-mcSCC	Missing	Risk of metastasis by variable Adjusted OR (95% CI)	P value	Risk of metastasis by variable Unadjusted OR (95% CI)	P value
Age at exact tumor diagnosis							
<50	3/85	8/218	0	4.70 (1.32–16.69)	0.017	1.08 (0.43–2.72)	0.867
50–59	2/85	12/218	0	0.43 (0.09–2.10)	0.297	0.48 (0.08–2.95)	0.429
60–69	12/85	49/218	0	2.54 (0.89–6.91)	0.165	0.71 (0.28–1.78)	0.461
70–79	38/85	80/218	0	5.87 (1.66–20.83)	0.006	2.18 (1.13–4.05)	0.012
80–89	26/85	75/218	0	1 (ref)		1 (ref)	
≥90	4/85	24/218	0	0.77 (0.15–3.97)	0.750	0.48 (0.14–1.61)	0.235
Gender							
Male	57/85	141/218	0	NA	NA	1.11 (0.63–1.95)	0.712
Female	28/85	77/218	0	NA	NA	1 (ref)	
Location							
Temple	10/85	29/217	1	2.94 (0.43–20.09)	0.272	3.53 (1.00–12.53)	0.050
Scalp	3/85	11/217	1	0.80 (0.10–6.38)	0.832	2.80 (0.54–14.53)	0.221
Forehead	4/85	6/217	1	15.55 (2.13–113.49)	0.007	6.83 (1.31–35.70)	0.023
Orbit	4/85	0/217	1	NA	NA	NA	NA
Nose	3/85	13/217	1	1.70 (0.05–59.35)	0.769	2.37 (0.46–12.06)	0.300
Lower lip	10/85	3/217	1	38.64 (5.41–279.75)	<0.001	34.17 (6.72–173.72)	<0.001
Upper lip	2/85	2/217	1	7.24 (1.00–52.29)	0.050	10.25 (1.11–94.36)	0.040
Cheek (excl. preauricular region)	4/85	41/217	1	1 (ref)		1 (ref)	
Preauricular region							
Preauricular	12/85	20/217	1	4.03 (0.45–35.84)	0.212	6.15 (1.69–22.38)	0.006
Auricle	12/85	23/217	1	1.06 (0.13–8.33)	0.958	5.35 (1.55–18.45)	0.008
Retrauricular	3/85	3/217	1	0.74 (0.07–7.46)	0.799	10.25 (1.23–85.52)	0.032
Neck	3/85	5/217	1	5.27 (0.48–57.88)	0.174	6.15 (1.06–35.74)	0.043
Upper limb	6/85	29/217	1	2.97 (0.38–22.99)	0.297	2.12 (0.59–7.64)	0.250
Lower limb	7/85	22/217	1	3.47 (0.40–30.46)	0.281	3.26 (0.87–12.27)	0.080
Trunk	2/85	10/217	1	0.68 (0.04–11.10)	0.790	2.05 (0.25–14.88)	0.478
Local recurrence prior to metastasis detection	28/85	24/218	0	1.82 (0.65–5.11)	0.258	3.97 (2.03–7.77)	<0.001
Diameter							
<10mm	8/84	89/218	1	1 (ref)		1 (ref)	
10–19.9mm	27/84	85/218	1	2.62 (0.73–9.39)	0.140	3.53 (1.53–8.08)	0.003
20–29.9mm	19/84	19/218	1	6.31 (1.31–30.49)	0.022	11.13 (4.33–28.58)	<0.001
≥30mm	30/84	25/218	1	3.64 (0.69–19.09)	0.127	13.35 (5.33–33.45)	<0.001
Differentiation							
Good	17/81	123/215	7	1 (ref)		1 (ref)	
Moderate	40/81	70/215	7	2.87 (0.95–8.61)	0.061	4.13 (2.47–6.94)	<0.001
Poor	24/81	22/215	7	2.17 (0.45–10.45)	0.335	7.89 (3.60–17.33)	<0.001
AK or cSCCIS among primary tumor and/or previously histopathologically confirmed at same exact location	12/82	66/218	3	NA	NA	0.40 (0.21–0.76)	0.005
Necrosis among primary tumor	12/78	10/218	7	0.79 (0.24–2.64)	0.705	3.78 (1.54–9.32)	0.004
Clark's level							
2–4	8/75	169/216	12	1 (ref)		1 (ref)	
5	67/75	47/216	12	10.18 (2.35–44.08)	0.002	30.11 (13.18–68.79)	<0.001
Invasion beyond fat	47/79	20/218	6	1.58 (0.51–4.87)	0.428	14.54 (7.78–27.16)	<0.001
Diffuse growth pattern	13/78	6/218	7	1.67 (0.49–5.73)	0.415	7.07 (2.60–19.20)	<0.001
AJCC-8							
T1	16/65	120/156	82	NA	NA	1 (ref)	
T2	3/65	11/156	82	NA	NA	2.05 (0.52–7.99)	0.303
T3	42/65	22/156	82	NA	NA	14.20 (6.89–29.79)	<0.001
T4a–T4b	4/65	3/156	82	NA	NA	10.00 (2.12–47.18)	0.004
BWH							
T1	13/77	157/215	11	NA	NA	1 (ref)	
T2a	20/77	37/215	11	NA	NA	6.53 (2.98–14.29)	<0.001
T2b	38/77	18/215	11	NA	NA	25.50 (11.30–57.52)	<0.001
T3	6/77	3/215	11	NA	NA	24.15 (5.47–106.59)	<0.001

Binary logistic regression analysis of mcSCC characteristics	Included into logistic regression analysis (positive/total) Questionnaire not achieved	Duration not achieved	Missing	Risk of poor prognosis by variable Adjusted OR (95% CI)	P value	Risk of poor prognosis by variable Unadjusted OR (95% CI)	P value
Age at primary tumor diagnosis							
<70	9/50	8/31	4	0.35 (0.21–0.66)	0.842	1.13 (0.33–3.80)	0.849
70–79	17/50	17/31	4	1 (ref)		1 (ref)	
80–89	20/50	6/31	4	3.27 (0.57–18.92)	0.186	3.33 (1.06–10.44)	0.038
≥90	4/50	0/31	4	NA	NA	NA	NA
Gender							
Male	32/50	22/31	4	NA	NA	0.73 (0.21–2.95)	0.527
Female	18/50	9/31	4	NA	NA	1 (ref)	
Immunocompromised							
SOTR	9/50	8/31	4	NA	NA	0.63 (0.20–1.97)	0.427
	1/50	1/31	4	NA	NA	0.61 (0.04–9.71)	0.728
Thiazide	16/50	15/31	4	NA	NA	0.50 (0.19–1.31)	0.158
5α-reductase inhibitor	7/50	4/31	4	NA	NA	2.36 (0.46–12.22)	0.286
Alpha-1 blocker	7/50	2/31	4	NA	NA	1.32 (0.36–4.40)	0.569
Aspirin	14/50	7/31	4	NA	NA	1.33 (0.44–3.98)	0.614
Isosorbide mono-/ dinitrate	2/50	4/31	4	NA	NA	0.23 (0.05–1.04)	0.109
Primary tumor characteristics							
Location							
Temple	7/50	3/31	4	NA	NA	1 (ref)	
Scalp	2/50	1/31	4	NA	NA	0.86 (0.06–15.48)	0.913
Forehead	3/50	1/31	4	NA	NA	1.29 (0.19–7.95)	0.852
Orbit	2/50	2/31	4	NA	NA	0.43 (0.04–6.64)	0.486
Nose	2/50	1/31	4	NA	NA	0.86 (0.06–13.48)	0.913
Lower lip	3/50	7/31	4	NA	NA	0.16 (0.03–0.74)	0.082
Upper lip	0/50	1/31	4	NA	NA	NA	NA
Cheek (excl. preauricular region)	1/50	3/31	4	NA	NA	0.14 (0.01–2.00)	0.148
Preauricular region							
Preauricular	7/50	4/31	4	NA	NA	0.75 (0.12–4.66)	0.758
Auricle	9/50	2/31	4	NA	NA	1.93 (0.25–14.89)	0.539
Retrauricular	2/50	1/31	4	NA	NA	0.86 (0.06–13.48)	0.913
Neck	2/50	1/31	4	NA	NA	0.86 (0.06–13.48)	0.913
Upper limb	3/50	2/31	4	NA	NA	0.64 (0.07–6.06)	0.699
Lower limb	5/50	2/31	4	NA	NA	1.07 (0.13–8.98)	0.949
Trunk	2/50	0/31	4	NA	NA	NA	NA
Local recurrence, overall	24/50	8/31	4	NA	NA	2.65 (1.07–6.06)	0.051
AJCC-8							
T1	6/36	10/26	23	NA	NA	1 (ref)	
T2	2/36	1/26	23	NA	NA	3.33 (0.25–45.11)	0.365
T3	26/36	14/26	23	NA	NA	3.10 (0.93–10.31)	0.066
T4a–T4b	2/36	1/26	23	NA	NA	3.33 (0.25–45.11)	0.365
BWH							
T1	7/44	6/29	12	NA	NA	1 (ref)	
T2a	10/44	10/29	12	NA	NA	0.86 (0.27–3.47)	0.829
T2b	23/44	12/29	12	NA	NA	1.64 (0.45–6.00)	0.452
T3	4/44	1/29	12	NA	NA	3.43 (0.30–39.64)	0.324
Metastasis characteristics							
Distant metastasis	13/50	0/31	4	NA	NA	NA	NA
≥3 nodal metastases	30/50	7/31	4	10.16 (2.19–47.14)	0.003	6.66 (2.34–18.92)	<0.001
ENE	40/49	6/30	6	8.19 (1.79–37.52)	0.007	17.78 (5.65–55.97)	<0.001
Largest nodal metastasis							
<30mm	15/49	24/30	6	1 (ref)		1 (ref)	
≥30mm	19/49	4/30	6	2.35 (0.44–12.51)	0.316	7.60 (2.16–26.70)	0.002
>60mm	15/49	2/30	6	5.89 (0.86–38.29)	0.056	12.60 (2.55–56.47)	0.002
AJCC-8							
N1	3/40	11/27	18	NA	NA	1 (ref)	
N2a–c	6/40	12/27	18	NA	NA	1.83 (0.37–9.17)	0.460
N3a–b	31/40	4/27	18	NA	NA	28.42 (5.17–147.58)	<0.001

Table 4: Factors associated with poor prognosis in mcSCC; ENE = extranodal extension; AJCC-8 tumor (T) and node (N) staging applied solely for head and neck tumors

Table 3: Tumor-level factors associated with the risk of metastasis; AJCC-8 = American Joint Committee on Cancer tumor (T) staging, applied solely for head and neck tumors; BWH = Brigham and Women's Hospital tumor (T) staging, applied regarding every location; AK = actinic keratosis; cSCCIS = cSCC in situ

On patient-level, actinic keratosis (AK) or basal cell carcinoma (BCC) as a comorbidity regardless time association to cSCC as well as prior aspirin and isosorbide mono-/ dinitrate usage especially in combination was associated with lower risk of metastasis (**Table 2**).

On tumor-level, local recurrence, increasing tumor diameter, moderate and poor histologic differentiation, necrosis among primary tumor, diffuse growth pattern, Clark's level 5, invasion beyond fat, several tumor locations and age at tumor diagnosis between 70 and 79 years were associated with increased risk of metastasis with significant crude odds ratios (ORs). Independent risk factors for metastasis with significant adjusted ORs comprehended Clark's level 5, tumor diameter 20–29.9mm, age at tumor diagnosis <50 or 70–79 years as well as lower lip and forehead locations. On the other hand, AK or cSCC in situ (cSCCIS) among or confirmed preceding primary cSCC was associated with decreased risk of metastasis (**Table 3**).

Poor prognosis of mcSCC was associated with the number of nodal metastases and extranodal extension of nodal metastasis. (**Table 4**).

The association between tumor stage and metastasis risk was non-linear and Clark's level 5 provided higher crude OR for the risk of metastasis than either of the staging systems (**Table 3**). Poor prognosis was strongly associated with AJCC-8 regional lymph node category N3a–N3b, but not with BWH or AJCC-8 tumor (T) staging (**Table**