Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1.

Evaluation of Cohort Studies – Risk Factor (Level 4 Evidence)

Citation	Author (Year)	Location	Number of patients	Number of cSCCs	Newcastle-Ottawa Scale for Cohort Studies			Risk Factor	Outcomes	Inclusion Criteria	Follow up (years)	REA?	IP?
					Selection (4 stars)	Comparability (1 star)	Outcome (3 stars)						
(1)	Alam et al. (2011)	United States	6271	289	***	*	***	Cardiac transplant.	All-cause death.	All patients with cutaneous malignancies included in the Cardiac Transplant Research Database.	10.0	No	Yes
(2)	Baker et al. (2001)	Shoreham-by-the-Sea, UK	227	227	***	-	**	Location.	Local recurrence, nodal metastasis.	All patients with cSCC of head and neck region excised.	2.0	Yes	Yes
(3)	Breuninger et al. (2012)	Tübingen, Germany	615	615	***	-	**	Immunosuppression, desmoplasia, location, location, tumor size, poor differentiation.	Any metastasis.	All patients with invasive SCC.	7.0	No	No
(4)	Brinkman et al. (2015)	Rotterdam, Netherlands	131	155	***	*	***	Differentiation.	Local recurrence, any metastasis, all-cause death.	All patients with invasive SCC.	6.8	Yes	Yes
(5)	Brougham et al. (2012)	Central New Zealand	6164	8997	****	*	***	Sex, location, perineural invasion, lymphovascular invasion, differentiation.	Any metastasis.	All patients with SCC in a database covering Central New Zealand.	5.9	Yes	No
(6)	Conde-Ferreiras et al. (2021)	Spain	140	124	***	*	***	Perineural invasion.	Local recurrence, lymphatic metastasis, all-cause death.	All patients with SCC with incidental perineural invasion.	3.3	No	Yes
(7)	Demirdover et al. (2020)	Turkey	164	164	**	*	***	Immunosuppression, perineural or vascular invasion.	Nodal metastasis.	All patients with high-risk features sent for lymph node dissection.	1.3	Yes	Yes
(8)	Dimonitsas et al. (2021)	Greece	1524	1524	***	*	***	Age, sex, anatomical site, ulceration, immunosuppression, tumor size, differentiation, invasion beyond subcutaneous fat, perineural invasion, lymphovascular invasion, lymphatic infiltrate.	Local recurrence, lymphatic metastasis, all-cause death.	All patients with cSCC.	4.0	Yes	No
(9)	Dormand et al. (2010)	London, UK	243	419	***	-	**	Perineural and lymphovascular involvement, differentiation, organ transplantation.	Local recurrence, any metastasis.	All patients with cSCC of the extremities.	6.2	Yes	Yes
(10)	Duran et al. (2017)	Boston, Massachusetts	100	100	***	*	***	Sex.	Local recurrence, nodal metastasis, all-cause death.	All patients with T2b and T3 cSCCs of the head and neck.	3.7	Yes	No
(11)	Eigentler et al. (2017)	Tubingen, Germany	1434	2149	****	*	***	Tumor thickness, tumor size, poor differentiation, desmoplasia, location, immunosuppression.	Disease-specific death.	All patients with cSCC.	3.0	Yes	Yes
(12)	Fujimoto et al. (2016)	Wakayama, Japan	151	171	**	-	***	Age > 80, male sex, location, tumor size, tumor thickness, invasion beyond subcutaneous fat, poor differentiation, perineural invasion.	Nodal metastasis.	All patients with cSCC.	1.0	Yes	Yes
(13)	Genders et al. (2018)	Leiden, The Netherlands	593	1643	***	*	***	Organ transplant, male sex, location, tumor size, poor differentiation.	Any metastasis.	All patients diagnosed with primary cSCC.	4.0	Yes	Yes
(14)	Gonzalez et al. (2017)	Boston, Massachusetts	106	412	***	*	***	Immunosuppression.	Local recurrence, nodal metastasis.	All immunosuppressed patients treated for cSCC.	4.2	No	Yes
(15)	Jansen et al. (2019)	Essen, Germany	114	114	***	*	***	Tumor thickness, location, ulceration, perineural invasion, immunosuppression.	Distant metastasis.	Patients with high risk cSCC who accepted sentinel lymph node biopsy.	2.0	Yes	No
(16)	Kovatch et al. (2018)	Ann Arbor, Michigan	112	112	***	*	***	Location.	Local recurrence, any metastasis.	All patients with SCC of the ear.	2.0	No	Yes

(17)	Manyam et al. (2016)	Cleveland, Ohio; St. Louis, Missouri; San Francisco, California	205	205	***	-	***	Immunosuppression, poor differentiation, perineural invasion.	Local recurrence, all-cause death.	All patients with cSCC who underwent surgical resection and adjuvant radiotherapy.	1.9	Yes	Yes
(18)	Manyam et al. (2015)	Cleveland, Ohio	59	59	***	*	***	Immunosuppression, poor differentiation, perineural invasion.	Local recurrence.	All patients with cSCC who underwent surgical resection and adjuvant radiotherapy.	1.5	No	No
(19)	Melo et al. (2014)	Botucatu, Brazil	61	100	***	*	***	Location, lymphovascular invasion, perineural invasion.	Local recurrence.	All patients with cSCC of the head and neck with outpatient follow up of > 1 year.	4.8	Yes	Yes
(20)	Ong et al. (1999)	Sydney, Australia	152	113	***	-	***	Organ transplant.	Disease-specific death.	All patients undergoing heart transplant.	6.0	No	Yes
(21)	Roozeboom et al. (2012)	Maastricht, The Netherlands	235	235	***	*	***	Sex, location, immunosuppression.	Local recurrence, any metastasis.	All patients diagnosed with cSCC.	3.6	Yes	Yes
(22)	Ross et al. (2009)	Philadelphia, Pennsylvania	48	48	***	*	***	Perineural invasion.	Local recurrence, nodal metastasis, distant metastasis, disease-specific death, all-cause death.	All patients with cSCC with perineural invasion.	3.0	No	Yes
(23)	Salmon et al. (2011)	San Francisco, California; Tauranga, New Zealand	56	56	***	-	***	Desmoplasia.	Local recurrence.	All patients with desmoplasia identified at 2 centers	3.0	No	Yes
(24)	Seddon et al. (2016)	Christchurch, New Zealand	168	168	****	*	***	Sex, immunosuppression, tumor thickness, tumor size, poor differentiation, perineural invasion.	All-cause death.	All patients with cSCC without HIV, malignancies, or on chemotherapy.	6.0	Yes	Yes
(25)	Shaw et al. (2015)	Auckland, New Zealand	303	303	**	-	***	Immunosuppression.	Local recurrence, disease-specific death.	All patients with cSCC.	14-19	Yes	Yes
(26)	Stevenson et al. (2020)	New York, New York	31	31	***	*	***	Perineural invasion.	Local ecurrence, nodal metastasis.	All patients with cSCC and perineural invasion.	> 5.0	No	Yes
(27)	Tam et al. (2020)	Houston, Texas	796	796	****	*	***	Immunosuppression.	Disease-specific death.	All patients with cSCC.	2.7	Yes	No
(28)	Terra et al. (2017)	Groningen, The Netherlands	151	151	***	*	***	Tumor size, poor differentiation, tumor thickness, perineural invasion, lymphovascular invasion, male sex, age > 70.	Local recurrence.	All patients with cSCC of the head and neck treated with radiotherapy.	1.9	Yes	No
(29)	Thiem et al. (2020)	Rockstock, Germany	142	142	***	*	**	Location, poor differentiation.	Local recurrence.	All patients with cSCC of the head and neck treated with excision.	5.0	Yes	No
(30)	Tomaszewski et al. (2012)	Melbourne, Australia	42	42	****	*	**	CLL.	Local recurrence, nodal metastasis, distant metastasis, disease-specific death, all-cause death.	All patients with cSCC and CLL.	3.6	No	Yes
(31)	Vinicius et al. (2011)	São Paolo, Brazil	55	55	***	*	***	Sex, tumor thickness, lymphovascular invasion, perineural invasion, eGFR positive, HER-2/HER-3/membrane E-cadherin/cytoplasm E-cadherin/podoplanin expression.	Nodal metastasis, disease-specific death.	All patients with T3 or T4 cSCC.	0.8	Yes	Yes
(32)	Yung et al. (2021)	Sydney, Australia	297	297	***	*	***	Perineural invasion, location.	Locoregional recurrence, all-cause death, disease-specific death.	All patients with cSCC of the vermillion lip.	4.1	Yes	Yes
(33)	Amaral et al. (2019)	Tübingen, Germany	195	195	***	-	***	Tumor thickness.	All-cause death.	All patients with advanced cSCC.	1.8	Yes	No
(34)	Arbab et al. (2019)	Boston, Massachusetts	111	111	***	*	***	Perineural invasion, lymphovascular invasion, immunosuppression.	Locoregional recurrence.	All patients with advanced cSCC treated with any radiation.	0.6	Yes	Yes

(35)	Arron et al. (2021)	33 clinical sites	278	278	***	*	***	Sex, location, immunosuppression, poor differentiation, perineural invasion, invasion beyond subcutaneous fat, 40-GEP risk.	Any metastasis.	All patients with head and neck cSCC.	5.0	Yes	No
(36)	Blechman et al. (2019)	New York, New York	58	263	***	-	***	Immunosuppression.	Local recurrence, nodal metastasis, disease-specific death.	All immunosuppressed patients treated for cSCC.	3.0	No	Yes
(37)	Bourlidou et al. (2019)	Thessaloniki, Greece	531	114	***	*	***	Poor differentiation.	Locoregional recurrence.	All patients with cSCC of the mid-face.	2.9	Yes	No
(38)	Bovill et al. (2012)	United Kingdom	84	84	****	-	***	Poor differentiation, location.	Locoregional recurrence.	All patients with cSCC undergoing re-excision for positive margins.	2.3	Yes	No
(39)	Brantsch et al. (2008)	Tübingen, Germany	615	615	****	*	***	Tumor thickness, tumor size, poor differentiation, desmoplasia, location, immunosuppression.	Any metastasis, local recurrence.	Patients with cSCC referred by Dermatologists and general practitioners from SW Germany.	3.6	Yes	Yes
(40)	Brewer et al. (2015)	Olmsted County, Minnesota	717	446	****	*	***	CLL, non-CLL non-Hodgkin's lymphoma, non-Hodgkin's lymphoma.	Any metastasis, local recurrence.	All patients with non-Hodgkin's lymphoma and cSCC in the Rochester Epidemiology Project database.	0.6	No	Yes
(41)	Cañueto et al. (2017)	Spain	94	94	***	-	***	Poor differentiation, lymphovascular invasion, perineural invasion, EGFR over expression.	Nodal metastasis.	All patients with cSCCs.	NS	Yes	Yes
(42)	Cañueto et al. (2018)	Salamanca, Spain	90	90	***	-	***	Growth rate.	Local recurrence, nodal metastasis.	Randomly selected patients intentionally biased towards a higher proportion of tumors with poor outcomes	4.2	Yes	Yes
(43)	Carter et al. (2013)	Boston, Massachusetts	114	114	****	*	***	Perineural invasion.	Local recurrence, nodal metastasis, disease-specific death, all-cause death.	All patients with cSCC and perineural invasion.	2.7-4.0	No	No
(44)	Chabrillac et al. (2019)	Toulouse, France	69	69	****	-	***	Sex, diabetes, immunosuppression, tumor thickness, tumor size, poor differentiation, perineural invasion.	Nodal metastasis.	All patients with cSCC undergoing sentinel lymph node biopsy.	2.0	Yes	Yes
(45)	Conde-Ferreirós et al. (2021)	Salamanca, Spain	196	196	***	*	***	T stage.	Local recurrence, disease, specific poor outcomes, disease-specific death, distant metastasis.	All patients with T3 cSCC.	4.9	No	No
(46)	Durham et al. (2016)	Ann Arbor, Michigan	53	54	***	*	**	Lymphovascular invasion, perineural invasion.	Nodal metastasis.	All patients with cSCC who underwent wide local excision and sentinel lymph node biopsy.	2.1	Yes	No
(47)	Dzubow et al. (1982)	New York, New York	414	414	***	-	***	Sex, location, age, diameter.	Local recurrence.	All patients treated with Mohs surgery.	1.6	Yes	Yes
(48)	Erkan et al. (2017)	Murdoch, Australia	21	21	***	-	**	Perineural invasion.	Local recurrence, nodal metastasis.	All patients with perineural invasion of cranial nerves.	1.5	No	Yes
(49)	Estall et al. (2017)	Melbourne, Australia	235	235	****	*	***	Location, immunosuppression, perineural invasion, lymphovascular invasion.	Local recurrence, nodal metastasis, all-cause death.	All patients with cSCC of the scalp.	4.5	Yes	Yes
(50)	Farberg et al. (2020)	23 independent centers	300	300	***	-	***	40-GEP high risk, 40-GEP intermediate risk.	Any metastasis.	All patients with high risk cSCC.	4.0	Yes	Yes
(51)	Gore et al. (2016)	Sydney, Australia	57	57	***	-	***	Perineural invasion, lymphovascular invasion.	Nodal metastasis.	Patients with high risk cSCC undergoing sentinel lymph node biopsy.	1.6	Yes	No

(52)	Grover et al. (2021)	Melbourne, Australia	129	129	****	-	***	Immunosuppression, perineural invasion, lymphovascular invasion.	All-cause death, disease-specific death, local recurrence, or nodal/distal metastasis.	All patients with head and neck cSCC discussed at multi-disciplinary meetings in Western Australia.	3.7	Yes	No
(53)	Gupta et al. (2021)	Boston, Massachusetts; Cleveland, Ohio	1297	1297	****	-	***	Poor differentiation, location, tumor size, invasion beyond subcutaneous fat, perineural invasion, lymphovascular invasion, age > 65, immunosuppression, organ transplant, CLL.	Local recurrence, nodal metastasis, distant metastasis, disease-specific death.	All patients with BWH Stage 2a cSCCs.	5.0	Yes	Yes
(54)	Haisma et al. (2016)	Groningen, The Netherlands	336	545	****	*	***	Age > 70, sex, immunosuppression, location, poor differentiation, tumor size, tumor thickness, perineural invasion, lymphovascular invasion.	Nodal metastasis.	All biopsies with proven primary head and neck cSCC.	3.5	Yes	No
(55)	Harris et al. (2017)	Sacramento, California	212	212	****	*	***	Sex, age > 70, immunosuppression, location, diameter, tumor thickness, poor differentiation.	Nodal metastasis, local recurrence.	All patients with cSCC undergoing surgery with curative intent.	2.9	Yes	No
(56)	Harris et al. (2019)	Sacramento, California; St. Louis, Missouri	349	349	****	*	***	Age > 70, immunosuppression, perineural invasion.	All-cause death.	All patients with cSCC of the head and neck with at least 3 months follow up.	3.1	Yes	No
(57)	Haug et al. (2020)	Tübingen, Germany	1399	1399	***	*	***	Desmoplasia.	Local recurrence, nodal metastasis, distant metastasis, disease-specific death.	All patients with cSCC with follow up information.	3.0	Yes	Yes
(58)	Hausauer et al. (2013)	San Francisco, California	1198	376	***	*	***	HIV.	Local recurrence.	All patients with non-genital cSCC.	7.3	Yes	No
(59)	Jackson et al. (2009)	Brisbane, Australia; Sydney, Australia	97	71	***	-	***	Perineural invasion.	Nodal metastasis.	All patients with keratinocyte carcinomas.	7.0	No	Yes
(60)	Jambusaria-Pahlajani et al. (2013)	Philadelphia, Pennsylvania	237	256	***	*	***	Poor differentiation, tumor size, perineural invasion, invasion beyond subcutaneous fat, immunosuppression.	Local recurrence, nodal metastasis, disease-specific death.	All patients with cSCC and one or more of a group of defined risk factors.	3.7	Yes	No
(61)	Jenkins et al. (2014)	York, United Kingdom	101	101	***	-	**	Location.	Local recurrence, nodal metastasis.	All patients with cSCC of the scalp.	0.5	No	Yes
(62)	Kadakia et al. (2016)	Fort Worth, Texas	53	53	***	-	**	Immunosuppression.	Local recurrence, nodal metastasis, distant metastasis.	A cohort of immunosuppressed patients with cSCC of the scalp.	> 3.0	No	Yes
(63)	Kamiya et al. (2020)	Sapporo, Japan	46	46	***	*	***	Tumor size, tumor thickness, poor differentiation, high PDL-1 intensity.	Nodal metastasis.	A cohort of patients with cSCC who underwent imaging to assess nodal metastasis.	0.7	Yes	No
(64)	Karia et al. (2014)	Boston, Massachusetts	1818	974	****	*	***	Sex, immunosuppression, organ transplantation, rheumatoid arthritis immunosuppressive therapy, CLL, location, size, poor differentiation, invasion subcutaneous fat, perineural invasion.	Local recurrence, nodal metastasis, disease-specific death, all-cause death.	All patients with cSCC.	5.9	Yes	Yes
(65)	Kato et al. (2018)	Sapporo, Japan	42	42	***	-	***	Cytokeratin-19 expression.	Any metastasis.	Patients with cSCC.	NS	Yes	Yes
(66)	Knuutila et al. (2020)	Turku, Finland	207	324	***	*	***	Age, sex, immunocompromised, organ transplant, location, tumor size, poor differentiation.	Any metastasis.	All patients treated for cSCC from Finnish Cancer Registry.	5.0	Yes	No

(67)	Korhonen et al. (2020)	Pirkanmaa, Finland	774	774	****	-	***	Sex, age, immunosuppression, location, poor differentiation, tumor thickness.	Local recurrence, any metastasis.	All patients treated for cSCC in a region of Finland extracted from a pathology base.	NS	Yes	Yes
(68)	Krediet et al. (2015)	Berlin, Germany	143	143	****	*	**	Sex, location, poor differentiation, immunosuppression.	Local recurrence, any metastasis.	All patients treated for cSCC with histopathology and clinical information.	2.0	Yes	Yes
(69)	Kreppel et al. (2013)	Cologne, Germany	63	63	***	*	***	Podoplanin expression, immunosuppression.	All-cause death.	A cohort of treatment-naïve patients with cSCC.	3.4	Yes	No
(70)	Kropp et al. (2013)	Gainesville, Florida	36	32	****	*	***	Perineural invasion.	Locoregional recurrence or distant metastasis.	All patients with cSCC with perineural invasion.	4.2	No	Yes
(71)	Kyrgidis et al. (2010)	Thessaloniki, Greece	315	315	****	-	***	Perineural invasion, invasion beyond subcutaneous fat.	Local recurrence or nodal/distant metastasis, all-cause death.	A cohort of patients with head and neck cSCC.	3.9	Yes	No
(72)	Leibovitch et al. (2005)	Australia	1263	315	***	-	***	Perineural invasion.	Local recurrence.	All cSCCs treated with Mohs recorded prospectively in a Mohs surgery database.	> 5.0	Yes	No
(73)	Leus et al. (2021)	Groningen, The Netherlands	672	672	****	*	***	Age > 75.	Local recurrence, nodal metastasis, distant metastasis.	All immunocompetent patients treated for cSCC	5.0	Yes	Yes
(74)	Matsumoto et al. (2021)	Dallas, Texas	842	842	***	*	***	Age > 80, sex, immunosuppression, tumor size, poor differentiation, perineural invasion, invasion beyond subcutaneous fat, location, HIV, organ transplant.	Local recurrence, any metastasis, disease-specific death, all-cause death.	All patients with cSCC.	2.4	Yes	Yes
(75)	Mayo et al. (2017)	Southampton, United Kingdom	192	192	***	-	***	Poor differentiation, tumor thickness, location, ulceration, perineural invasion, lymphovascular invasion.	Local recurrence, nodal metastasis.	All patients with cSCC of the ear.	> 2.0	Yes	Yes
(76)	McLaughlin et al. (2017)	Philadelphia, Pennsylvania	130	383	***	-	***	Organ transplant.	Nodal metastasis.	All patients with a history of organ transplant and head and neck cSCC who underwent surgery.	3.4	No	Yes
(77)	Mo et al. (2021)	Philadelphia, Pennsylvania	432	432	****	*	***	Immunosuppression, poor differentiation, invasion beyond subcutaneous fat, tumor size, location.	Any metastasis.	All patients with cSCC > 2 cm located on lip, ear, scalp, or pretibial leg treated with Mohs.	NS	Yes	Yes
(78)	Moore et al. (2005)	Houston, Texas	193	193	***	*	***	Location, lymphovascular invasion, poor differentiation, perineural invasion.	Nodal metastasis.	All patients with cSCC of the head and neck.	1.7	Yes	Yes
(79)	Mourouzis et al. (2009)	West Sussex, United Kingdom	194	218	***	-	**	Poor differentiation, location.	Nodal metastasis.	All patients with cSCC of the head and neck treated with surgical excision.	2.5-5	Yes	Yes
(80)	Mullen et al. (2006)	Houston, Texas	136	149	****	*	***	Tumor size, poor differentiation.	Local recurrence, nodal/distant metastasis, or disease-specific death.	All patients with cSCC of the trunk and extremities not treated with Mohs.	2.4	Yes	No
(81)	Nelson et al. (2017)	Isle of Wight, United Kingdom	1122	1495	****	-	***	Sex, location, tumor size, tumor thickness.	Any metastasis, local recurrence.	All patients with cSCC.	6.6	Yes	No
(82)	Obermeier et al. (2017)	Munich, Germany	99	99	***	-	***	Location, tumor thickness.	Nodal metastasis.	All patients who underwent inpatient treatment of facial cSCC.	2.8	Yes	No
(83)	Ogawa et al. (2017)	Sacramento, California	103	103	***	*	**	Acantholytic subtype.	Local recurrence, nodal metastasis.	All patients with acantholytic cSCC.	3.0	No	Yes

(84)	Oh et al. (2020)	Seoul, South Korea	237	237	****	*	***	Sex, location, tumor size, poor differentiation, invasion beyond subcutaneous fat, perineural invasion, ulceration.	Local recurrence, distant metastasis.	All patients undergoing Mohs surgery.	1.5	Yes	Yes
(85)	Saito et al. (2021)	Niigata, Japan	540	540	****	*	***	Tumor size, tumor thickness, invasion beyond subcutaneous fat, poor differentiation.	Nodal metastasis.	All patients who underwent treatment of cSCC.	3.2	Yes	No
(86)	Sayan et al. (2020)	Dorset, United Kingdom	108	108	****	-	***	Location, poor differentiation, perineural or lymphovascular invasion.	Nodal metastasis.	All patients with cSCC of the pinna.	3.0	Yes	Yes
(87)	Takeda et al. (2013)	Sagamihara, Japan	164	164	****	-	***	Location.	Nodal metastasis.	All patients treated for cSCC.	NS	Yes	Yes
(88)	Tanamal et al. (2022)	Dallas, Texas	178	178	***	-	***	Sex, smoker, immunosuppression, perineural invasion, lymphovascular invasion.	Local recurrence, nodal metastasis, locoregional recurrence.	All patients with cSCC of the external ear with >12 months follow up.	2.7	Yes	Yes
(89)	Thomas et al. (2007)	Danville, Pennsylvania	174	99	***	-	***	Poor differentiation.	Local recurrence.	All patients with poorly differentiated cSCC, DFSP, MAC, EMPD, MCC, and sebaceous carcinoma.	3.3	No	Yes
(90)	Tschetter et al. (2020)	Pittsburg, Pennsylvania	637	745	***	*	***	Sex, immunosuppression, tumor thickness, tumor size, location, poor differentiation, invasion beyond subcutaneous fat, perineural invasion.	Local recurrence, nodal metastasis, disease-specific death, all-cause death.	All patients with cSCC treated with Mohs surgery over a 25-working day period.	5.1	Yes	No
(91)	van Lee et al. (2019)	Rotterdam, the Netherlands; Zwolle, the Netherlands	631	738	****	*	**	Tumor size.	Local recurrence.	All patients receiving treatment with standard excision or Mohs surgery for cSCC of the head and neck.	0.4-0.5	Yes	No
(92)	Venables et al. (2019)	England	93890	93890	***	*	***	Sex, age, location, immunosuppression.	Any metastasis, all-cause death.	All patients with first cSCC identified in the English National Cancer Registration and Analysis Service database between 2013 and 2015.	1.3	Yes	Yes
(93)	Warren et al. (2016)	Brisbane, Australia	50	50	****	-	***	Perineural invasion.	Local recurrence, nodal/distant metastasis, disease-specific death.	Cohort of patients with cSCC with perineural invasion.	4.2	No	Yes
(94)	Wu et al. (2020)	Boston, Massachusetts	84	84	****	*	***	Immunosuppression.	Local recurrence, nodal metastasis, or disease-specific death.	All patients with head and neck cSCC undergoing sentinel lymph node biopsy.	1.7	Yes	No
(95)	Xiong et al. (2020)	Cleveland, Ohio	366	366	***	*	***	Sex, immunosuppression, poor differentiation, invasion beyond subcutaneous fat, perineural invasion, tumor size.	Local recurrence, nodal/distal metastasis, disease-specific death.	All patients with cSCC.	2.8	Yes	Yes
(96)	Xu et al. (2018)	San Francisco, California	101	101	****	*	***	Immunosuppression, lymphovascular invasion	Locoregional recurrence.	All patients with cSCC receiving surgery and radiotherapy.	2.0	Yes	No
(97)	Warren et al. (2016)	Brisbane, Queensland, Australia	120	120	****	*	**	Perineural invasion.	Nodal metastasis, distant metastasis.	All patients with high-risk SCCs with perineural invasion.	5.0	No	Yes

*NS: not stated.

eTable 1 (cont)

Evaluation of Case-Control Studies – Risk Factors (Level 3 Evidence)

Study number	Author (year)	Location	Number of patients	Number of cSCC	Newcastle-Ottawa Scale for Case-Control Studies			Risk Factor	Outcomes	Inclusion Criteria	Follow up (years)	OR?	IP?
					Selection (4 stars)	Comparability (1 stars)	Outcome (3 stars)						
(98)	Agar et al. (2015)	New Zealand	49	49	***	-	***	Tumor thickness, differentiation, location, pattern of invasion, perineural invasion.	Nodal metastasis.	All patients with cSCC with metastatic spread and 32 case-matched controls.	NS	Yes	No
(99)	Fujimoto et al. (2019)	Wakayama, Japan	48	48	***	*	***	Age, sex, location, tumor size, tumor thickness, tumor thickness, invasion beyond subcutaneous fat, poor differentiation, perineural invasion.	Nodal metastasis.	Patients with metastasizing cSCCs < 4 cm and 24 matched non-metastasizing cSCCs.	4.4	No	No
(100)	García-Pedrero et al. (2017)	Oviedo, Spain	100	100	***	*	***	Tumor PDL-1 expression.	Nodal metastasis.	Patients with cSCC with nodal metastasis and 50 random controls without metastasis.	> 4.0	Yes	No
(101)	Gonzalez-Guerrero et al. (2017)	Oviedo, Spain	98	98	**	*	***	Sex, tumor thickness, tumor size, poor differentiation, desmoplasia, location, immunosuppression, perineural invasion, lymphovascular invasion, tumor budding.	Nodal metastasis.	Patients with cSCC with nodal metastasis and 49 random controls without metastasis.	4.3	Yes	No
(102)	Hernández-Ruiz et al. (2019)	Spain	102	102	**	*	***	Location, tumor size, immunosuppression, poor differentiation, tumor thickness, perineural invasion, lymphovascular invasion, desmoplasia, tumor budding.	Any metastasis.	Consecutive patients with cSCC with nodal metastasis and 52 matched controls without metastasis.	> 5.0	Yes	No
(103)	Karayannopoulou et al. (2020)	Lyon, France	52	52	**	-	***	Tumor budding, tumor size.	Local recurrence, distant metastasis, or nodal metastasis.	Organ transplant recipients with aggressive cSCC and 27 matched controls without metastasis.	NS	Yes	No
(104)	Khandelwal et al. (2016)	Shreveport, Louisiana	37	37	***	*	***	Location, tumor size, lymphovascular invasion, perineural invasion.	Nodal metastasis.	Patients with parotid metastasis and 17 patients without parotid metastasis.	NS	Yes	No
(105)	Lobl et al. (2022)	Los Angeles, California and Omaha, Nebraska	260	260	****	*	***	Poor differentiation, perineural invasion, lymphovascular invasion, tumor size, hyperthyroidism, invasion beyond subcutaneous fat, immunosuppression, smoking history.	Nodal metastasis.	cSCCs with nodal metastasis and 195 site matched controls.	5.1	Yes	No
(106)	Munguía-Calzada et al. (2019)	Oviedo, Spain	100	100	***	*	***	Fak expression, cortactin expression.	Nodal metastasis, disease-specific death, all-cause death.	Consecutive patients with head and neck cSCC with nodal metastases and 50 random primary cSCC patients without metastasis with 4 years of follow-up	> 4.0	Yes	No
(107)	Cañueto et al. (2019)	Salamanca, Spain	186	186	****	-	***	Poor differentiation, perineural invasion, invasion beyond subcutaneous fat, immunosuppression, history of smoking, thickness.	Local recurrence, nodal/distant metastasis, disease-specific death.	All patients with cSCC and poor outcomes and complete clinical data and 1 of every 10 consecutive patients with cSCC and good outcomes.	6.6	Yes	No
(108)	Cheng et al. (2018)	New Haven, Connecticut	98	98	**	-	***	Organ transplant.	Nodal metastasis, all-cause death.	All patients with cSCC at compared with 40 random controls.	3.8	Yes	Yes
(109)	Gonzalez et al. (2019)	Boston, Massachusetts (Tufts)	318	703	****	*	***	Immunosuppression, organ transplant.	Local recurrence, nodal metastasis.	1:2 matched cSCCs comparing immunosuppressed patients to controls.	2.9	Yes	No

(110)	Kanitakis et al. (2015)	Thessaloniki, Greece	375	1244	**	-	***	Organ transplant.	Local recurrence, any metastasis.	All organ transplant patients developing cSCC and a subsequent case-control study comparing 34 patients with aggressive cSCC and 25 controls.	NS	No	Yes
(111)	Karayannopoulou et al. (2016)	Thessaloniki, Greece	52	52	***	-	***	Organ transplant.	Locoregional recurrence.	Organ transplant patients with aggressive cSCCs and 21 organ transplant patients without cSCCs.	NS	No	No
(112)	Krediet et al. (2016)	Berlin, Germany	30	30	***	*	***	Lymphatic vascular density.	Any metastasis.	Patients with metastatic cSCC and 15 patients with matched non-metastatic cSCC	2.8	Yes	No
(113)	Peat et al. (2012)	Auckland, New Zealand	170	170	****	*	***	Immunosuppression, ulceration, poor differentiation, lymphovascular invasion.	Any metastasis.	All patients with metastatic cSCCs compared to 92 control patients.	> 5.0	Yes	No
(114)	Santos-Juanes et al. (2019)	Oviedo, Spain	100	100	***	*	***	Lectin-like transcript 1 expression.	Nodal metastasis, disease-specific death.	50 cSCC with nodal metastasis and 50 randomly selected controls without metastasis	> 4.0	Yes	No
(115)	Sepehripour et al. (2020)	East Grinsted, United Kingdom	88	88	***	*	***	Location, poor differentiation.	Local recurrence.	All patients with cSCC with local recurrence after surgical excision with age and size matched controls.	> 5.0	Yes	No

eTable 1 (cont)

Evaluation of Studies – Treatment

Study Number	Author (Year)	Location	Study Type	Level of Evidence	Number of Patients	Number of cSCCs	Newcastle-Ottawa Scale: Selection (4 stars)	Newcastle-Ottawa Scale: Comparability (1 star)	Newcastle-Ottawa Scale: Outcome/Exposure (3 stars)	Treatment	Outcomes	Inclusion Criteria	Follow up (years)
(116)	Howard et al. (2012)	Tallahassee, Florida	Cohort	4	1149	133	****	*	***	Radiotherapy.	Local recurrence.	All patients with non-aggressive cSCCs treated with superficial X-ray therapy.	2.6
(28)	Terra et al. (2017)	Groningen, The Netherlands	Cohort	4	151	52	***	*	***	Radiotherapy.	Local recurrence.	All patients with cSCC of the head and neck treated with radiotherapy.	1.9
(29)	Thiem et al. (2020)	Rockstock, Germany	Cohort	4	142	142	***	*	**	Excision.	Local recurrence.	All patients with cSCC of the head and neck treated with excision.	0.4
(34)	Arbab et al. (2019)	Boston, Massachusetts	Cohort	4	111	111	***	*	***	Radiotherapy.	Locoregional recurrence.	All cases of advanced cSCC treated with any radiation.	0.6
(47)	Dzubow et al. (1982)	New York, New York	Cohort	4	414	414	***	-	***	Mohs micrographic surgery.	Local recurrence.	All patients treated with Mohs surgery.	1.6
(117)	Hernández-Machin et al. (2007)	Las Palmas de Gran Canarias, Spain	Cohort	4	710	106	****	*	***	Radiotherapy.	Local recurrence.	All patients treated with radiotherapy with curative intent.	> 1.0
(118)	Kim et al. (2018)	New York, New York	Cohort	4	71	46	****	-	***	Radiotherapy.	Disease-specific death.	All patients with T3/T4 non-melanoma skin cancer treated with radiotherapy.	0.8
(119)	Košec et al. (2013)	Zagreb, Croatia	Cohort	4	103	103	****	-	***	Surgical excision.	Local recurrence, nodal metastasis.	All patients with head and neck cSCC treated with surgical excision.	> 3.0
(120)	Leibovitch et al. (2005)	Australia	Cohort	4	1263	229	***	-	***	Mohs micrographic surgery.	Local recurrence, nodal/distant metastasis.	All histologically confirmed cSCC treated with Mohs recorded by Australian Mohs surgery database.	5.0
(90)	Tschetter et al. (2020)	Pittsburg, Pennsylvania	Cohort	4	637	745	***	*	***	Mohs micrographic surgery.	Local recurrence, nodal metastasis, disease-specific death, all-cause death.	All patients with cSCC treated by Mohs surgery over a 25-working day period.	5.1
(121)	Choi et al. (2017)	Busan, South Korea	RCT	2	45	45	&	&	&	AFL-PDT, MAL-PDT.	Local recurrence.	Selected patients with microinvasive cSCC randomized to receive AFL- or MAL-PDT, single-blind.	2.0
(122)	Ruiz et al. (2020)	Boston, Massachusetts	Case-control	3	62	62	****	-	***	Surgical excision, surgery, and radiotherapy.	Nodal metastasis.	All patients with cSCC at a single institution treated with curative intent.	2.7-4.1
(123)	Diana et al. (2020)	Zurich, Switzerland	Cohort	4	145	159	****	*	***	Radiotherapy	Local recurrence.	All patients with periocular lesions.	3.6
(124)	Hutting et al. (2018)	The Netherlands	Cohort	4	152	160	***	*	***	Excision with whole section intraoperative frozen section analysis.	Local recurrence, any metastasis.	All patients with cSCCs treated with surgical excision.	3.4
(125)	Stanciu et al. (2020)	Bucharest, Romania	Cohort	4	1356	1356	****	*	***	Mohs micrographic surgery.	Local recurrence.	All skin lesions treated with Mohs micrographic surgery.	NS

(126)	Fernanda Sachse et al. (1988)	Lisbon, Portugal	Cohort	4	545	623	***	*	***	Cryotherapy.	Local recurrence.	All patients with Bowen's disease, lentigo maligna, SCCs, or BCCs	NS
(127)	Marrazzo et al. (2019)	Hickory, North Carolina, and Pittsburg, Pennsylvania	Cohort	4	647	647	****	*	***	Mohs micrographic surgery.	Local recurrence, nodal metastasis, distant metastasis, any metastasis, disease-specific death.	All patients with high-risk SCCs	3.0
(128)	Pereira et al. (1994)	Barreiro, Portugal	Cohort	4	224	224	***	*	**	Cryotherapy.	Local recurrence.	All patients treated with cryotherapy and 4 years of follow-up	4.0
(129)	Turner et al. (2000)	Newcastle upon Tyre, United Kingdom	Cohort	4	61	61	****	*	**	Mohs micrographic surgery.	Local recurrence, any metastasis.	All patients with SCC treated with Mohs micrographic surgery with follow-up.	4.0
(2)	Baker et al. (2001)	Shoreham-by-the-Sea, UK	Cohort	4	227	227	***	-	**	Standard excision.	Local recurrence, nodal metastasis, all-cause death	All patients with cSCC of head and neck region excised.	2.0
(4)	Brinkman et al. (2015)	Rotterdam, Netherlands	Cohort	4	131	155	***	*	***	Differentiation.	Local recurrence, any metastasis, all-cause death.	All patients with invasive SCC.	6.8
(21)	Roozeboom et al. (2012)	Maastricht, The Netherlands	Cohort	4	235	235	***	*	***	Sex, location, immunosuppression.	Local recurrence, any metastasis.	All patients diagnosed with cSCC.	3.6
(35)	Arron et al. (2021)	33 clinical sites	Cohort	4	278	278	***	*	***	Mohs micrographic surgery, standard excision	Any metastasis.	All patients with head and neck cSCC.	5.0
(53)	Gupta et al. (2021)	Boston, Massachusetts; Cleveland, Ohio	Cohort	4	1297	1297	****	-	***	Mohs micrographic surgery, standard excision	Local recurrence, nodal metastasis, distant metastasis, disease-specific death.	All patients with BWH Stage 2a cSCCs.	5.0
(74)	Matsumoto et al. (2021)	Dallas, Texas	Cohort	4	842	842	***	*	***	Mohs micrographic surgery	Local recurrence, any metastasis, disease-specific death	All patients with cSCC.	2.4
(84)	Oh et al. (2020)	Seoul, South Korea	Cohort	4	237	237	****	*	***	Mohs micrographic surgery	Local recurrence, distant metastasis.	All patients undergoing Mohs surgery.	1.5
(91)	van Lee et al. (2019)	Rotterdam, the Netherlands; Zwolle, the Netherlands	Cohort	4	631	738	****	*	**	Mohs micrographic surgery, standard excision	Local recurrence, any metastasis, all-cause death.	All patients receiving treatment with standard excision or Mohs surgery for cSCC of the head and neck.	0.4-0.5
(95)	Xiong et al. (2020)	Cleveland, Ohio	Cohort	4	366	366	***	*	***	Mohs micrographic surgery, standard excision	Local recurrence, nodal/distal metastasis, disease-specific death.	All patients with cSCC.	2.8

*NS: not stated. & Refer to Supplemental Table 1 for Risk of Bias Assessment.

eTable 2. Results of random effects analysis: risk ratio for each risk factor and distant metastasis, any metastasis, locoregional recurrence, and combined outcomes

Distant metastasis

Risk Factor	*Risk ratio (95% CI)*	*p-value*	*Number of Studies*	I^2
Desmoplasia	17.3 (4.4 - 68.4)	**<0.0001**	1	0
Lymphovascular Invasion	9.3 (1.3 - 66.0)	**0.0257**	1	0
Perineural invasion	4.8 (2.2 - 10.4)	**<0.0001**	3	0
Poor Differentiation	3.9 (1.9 - 8.2)	**0.0003**	2	0
Age > 65	3.1 (0.4 - 23.7)	0.2770	1	0
Invasion Beyond Subcutaneous Fat	2.8 (0.4 - 20.9)	0.3194	1	0
Location on Ear or Lip	2.1 (0.5 - 9.3)	0.3373	1	0
Solid Organ Transplant	1.9 (0.5 - 7.8)	**0.3517**	1	0
Tumor Thickness ≥ 2 mm	1.7 (0.6 - 4.4)	**0.3085**	1	0
Ulceration	1.6 (0.5 - 5.1)	0.4509	2	0
Location on Head and Neck	1.1 (0.3 - 3.8)	0.8500	1	0
Tumor Thickness ≥ 6 mm	1.1 (0.3 - 4.0)	0.8857	1	0
Immunosuppression	0.9 (0.4 - 2.2)	0.8279	2	0
Tumor Size ≥ 2 cm	0.8 (0.1 - 5.7)	0.8263	2	0
Male Sex	0.8 (0.3 - 2.0)	0.5933	1	0

Any metastasis

Risk Factor	*Risk ratio (95% CI)*	*p-value*	*Number of Studies*	I^2
Tumor Thickness ≥ 4 mm	12.5 (5.0 - 31.6)	**<0.0001**	1	0
Relative area occupied by lymphatics	9.1 (1.0 - 86.8)	0.0554	1	0
Tumor Size ≥ 5 cm	5.8 (2.5 - 13.5)	**<0.0001**	1	0
Tumor Thickness ≥ 2 mm	5.2 (1.5 - 17.4)	**0.0080**	1	0
Perineural invasion	5.0 (2.3 - 11.1)	**0.0001**	6	0
Invasion Beyond Subcutaneous Fat	4.0 (2.4 - 6.5)	**<0.0001**	6	14.3
Lymphovascular Invasion	3.2 (2.1 - 5.0)	**<0.0001**	4	61.2
40-GEP High Risk	3.0 (1.0 - 8.5)	**0.0431**	2	0
Poor Differentiation	2.9 (1.6 - 5.1)	**0.0002**	13	25.9
Location on Head and Neck	2.9 (0.7 - 12.3)	0.1548	3	0
Tumor Size ≥ 2 cm	2.9 (1.6 - 5.1)	**0.0004**	6	0
Age > 60	2.6 (0.1 - 58.1)	0.5526	2	0
Tumor Budding	2.0 (1.3 - 3.2)	**0.0019**	1	0
Tumor Thickness ≥ 6 mm	2.0 (1.3 - 3.1)	**0.0026**	2	0
Location on Ear	2.0 (1.2 - 3.2)	**0.0059**	9	25.7
Location on Lip	1.8 (1.4 - 2.4)	**<0.0001**	8	6.4
Solid Organ Transplant	1.8 (0.7 - 4.9)	0.2480	3	11.5
Location on Ear or Lip	1.7 (0.7 - 4.6)	0.2592	1	0
Immunosuppression	1.6 (1.2 - 2.2)	**0.0041**	11	18.5
40-GEP Moderate Risk	1.5 (1.1 - 2.2)	**0.0194**	2	0
Male Sex	1.5 (1.2 - 2.0)	**0.0013**	10	0
Location on Scalp	1.5 (1.0 - 2.1)	**0.0444**	6	32.9
Age > 70	1.4 (0.2 - 11.1)	0.7430	2	0
Desmoplasia	1.4 (0.5 - 3.7)	0.5148	3	25
Lymphatic Vascular Density	1.1 (1.0 - 1.2)	0.0734	1	0
Age > 80	1.1 (1.0 - 1.2)	0.2171	4	0
Ulceration	1.1 (0.5 - 2.4)	0.8683	3	0
Tumor Size ≥ 4 cm	1.0 (0.2 - 5.0)	0.9971	1	0
Age > 90	1 (0.8 - 1.1)	0.6013	1	0

All-cause death

Risk Factor	*Risk ratio (95% CI)*	*p-value*	*Number of Studies*	I^2
Age > 90	5.6 (5.3 - 5.8)	**<0.0001**	1	0
Location on Head and Neck	2.7 (1.3 - 5.9)	**0.0108**	1	0
Immunosuppression	2.7 (1.5 - 4.6)	**0.0004**	7	35.86
Tumor Thickness ≥ 5 mm	2.1 (0.8 - 5.7)	0.1296	1	0
Tumor Thickness ≥ 6 mm	2.0 (1.0 - 4.0)	0.0503	2	0
Podoplanin expression	1.9 (0.6 - 5.6)	0.2595	1	0
Lymphovascular Invasion	1.9 (1.0 - 3.6)	0.0673	2	0
Age > 80	1.8 (1.2 - 2.9)	**0.0110**	1	0
Tumor Size ≥ 2 cm	1.8 (1.3 - 2.6)	**0.0006**	4	0
Age > 70	1.8 (1.2 - 2.7)	**0.0045**	1	0
Perineural invasion	1.8 (1.4 - 2.3)	**<0.0001**	7	1.81
Poor Differentiation	1.6 (1.1 - 2.4)	**0.0231**	5	5.91
Male Sex	1.5 (1.0 - 2.3)	**0.0443**	4	0
Location on Lip	1.5 (0.8 - 2.7)	0.2193	3	0
Location on Ear	1.3 (1.1 - 1.6)	**0.0006**	3	8
Age > 78	1.1 (1.0 - 1.1)	**0.0500**	1	0
Location on Scalp	1.0 (1.0 - 1.1)	0.4104	1	0
Invasion Beyond Subcutaneous Fat	1.0 (0.1 - 12.4)	0.9906	2	0
Cortactin	0.9 (0.6 - 1.5)	0.7420	1	0
FAK expression	0.7 (0.5 - 1.2)	0.2145	1	0
Solid Organ Transplant	0.6 (0.3 - 1.5)	0.2920	1	0

Locoregional recurrence

Risk Factor	*Risk ratio (95% CI)*	*p-value*	*Number of Studies*	I^2
Lymphovascular Invasion	3.3 (0.8 - 13.0)	0.0945	3	14.8
Immunosuppression	2.9 (2.0 - 4.2)	**<0.0001**	4	0
Poor Differentiation	2.6 (1.7 - 4.0)	**<0.0001**	3	0
Perineural invasion	1.5 (0.8 - 3.1)	0.2314	4	46.3
Smoker	1.0 (0.2 - 4.4)	0.9826	1	0

Local recurrence, nodal metastasis, or distal metastasis

Risk Factor	*Risk ratio (95% CI)*	*p-value*	*Number of Studies*	I^2
Perineural invasion	6.5 (2.0 - 20.9)	**0.0016**	2	0
Invasion Beyond Subcutaneous Fat	4.7 (2.5 - 8.8)	**<0.0001**	1	0
Immunosuppression	2.2 (0.4 - 13.2)	0.3757	2	0
Tumor Budding	2.2 (1.1 - 4.1)	**0.0205**	1	0
Location on Ear	1.4 (0.1 - 14.9)	0.7600	1	0
Location on Lip	1.4 (0.5 - 3.9)	0.4700	1	0
Age > 70	1.3 (0.5 - 3.6)	0.6400	1	0
tumor size ≥ 4 cm	1.2 (0.6 - 2.4)	0.5100	1	0
Poor Differentiation	1.2 (0.7 - 2.1)	0.4900	1	0
Tumor Thickness ≥ 2 mm	1.0 (0.5 - 1.9)	0.9500	1	0
Female sex	1.0 (0.9 - 1.0)	0.2200	1	0
Tumor Size ≥ 2 cm	0.5 (0.4 - 0.8)	**0.0007**	1	0

Local recurrence, nodal metastasis, or disease specific death

Risk Factor	*Risk ratio (95% CI)*	*p-value*	*Number of Studies*	I^2
Perineural invasion	6.7 (3.2 - 14.3)	**<0.0001**	1	0
Poor Differentiation	4.3 (2.2 - 8.4)	**<0.0001**	2	0
Location on Ear or Lip	2.8 (1.0 - 7.5)	**0.0456**	1	0

Immunosuppression	2.7 (0.7 - 10.1)	0.1385	2	0
Tumor Thickness ≥ 6 mm	2.6 (1.3 - 5.3)	**0.0090**	1	0
Invasion Beyond Subcutaneous Fat	2.2 (0.9 - 5.6)	0.0954	1	0
Male Sex	2.1 (0.6 - 7.3)	0.2249	1	0
Tumor Size ≥ 2 cm	0.8 (0.1 - 10.2)	0.8724	2	0
Tumor Size ≥ 4 cm	0.5 (0.1 - 3.7)	0.5072	1	0

eTable 3. Incidence proportion for each risk factor modality per outcome across all studies

Risk Factor	Outcome	Total N	Incidence Rate	Lower 95% Confidence Inteval	Upper 95% Confidence Inteval	I^2	Number of Studies
			Local recurrence				
Tumor Thickness > 8 mm	*Local Recurrence*	8	0.250	0.063	0.623	0.0	1
Desmoplasia	*Local Recurrence*	381	0.197	0.068	0.450	0.0	3
Perineural Invasion	*Local Recurrence*	503	0.187	0.132	0.259	0.0	12
Invasion beyond subcutaneous fat	*Local Recurrence*	89	0.182	0.019	0.723	0.0	2
Lymphovascular Invasion	*Local Recurrence*	28	0.170	0.078	0.333	0.0	4
Growth Rate > 4 mm/month	*Local Recurrence*	37	0.162	0.075	0.317	0.0	1
Location on Ear	*Local Recurrence*	357	0.140	0.074	0.249	0.0	5
Ulceration	*Local Recurrence*	19	0.111	0.072	0.167	26.5	3
HIV	*Local Recurrence*	9	0.111	0.015	0.500	0.0	1
CLL	*Local Recurrence*	341	0.098	0.053	0.175	0.0	3
Age > 75	*Local Recurrence*	356	0.084	0.060	0.118	0.0	1
Solid Organ Transplant	*Local Recurrence*	1764	0.084	0.028	0.223	13.3	5
Poor Differentiation	*Local Recurrence*	700	0.083	0.046	0.145	16.8	8
Location on Scalp	*Local Recurrence*	431	0.075	0.049	0.113	48.1	4
Location on Lip	*Local Recurrence*	376	0.068	0.046	0.098	0.0	4
Immunosuppression	*Local Recurrence*	1470	0.067	0.037	0.117	15.3	10
Hematologic Malignancy	*Local Recurrence*	446	0.063	0.044	0.089	0.0	1
Tumor Size > 2 cm	*Local Recurrence*	1327	0.057	0.016	0.185	4.0	4
Non-Hodgkins Lymphoma	*Local Recurrence*	608	0.056	0.029	0.103	0.0	2
Male Sex	*Local Recurrence*	1466	0.055	0.037	0.081	0.0	6
Location on Head and Neck	*Local Recurrence*	1195	0.054	0.032	0.091	0.0	3
Tumor Size > 5 cm	*Local Recurrence*	40	0.050	0.013	0.179	7.5	1
Tumor Thickness > 2 mm	*Local Recurrence*	277	0.047	0.016	0.128	0.0	2
Age > 60	*Local Recurrence*	856	0.045	0.023	0.089	0.0	2
Tumor Thickness > 4 mm	*Local Recurrence*	112	0.045	0.019	0.103	0.0	1
Age > 70	*Local Recurrence*	655	0.035	0.023	0.052	0.0	1
Age > 80	*Local Recurrence*	417	0.031	0.018	0.053	0.0	1
Location on Ear or Lip	*Local Recurrence*	108	0.028	0.009	0.083	0.0	1
Age > 65	*Local Recurrence*	1049.02	0.017	0.011	0.027	0.0	1
Acantholytic Subtype	*Local Recurrence*	103	0.010	0.001	0.066	0.0	1
			Nodal Metastasis				
Perineural or vascular involvement	*Nodal Metastasis*	25	0.544	0.085	0.939	12.4	3

Podoplanin	*Nodal Metastasis*	23	0.522	0.325	0.712	0.0	1
HER-3 Positive	*Nodal Metastasis*	48	0.500	0.362	0.638	0.0	1
Lymphovascular Invasion	*Nodal Metastasis*	71	0.445	0.244	0.665	24.1	6
EGFR-positive	*Nodal Metastasis*	47	0.401	0.162	0.698	0.0	2
Membrane E-cadherin	*Nodal Metastasis*	26	0.385	0.221	0.579	0.0	1
Cytoplasm E-Cadherin	*Nodal Metastasis*	16	0.375	0.179	0.623	0.0	1
HER-4 Positive	*Nodal Metastasis*	26	0.346	0.191	0.543	0.0	1
Tumor Thickness > 8 mm	*Nodal Metastasis*	28	0.325	0.071	0.753	0.0	2
Tumor Budding	*Nodal Metastasis*	51	0.275	0.170	0.412	0.0	1
Growth Rate > 4 mm/month	*Nodal Metastasis*	37	0.243	0.132	0.405	0.0	1
CLL	*Nodal Metastasis*	57	0.240	0.083	0.524	0.0	2
Diabetes	*Nodal Metastasis*	9	0.222	0.056	0.579	0.0	1
Cytokeratin 19 expression	*Nodal Metastasis*	42	0.214	0.115	0.363	0.0	1
Tumor Thickness > 5 mm	*Nodal Metastasis*	52	0.212	0.121	0.343	0.0	1
Tumor Thickness > 4 mm	*Nodal Metastasis*	68	0.206	0.126	0.318	0.0	1
Hematologic Malignancy	*Nodal Metastasis*	5	0.200	0.027	0.691	0.0	1
Poor Differentiation	*Nodal Metastasis*	719	0.184	0.120	0.272	1.7	11
HIV	*Nodal Metastasis*	2	0.167	0.010	0.806	0.0	1
Desmoplasia	*Nodal Metastasis*	145	0.166	0.113	0.235	0.0	1
Invasion beyond subcutaneous fat	*Nodal Metastasis*	90	0.163	0.028	0.565	2.9	4
Perineural Invasion	*Nodal Metastasis*	641	0.152	0.107	0.212	0.0	16
Tumor Size > 4 cm	*Nodal Metastasis*	7	0.143	0.020	0.581	0.0	1
Location on Lip	*Nodal Metastasis*	353	0.140	0.048	0.346	0.0	4
Tumor Thickness > 3 mm	*Nodal Metastasis*	23	0.130	0.043	0.335	0.0	1
Location on Ear	*Nodal Metastasis*	373	0.117	0.071	0.188	13.5	5
Male Sex	*Nodal Metastasis*	945	0.100	0.034	0.260	5.2	5
Age > 75	*Nodal Metastasis*	356	0.093	0.067	0.128	0.0	1
Tumor Size > 2 cm	*Nodal Metastasis*	1399	0.083	0.029	0.216	0.0	5
Location on Scalp	*Nodal Metastasis*	413	0.077	0.054	0.110	0.0	5
Age > 80	*Nodal Metastasis*	87	0.069	0.031	0.145	0.0	1
Immunosuppression	*Nodal Metastasis*	1452	0.062	0.023	0.158	33.3	9
Location on Ear or Lip	*Nodal Metastasis*	108	0.056	0.025	0.118	0.0	1
Solid Organ Transplant	*Nodal Metastasis*	579	0.049	0.018	0.122	24.2	5
Ulceration	*Nodal Metastasis*	99	0.040	0.015	0.103	0.0	1
Location on Head and Neck	*Nodal Metastasis*	772	0.038	0.027	0.054	0.0	2
Age > 65	*Nodal Metastasis*	1067	0.024	0.017	0.036	0.0	1
Acantholytic Subtype	*Nodal Metastasis*	103	0.010	0.001	0.066	0.0	1
			Distant Metastasis				

CLL	*Distant Metastasis*	42	0.143	0.066	0.283	0.0	1
Solid Organ Transplant	*Distant Metastasis*	16	0.125	0.031	0.386	0.0	1
Tumor Thickness > 2 mm	*Distant Metastasis*	62	0.097	0.044	0.199	0.0	1
Lymphovascular Invasion	*Distant Metastasis*	12	0.083	0.012	0.413	0.0	1
Poor Differentiation	*Distant Metastasis*	286	0.073	0.005	0.565	0.0	2
Location on Head and Neck	*Distant Metastasis*	185	0.070	0.041	0.117	0.0	1
Ulceration	*Distant Metastasis*	62	0.065	0.024	0.160	0.0	1
Male Sex	*Distant Metastasis*	117	0.060	0.029	0.120	0.0	1
Perineural Invasion	*Distant Metastasis*	311	0.057	0.018	0.169	8.8	5
Desmoplasia	*Distant Metastasis*	145	0.041	0.019	0.089	0.0	1
Invasion beyond subcutaneous fat	*Distant Metastasis*	29	0.034	0.005	0.208	0.0	1
Immunosuppression	*Distant Metastasis*	469	0.034	0.003	0.308	0.0	2
Tumor Size > 2 cm	*Distant Metastasis*	1078	0.026	0.001	0.340	0.0	1
Location on Ear or Lip	*Distant Metastasis*	108	0.019	0.005	0.071	0.0	1
Age > 75	*Distant Metastasis*	356	0.017	0.008	0.037	0.0	1
Age > 65	*Distant Metastasis*	1067	0.011	0.006	0.020	0.0	1
			Any Metastasis				
40-GEP high risk	*Any Metastasis*	24	0.625	0.422	0.792	0.0	1
Invasion beyond subcutaneous fat	*Any Metastasis*	14	0.286	0.111	0.561	0.0	1
40-GEP intermediate risk	*Any Metastasis*	87	0.207	0.134	0.305	0.0	1
Perineural Invasion	*Any Metastasis*	142	0.206	0.127	0.316	0.0	2
Poor Differentiation	*Any Metastasis*	338	0.138	0.051	0.321	0.0	5
Location on Ear	*Any Metastasis*	9363	0.102	0.031	0.286	0.0	5
Immunosuppression	*Any Metastasis*	150	0.084	0.033	0.197	0.0	3
Location on Ear or Lip	*Any Metastasis*	83	0.072	0.033	0.152	0.0	1
Age > 60	*Any Metastasis*	739	0.060	0.045	0.079	0.0	1
Tumor Thickness > 4 mm	*Any Metastasis*	103	0.058	0.026	0.124	0.0	1
Tumor Size > 2 cm	*Any Metastasis*	130	0.054	0.026	0.109	0.0	1
Age > 70	*Any Metastasis*	655	0.053	0.039	0.074	0.0	1
Male Sex	*Any Metastasis*	61637	0.050	0.017	0.137	0.0	5
Ulceration	*Any Metastasis*	69	0.043	0.014	0.126	0.0	1
Tumor Thickness > 2 mm	*Any Metastasis*	415	0.043	0.027	0.068	0.0	1
Desmoplasia	*Any Metastasis*	177	0.040	0.019	0.081	0.0	1
Solid Organ Transplant	*Any Metastasis*	1496	0.039	0.017	0.090	0.0	3
Location on Scalp	*Any Metastasis*	15843	0.037	0.011	0.112	0.0	3
Location on Lip	*Any Metastasis*	1722	0.034	0.014	0.078	0.0	3
Non-Hodgkins Lymphoma	*Any Metastasis*	134	0.030	0.011	0.077	0.0	1
Location on Head and Neck	*Any Metastasis*	765	0.026	0.017	0.040	0.0	1

Age > 80	*Any Metastasis*	47583	0.026	0.006	0.109	0.0	2
Age > 90	*Any Metastasis*	11393	0.011	0.009	0.013	0.0	1
			Disease Specific Death				
Lymphovascular Invasion	*Disease Specific Death*	12	0.333	0.131	0.624	0.0	1
Invasion beyond subcutaneous fat	*Disease Specific Death*	78	0.263	0.148	0.424	0.0	3
Tumor diameter > 50 mm	*Disease Specific Death*	83	0.157	0.093	0.251	0.0	1
Desmoplasia	*Disease Specific Death*	214	0.142	0.056	0.315	44.2	2
CLL	*Disease Specific Death*	65	0.128	0.006	0.772	0.0	2
Poor Differentiation	*Disease Specific Death*	720	0.096	0.037	0.229	24.0	5
Perineural Invasion	*Disease Specific Death*	394	0.095	0.063	0.141	0.0	6
Tumor thickness > 6 mm	*Disease Specific Death*	318	0.082	0.056	0.117	0.0	1
Location on Ear	*Disease Specific Death*	318	0.058	0.016	0.193	0.0	2
Location on Lip	*Disease Specific Death*	389	0.043	0.020	0.091	0.0	1
Immunosuppression	*Disease Specific Death*	1094	0.037	0.009	0.137	14.0	6
Solid Organ Transplant	*Disease Specific Death*	288	0.030	0.011	0.078	0.0	3
Tumor Size > 2 cm	*Disease Specific Death*	1237	0.028	0.008	0.090	0.0	2
Male Sex	*Disease Specific Death*	765	0.022	0.009	0.054	0.0	1
Location on Head and Neck	*Disease Specific Death*	680	0.019	0.011	0.033	0.0	1
Location on Ear or Lip	*Disease Specific Death*	108	0.019	0.005	0.071	0.0	1
Age > 65	*Disease Specific Death*	1067	0.017	0.011	0.027	0.0	1
			All-Cause Mortality				
CLL	*All Cause Death*	42	0.881	0.744	0.950	0.0	1
Poor Differentiation	*All Cause Death*	19	0.737	0.502	0.886	0.0	1
Immunosuppression	*All Cause Death*	173	0.473	0.152	0.817	14.9	3
Perineural Invasion	*All Cause Death*	48	0.333	0.215	0.477	0.0	1
Location on Lip	*All Cause Death*	297	0.300	0.250	0.354	0.0	1
Solid Organ Transplant	*All Cause Death*	347	0.187	0.139	0.246	0.0	2
Location on Ear	*All Cause Death*	112	0.170	0.111	0.251	0.0	1
			Locoregional Recurrence				

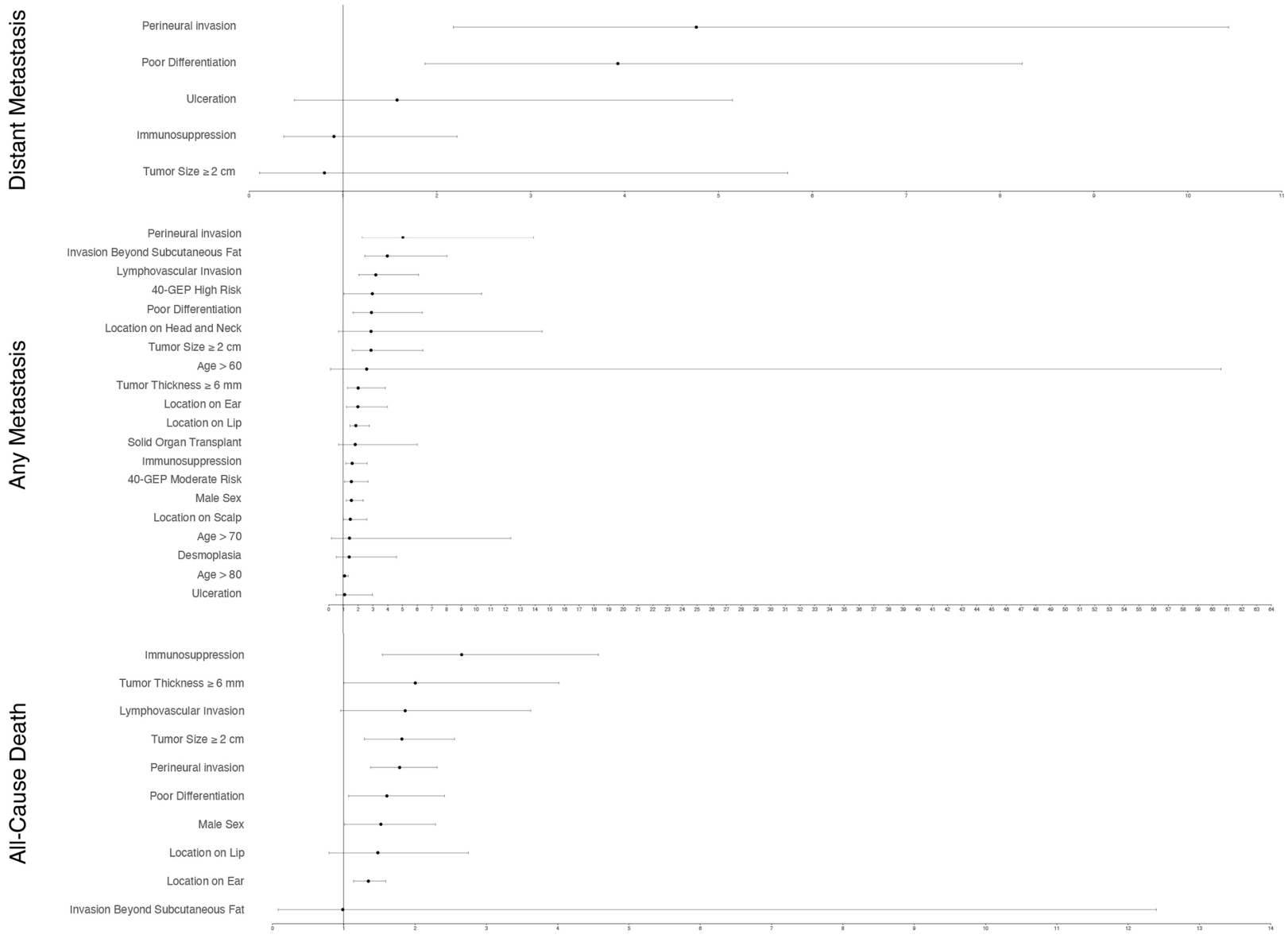
Lymphovascular Invasion	*Locoregional recurrence*	10	0.305	0.099	0.637	0.0	2
Immunosuppression	*Locoregional recurrence*	113	0.242	0.078	0.547	37.0	3
Perineural Invasion	*Locoregional recurrence*	50	0.201	0.112	0.336	0.0	2
Location on Lip	*Locoregional recurrence*	297	0.111	0.080	0.152	0.0	1
Male Sex	*Locoregional recurrence*	168	0.042	0.020	0.085	0.0	1
Smoker	*Locoregional recurrence*	101	0.040	0.015	0.101	0.0	1
	Local Recurrence OR Nodal Metastasis OR Distant Metastasis						
Perineural Invasion	Local Recurrence OR Nodal Metastasis OR Distant Metastasis	32	0.219	0.108	0.393	0	1
	Local Recurrence OR Nodal Metastasis OR Distant Metastasis						
Poor Differentiation	Local recurrence OR Nodal Metastasis OR Distant Metastasis OR Disease Specific Death	29	0.172	0.074	0.353	0.0	1
Invasion beyond subcutaneous fat	Local recurrence OR Nodal Metastasis OR Distant Metastasis OR Disease Specific Death	1	0.167	0.010	0.806	0.0	1
Immunosuppression	Local recurrence OR Nodal Metastasis OR Distant Metastasis OR Disease Specific Death	550	0.159	0.062	0.352	39.0	3
Perineural Invasion	Local recurrence OR Nodal Metastasis OR Distant Metastasis OR Disease Specific Death	6	0.071	0.004	0.577	0.0	1
Tumor Size > 2 cm	Local recurrence OR Nodal Metastasis OR Distant Metastasis OR Disease Specific Death	335	0.036	0.020	0.062	0.0	1
Tumor Size > 4 cm	Local recurrence OR Nodal Metastasis OR Distant Metastasis OR Disease Specific Death	40	0.025	0.004	0.157	0.0	1

eTable 4. Incidence proportion for each treatment modality per outcome across all studies

Treatment	Outcome	Total N	Event Rate	Lower 95% Confidence Interval	Upper 95% Confidence Interval	I^2	Number of Studies
			Local recurrence				
Standard Excision	*Local Recurrence*	1925	0.055	0.032	0.092	0	9
Mohs Micrographic Surgery	*Local Recurrence*	4585	0.026	0.018	0.039	5.267	12
AFL-PDT	*Local Recurrence*	19	0.105	0.026	0.337	0	1
MAL-PDT	*Local Recurrence*	21	0.619	0.402	0.797	0	1
Excision with Whole Section Intraoperative Frozen Section Analysis	*Local Recurrence*	131	0.046	0.021	0.098	0	1
Radiotherapy	*Local Recurrence*	329	0.091	0.049	0.163	0	6
Cryosurgery	*Local Recurrence*	66	0.076	0.027	0.194	0	2
All Non-MMS Modalities	*Local Recurrence*	2491	0.81	0.069	0.094	83.157	20
			Nodal Metastasis				
Standard Excision	*Nodal Metastasis*	1299	0.035	0.01	0.12	0	6
Mohs Micrographic Surgery	*Nodal Metastasis*	2409	0.016	0.06	0.038	0	5
Excision with Whole Section Intraoperative Frozen Section Analysis	*Nodal Metastasis*	131	0.015	0.004	0.059	0	1
Radiotherapy	*Nodal Metastasis*	17	0.176	0.058	0.427	0	1
All Non-MMS Modalities	*Nodal Metastasis*	1316	0.04	0.013	0.111	0	7
			Distant Metastasis				
Standard Excision	*Distant Metastasis*	969	0.015	0.003	0.087	41.773	4
Mohs Micrographic Surgery	*Distant Metastasis*	2646	0.013	0.004	0.037	0	6
			Any Metastasis				

Standard Excision	*Any Metastasis*	681	0.046	0.01	0.19	0	5
Mohs Micrographic Surgery	*Any Metastasis*	3323	0.023	0.008	0.069	0	9
Radiotherapy	*Any Metastasis*	3	0.333	0.043	0.846	0	1
All Non-MMS Modalities	*Any Metastasis*	815	0.394	0.048	0.011	0.189	5
			Disease Specific Death				
Standard Excision	*Disease Specific Death*	814	0.014	0.007	0.025	0	3
Mohs Micrographic Surgery	*Disease Specific Death*	3022	0.009	0.006	0.013	0	5
Radiotherapy	*Disease Specific Death*	34	0.382	0.237	0.553	0	1
All Non-MMS Modalities	*Disease Specific Death*	848	0.041	0.004	0.321	0	4
			All Cause Mortality				
Standard Excision	*All Cause Death*	447	0.359	0.087	0.767	0	2
Mohs Micrographic Surgery	*All Cause Death*	1066	0.16	0.09	0.269	0	2

eFigure 1. Forest plots of results of random effects analysis: risk ratio for each risk factor-and distant metastasis, any metastasis, and all-cause death identified in more than 1 study



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