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Risk factors for metastatic cutaneous squamous cell carcinoma: refinement and replication based on 2 nationwide nested case-control studies

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ABSTRACT

Background: Risk factors for cutaneous squamous cell carcinoma (cSCC) metastasis have been investigated only in relatively small datasets.

Objective: To analyze and replicate risk factors for metastatic cSCC.

Methods: From English and Dutch nationwide cancer registry cohorts, metastatic cases were selected and 1:1 matched to controls. The variables were extracted from pathology reports from the National Disease Registation Service in England. In the Netherlands, histopathologic slides from the Dutch Pathology Registry were revised by a dermatopathologist. Model building was performed in the English dataset using backward conditional logistic regression, whereas replication was performed using the Dutch dataset.

Results: In addition to diameter and thickness, the following variables were significant risk factors for metastatic cSCC in the English dataset (n=1774): poor differentiation (odds ratio (OR) 4.56, 95% CI 2.99-6.94), invasion in (OR 1.69, 95% CI 1.05-2.71)/beyond subcutaneous fat (OR 4.43, 95% CI 1.98-9.90), male sex (OR 2.59, 95% CI 1.70-3.96), perineural/lymphovascular invasion (OR 2.12, 95% CI 1.21-3.71), and facial localization (OR 1.57, 95% CI 1.02-2.41). Diameter and thickness showed significant non-linear relationships with metastasis. Similar ORs were observed in the Dutch dataset (n=434 cSCCs).

Limitations: Retrospective use of pathology reports in the English dataset.

Conclusion: cSCC staging systems can be improved by including differentiation, clinical characteristics such as sex and tumor location, and non-linear relationships for diameter and thickness.

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is one of the most common cancers worldwide with metastatic potential.[1,2] The high incidence of primary cSCC makes it challenging to correctly identify the small percentage (2-5%) of patients who are at high risk of metastasis and would benefit from intense surveillance and/or adjuvant treatment strategies. Studies investigating risk factors for metastasis showed the highest associations for tumors with thickness >6mm, diameter >2cm, poor differentiation, tumor location on temple, ear, or lip, perineural invasion, and immunosuppression.[3-6] However, these studies were mainly based on single-center retrospective cohorts with relatively small numbers of metastatic cSCC, resulting in insufficient power to draw firm conclusions. Brantsch et al. concluded that large independent validation studies (>1500 patients) are needed to reliably assess predictive factors for metastasis.[5] This is also important for further refinement of cSCC staging systems, which have been shown to be suboptimal in stratifying cSCCs by metastasis risk.[7-10] We aimed to analyze important patient- and tumor-based risk factors for metastasis using the largest dataset, to our knowledge, of metastatic cSCC so far and thereafter to replicate our results in a geographically separate patient population.

METHODS

Study design

We conducted 2 nested case-control studies using data from England and the Netherlands. Cases and controls were 1:1 matched on minimum follow-up time. Follow-up time for cases ended on the date of metastasis and, for controls, on the date of death or end of follow-up, whichever occurred first. Metastases from potential other sources than skin or unknown origin were excluded.

Patient populations

Main analyses (England)

Data from all patients with a histopathologically diagnosed primary cSCC with diagnosis and excision between January 1, 2013 and December 31, 2015, were included from the National Disease Registration Service (NDRS), England.[11] Patient inclusion and metastasis selection procedures have been described previously.[11,12] In short, patients with metastatic cSCC (cases) were identified by using an extensive algorithm and all identified reports were reviewed by ZCV with second opinion from BR in ambiguous cases. Thereafter, controls were randomly selected from patients with a cSCC in 2013 with no metastasis occurrence until end of follow-up (December 31, 2015).

Replication (the Netherlands)

Cases and controls were selected from a Dutch nationwide cohort of patients with a histopathologically confirmed first primary cSCC in 2007/2008, as registered by the Netherlands Cancer Registry (NCR), which has been linked to the nationwide network and registry of histo- and cytopathology (PALGA) for retrieval of subsequent and metastatic cSCCs up to December 31, 2018. The selection of metastatic cSCCs has been described before.[10] In summary, metastases were identified using an algorithm based on the pathology reports, after which all selected reports from potential cases were reviewed manually and non-metastatic controls were selected from the remaining patients.

Predictors

In the English dataset, patient characteristics were derived from the Patient Administration Systems (PAS). To assess for immunosuppression, registry data and Hospital Episode Statistics were analyzed for diagnosis/operation codes associated with solid organ transplantations or hematologic malignancies before the date of primary tumor diagnosis or within 183 days. In the Dutch dataset, age, sex, and data on hematologic malignancies were derived from the NCR and data on solid organ transplantations through linkage with the Netherlands Organ Transplant Registry (NOTR).[13] Number of previous cSCCs were retrieved from pathology reports and counted manually for each patient until the occurrence of the case or corresponding control.

All tumor characteristics were extracted from pathology reports for the English dataset and included: tumor location (face, scalp/neck, and trunk/limbs), macroscopic diameter as measured by a pathologist in mm, thickness in mm, differentiation grade (good/moderate vs poor/undifferentiated), morphology (acantholytic/desmoplastic/spindle vs none), perineural and/or lymphovascular invasion (yes/no), and a variable on the extent of tissue involvement (dermis/subcutaneous fat/beyond subcutaneous fat [i.e. in muscle/cartilage/bone]). If invasion depth was not stated in the pathology report, the tumor was assumed as not invading beyond subcutaneous fat. If a tumor was described as a "minimally invasive cSCC," it was assumed to be less than Clark level 5 and well differentiated. The used method for measuring thickness was assumed to follow the Royal College of Pathologists (RCPath) guidance.[14]

In the Netherlands, formalin-fixed paraffin-embedded (FFPE) specimens of the excisions of all cases and controls were retrieved from the pathology archives. A new histopathologic slide was scored by a dermatopathologist (ALM) who was blinded for the outcome of the aforementioned predictors. Tumor diameter was the only variable extracted from the pathology reports, comprising the macroscopic diameter as measured by the pathologist. Tumor thickness was measured according to Breslow criteria from the

granular layer of the skin to the deepest point of the tumor. Differentiation grade was scored following the adjusted Broder's classification system[15] (<25% undifferentiated cells: well, 25-75% undifferentiated cells: moderate, >75% undifferentiated cells: poor differentiation). In our analyses, we dichotomized differentiation grade into good/moderate differentiation vs poor differentiation.

Statistical analysis

Conditional logistic regression analyses with backward stepwise selection identified the set of statistically significant metastasis risk factors in the English dataset. A 2-sided statistical significance level of p=0.10 was used in the backward stepwise selection to reduce optimism and selection bias. Variance inflation factors were calculated, with no evidence for multicollinearity. Missing values for covariates were imputed 20 times using multivariate imputation by chained equations (MICE). The imputation model included all covariates, the outcome, and, for the English dataset, ethnicity and deprivation as auxiliary variables. For the continuous variables age, number of previous cSCCs, diameter, and thickness, restricted cubic splines with 3 knots were used to evaluate a possible non-linear relationship with the metastasis outcome. To facilitate interpretation, non-linear variables were categorized into clinically relevant categories based on two criteria: (1) increase of at least 2 odds ratio (OR) points per category per variable and (2) as little as possible overlap between the confidence intervals (CIs) of the categories within a variable. For comparison purposes, we categorized diameter and thickness following the American Joint Committee on Cancer 8th edition (AJCC8)[16] criteria and for diameter using the Brigham and Women's Hospital (BWH)[17] staging system. Since the BWH classification does not specify any criteria for thickness, this was included as a continuous variable. The discriminative ability of the final set of risk factors was assessed by Harrell's concordance index (c-index) in the main analyses. The final risk factors were replicated in the Dutch dataset to see if similar ORs would be found. The c-indices of the models could not be compared, because no absolute risk model was available. Our model fit was compared with that of the AJCC8 and BWH using Nagelkerke's pseudo R-squared measure, which explains the improvement in model likelihood over a null model and can be used to compare different models using the same dataset.[18] This measure ranges from 0 to 1 and the higher, the better the model predicts the outcome.

Ethical approval and informed consent were not required for analyzing data from the NDRS following section 251 of the NHS act 2006.[19] Approval was obtained by the scientific committees of the NCR, PALGA, Dutch Transplant Foundation, and a waiver of informed consent was granted by the Erasmus Medical Center (MEC-2020-0147). Statistical analyses were performed using SPSS 25.0 statistical software (SPSS Inc) and R statistical software version 3.4.1 with the clogit package (R Core Team, 2017).

RESULTS

In total, 887 metastatic cases and 887 non-metastatic controls (n=1774) were included from the English dataset for the main analyses, and 217 cases and 217 controls (n=434) were included from the Dutch dataset for the replication analyses (Table 1, Supplementary eFigure 1).

Table 1. Descriptive characteristics of the English (n=1774) and Dutch dataset (n=434), stratified by metastasis outcome.

Characteristic	English dataset		Dutch dataset	
	Metastatic cases (n=887) (%)	Non-metastatic controls (n=887) (%)	Metastatic cases (n=217) (%)	Non-metastatic controls (n=217) (%)
Follow-up duration (years), median [IQR]	0.50 [0.21-0.92]	2.49 [2.25-2.74]	0.74 [0.33-1.71]	0.77 [0.34-1.74]
Sex				
- **Male**	696 (78.5)	568 (64.0)	156 (71.9)	127 (58.5)
- **Female**	191 (21.5)	319 (36.0)	61 (28.1)	90 (41.5)
Age (years), median [IQR]	80.8 (73.4-86.6)	79.7 [72.7-86.4]	78.0 [70.0-84.0]	76.0 [67.0-81.0]
Previous cSCC				
- **0**	663 (74.7)	666 (75.1)	121 (55.8)	133 (61.3)
- **1**	121 (13.6)	147 (16.6)	33 (15.2)	31 (14.3)
- **>1**	103 (11.6)	74 (8.3)	63 (29.0)	53 (24.4)
Immunosuppressed				
- **No**	791 (89.2)	810 (92.4)	186 (85.7)	187 (86.2)
- **Yes**	96 (10.8)	77 (8.7)	31 (14.3)	30 (13.8)
Site of primary cSCC				
- **Trunk + limbs**	197 (22.2)	316 (35.6)	38 (17.5)	83 (38.2)
- **Face**	505 (56.9)	406 (45.8)	151 (69.6)	110 (50.7)
- **Scalp + neck**	185 (20.9)	162 (18.3)	25 (11.5)	24 (11.1)
- **Missing**	0 (0.0)	3 (0.3)	3 (1.4)	0 (0.0)
Site of first metastasis				
- **Neck/parotid**	669 (75.4)	NA	150 (69.1)	NA
- **Axilla**	123 (13.9)	NA	23 (10.6)	NA
- **Groin**	88 (9.9)	NA	8 (3.7)	NA
- **Distant metastasis**	5 (0.6)	NA	2 (0.9)	NA
- **Other**[1]	2 (0.2)	NA	34 (15.7)	NA
Tumor diameter				
- **Mean in mm (SD)**	29.7 (20.9)	14.1 (9.4)	19.2 (13.9)	11.1 (6.3)
- **Missing**	26 (2.9)	28 (3.2)	16 (7.4)	2 (0.9)

Characteristic	English dataset		Dutch dataset	
	Metastatic cases (n=887) (%)	Non-metastatic controls (n=887) (%)	Metastatic cases (n=217) (%)	Non-metastatic controls (n=217) (%)
Tumor thickness				
- **Mean in mm (SD)**	9.4 (8.1)	3.6 (2.6)	5.8 (4.7)	3.5 (2.2)
- **Missing**	66 (7.4)	85 (9.6)	9 (4.1)	2 (0.9)
Differentiation grade				
- **Well/moderate**	402 (45.3)	757 (85.3)	161 (74.2)	201 (92.6)
- **Poor/undifferentiated**	474 (53.4)	114 (12.9)	54 (24.9)	16 (7.4)
- **Missing**	11 (1.2)	16 (1.8)	2 (0.9)	0 (0.0)
Tissue involvement				
- **Dermis**	217 (24.5)	463 (52.2)	70 (32.3)	157 (72.4)
- **Subcutaneous fat**	338 (38.1)	122 (13.8)	65 (30.0)	45 (20.7)
- **Beyond subcutaneous fat**[2]	215 (24.2)	22 (2.5)	53 (24.4)	12 (5.5)
- **Missing**	117 (13.2)	280 (31.6)	29 (13.4)	3 (1.4)
Perineural and/or lymphovascular invasion				
- **No**	567 (63.9)	789 (89.0)	166 (76.5)	206 (94.9)
- **Yes**[3]	277 (31.2)	42 (4.7)	40 (18.4)	11 (5.1)
- **Missing**	43 (4.8)	56 (6.3)	11 (5.1)	0 (0.0)
Morphology				
- **None/other subtype**	802 (90.4)	847 (95.5)	191 (88.0)	199 (91.7)
- **Acantholytic /desmoplastic/ spindle**	85 (9.6)	40 (4.5)	26 (12.0)	18 (8.3)

[1]N=27 of 34 metastases from other locations (Dutch dataset) concerned cutaneous metastases.

[2]English dataset: n=132 metastatic cSCCs with invasion in muscle, n=60 with invasion in cartilage and n=16 with invasion in bone. Dutch dataset: n=40 metastatic cSCCs with invasion in muscle, n=3 with invasion in cartilage and n=1 with invasion in bone.

[3]English dataset: n=197 metastatic cSCCs with only perineural invasion, n=67 with only lymphovascular invasion and n=80 with both. Dutch dataset: n=32 metastatic cSCCs with only perineural invasion, n=4 with only lymphovascular invasion and n=4 with both. Abbreviations: IQR, interquartile range; cSCC, cutaneous squamous cell carcinoma; mm, millimeter; SD, standard deviation.

The full model contained 11 risk factors (Supplementary eTable 1). After backward stepwise selection, 7 remained significantly in the final model (Table 2, "English OR", Supplementary eTable 2 for univariable ORs). Poor differentiation (OR 4.56, 95% CI 2.99-6.94), invasion beyond subcutaneous fat (OR 4.43, 95% CI 1.98-9.90), and male sex (OR 2.59, 95% CI 1.70-3.96) had the highest ORs. The associations with perineural/lymphovascular invasion and tumor localization were more modest. Tumor diameter and thickness both showed a non-linear relationship with metastasis and therefore the associations are interpreted using an effect plot (Figure 1 and 2): a diameter up to 20mm corresponded with a maximum OR of 2.0. Tumors larger than 20mm showed a less steep increase in OR with saturation at OR=3.0. Regarding tumor thickness, the OR steeply increased up

to 2.0 for tumors of ≤8mm thickness and, similar to diameter, the increase in OR was less steep for thicker tumors. The discriminative ability of the final model was high (c-index of 0.96 [95% CI 0.95-0.97]). The pseudo R-squared was 0.71 (95% CI 0.65-0.79) compared to 0.50 (95% CI 0.43-0.58) for AJCC8 and 0.59 (95% CI 0.52-0.66) for BWH.

Table 2. Final model with significantly remaining risk factors for metastatic cSCC in the English data, replicated in the Dutch data.

Variable	English OR (95% CI)	Dutch OR (95% CI)
Sex		
- **Female**	1.00	1.00
- **Male**	2.59 (1.70-3.96)	1.95 (1.00-3.79)
Body site		
- **Trunk & limbs**	1.00	1.00
- **Face**	1.57 (1.02-2.41)	2.57 (1.24-5.34)
- **Scalp & neck**	0.74 (0.43-1.27)	1.36 (0.52-3.56)
Diameter	*Spline*	*Spline*
Thickness	*Spline*	*Spline*
Differentation		
- **Good/moderate**	1.00	1.00
- **Poor/undifferentiated**	4.56 (2.99-6.94)	4.26 (1.88-9.66)
Tissue involvement		
- **Dermis**	1.00	1.00
- **Subcutaneous fat**	1.69 (1.05-2.71)	1.97 (0.95-4.06)
- **Beyond subcutaneous fat**	4.43 (1.98-9.90)	4.22 (1.50-11.90)
Perineural/lymphovascular invasion		
- **No**	1.00	1.00
- **Yes**	2.12 (1.21-3.71)	1.87 (0.71-4.92)

Abbreviations: OR, odds ratio; CI, confidence interval.

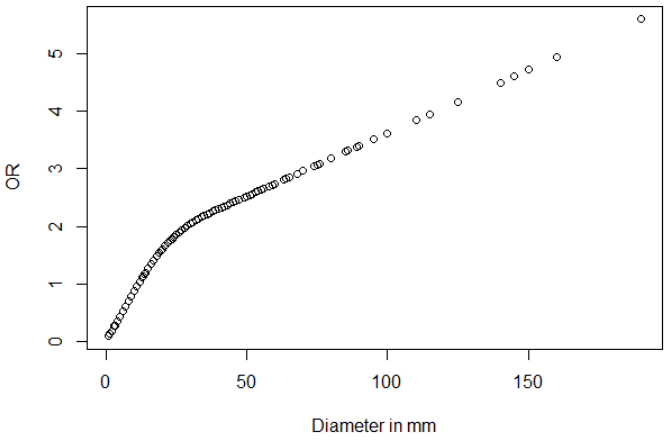

Figure 1. Effect plot of the spline function for diameter with the metastasis outcome.

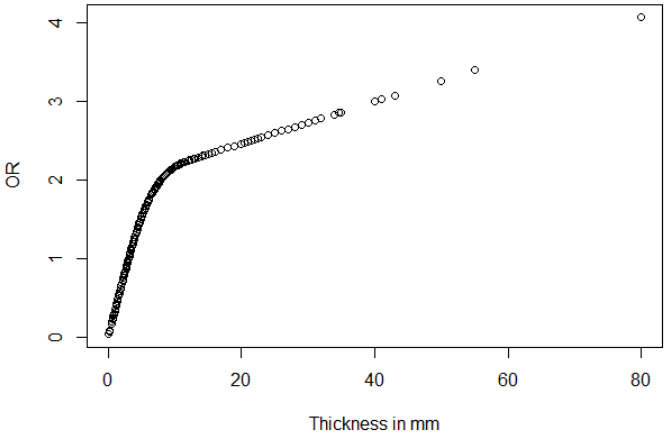

Figure 2. Effect plot of the spline function for thickness with the metastasis outcome.

Categorizations of diameter and thickness

Table 3 ("English OR") shows the categorizations of the continuous variables diameter and thickness into clinically relevant categories as defined a priori, adjusted for all other covariates from the final model. For diameter, the reference category consisted of tumors <15mm, with 15-30mm and ≥30mm producing increasing ORs with distinct CIs: 2.29 (95% CI 1.52-3.47) and 6.82 (95% CI 3.58-13.00), respectively. For thickness, the reference category included all cSCCs with a thickness <3mm, followed by the categories 3.0-8.0mm and ≥8.0mm. Although the ORs per category showed an increasing trend, the CIs were slightly overlapping: 3.21 (95% CI 1.98-5.22) and 5.59 (95% CI 2.75-11.36), respectively. Categorizing the diameter and thickness variables did not change the c-

index nor the pseudo R-squared of our final model. For comparison, ORs for diameter and thickness with cut-off values from the AJCC8 and BWH classifications were also calculated (Supplementary eTable 3).

Table 3. Categorizations for the spline functions of diameter and thickness in the English data, replicated in the Dutch data.

Variable*	English OR (95% CI)	Dutch OR (95% CI)
Diameter		
- **0.0-15 mm**	1.00	1.00
- **15-30 mm**	2.29 (1.52-3.47)	1.95 (1.03-3.70)
- **≥30 mm**	6.82 (3.58-13.00)	7.04 (1.61-30.77)
Thickness		
- **0.0-3.0 mm**	1.00	1.00
- **3.0-8.0 mm**	3.21 (1.98-5.22)	1.33 (0.69-2.57)
- **≥8.0 mm**	5.59 (2.75-11.36)	1.47 (0.55-3.98)

*Adjusted for all covariates in a multivariable model.
Abbreviations: OR, odds ratio; CI, confidence interval; mm, millimeter.

Replication

In the Dutch data, similar effect estimates were observed for all metastasis risk factors (Table 2, "Dutch OR"). The effect plots for the spline functions of diameter and thickness are shown in Supplementary eFigure 2-3. However, replication of the categorized diameter and thickness variables failed to meet our predefined criteria in the multivariable model (Table 3, "Dutch OR"): the diameter categories showed highly overlapping CIs and the thickness categories failed to produce an increasing trend, with almost equal ORs of 1.33 (95% CI 0.69-2.57) and 1.47 (95% CI 0.55-3.98). Nevertheless, univariable analyses showed increasing ORs with increasing diameter and thickness values and the distribution of both variables was distinct between cases and controls, comparable to the pattern observed in the English dataset (Supplementary eTable 4 and eFigure 4). The pseudo R-squared measure of the replicated model was 0.52 (95% CI 0.44-0.74) for the model with splines and 0.48 (95% CI 0.40-0.71) for the model with the categorized diameter and thickness variables compared to 0.25 (95% CI 0.14-0.42) for AJCC8 and 0.36 (95% CI 0.23-0.53) for BWH.

DISCUSSION

We analyzed the most common risk factors for metastatic cSCC using 2 large nationwide datasets. We confirmed the previously found significant associations for diameter, thickness, poor differentiation, deep invasion, and perineural/lymphovascular invasion.

Clinical parameters such as sex and body site were also significant risk factors, while immunocompromised host status did not remain in the model. Replication of our risk factors produced similar effect estimates, supporting our findings.

Compared with previous studies (number of metastatic cSCCs=26-232), we were able to provide more accurate ORs for all risk factors with narrower CIs and thus a greater capability to refine staging systems.[3-6,20] Sex is not included in current staging systems, but was an important risk factor in our study, which was previously also seen for melanoma.[21] This could be due to biological sex differences, delayed presentation, greater UV-exposure secondary to less protection from hair coverage, or outdoor occupations/hobbies. Differentiation grade is included in the BWH but has been omitted from the AJCC8 related to reproducibility issues.[22] We obtained good model discrimination by dichotomizing differentiation grade and believe that by removing the middle category, reproducibility may increase.

Despite being often considered as an independent risk factor for metastatic cSCC, immunosuppression did not remain in our final model.[4-6,10] Possibly, this may be due to immunosuppressed patients having worse tumor characteristics instead of being immunosuppressed itself underlying the higher risk. In our dataset, we confirmed that immunosuppressed patients were significantly more likely to have tumors which invade in/beyond subcutaneous fat and have perineural/lymphovascular invasion (data not shown). Another explanation might be an underestimation of immunosuppressed patients in the English dataset due to the use of diagnostic codes for immune suppression. However, in the Dutch dataset, there was nationwide coverage of organ transplantation and hematologic malignancies and yet immunosuppression still remained insignificant in the model. Lastly, a lack of statistical power could explain this result as only a small proportion of the patients (England: 10%, the Netherlands: 14%) were immunosuppressed.

The continuous variables diameter and thickness have been analyzed with a robust methodological approach using splines. To apply the results easily in clinical practice, variables were categorized thereafter, leaving the c-index of 0.96 unchanged. Although categorization of these variables failed to meet our predefined criteria in the Dutch dataset, the ORs showed a more gradual increase per category, there was less overlap between the CIs, and our model fit was better than the cut-offs from the AJCC8 and BWH. The risk estimates for diameter categories were comparable in both data sets; however, the risk estimates for thickness categories were lower in the Dutch dataset than in the English dataset. This could be due to the smaller sample size and correlation with other variables, as the ORs were increasing for increasing thickness categories in univariable

analyses. Also, the English dataset comprised larger and thicker tumors among cases and controls than the Dutch dataset. This could be due to differences in health care systems and the number of outliers and may also be a reason for the observed differences in the Dutch dataset.

Strengths and limitations

Important strengths are the magnitude of our dataset and the availability of a second geographically separate dataset for replication, which is essential to determine the reproducibility and generalizability.[23] Furthermore, the Dutch dataset contained very few missing values as all histopathological slides were reassessed by a dermatopathologist. Limitations included the use of routine pathology reports and the assumption of reporting according to RCPath standards in the English dataset without a possibility for reassessment of histological slides. An underestimation of thickness could have occurred in both datasets if the tumor was incompletely excised at the bottom. In the English dataset, data on immune status were incomplete and the number of previous cSCCs was assessed during 2013-2015 with incomplete access to earlier years. Moreover, perineural/lymphovascular invasion and several body sites were grouped together owing to otherwise too small sample sizes, which hindered analyzing the effect of each variable separately. Also, no data on nerve diameter were available for perineural invasion. Lastly, our model is not suitable to provide absolute metastasis risks, due to its nested case-control design. The current challenge remains in translating the relative risks of this population-based model into an individual prediction model that provides absolute risks.

Conclusion

Using 2 large nationwide datasets with in total 1104 metastatic cSCCs, we identified patient- and tumor-based risk factors with a c-index of 0.96 in the development dataset. Comparison of our final set of risk factors with the AJCC8 and BWH showed higher pseudo R-squared measures in both datasets. Following tumor diameter and thickness, poor differentiation proved an important risk factor for metastasis, despite being omitted from the AJCC8, thereby emphasizing the importance of reviewing and refining current staging systems.

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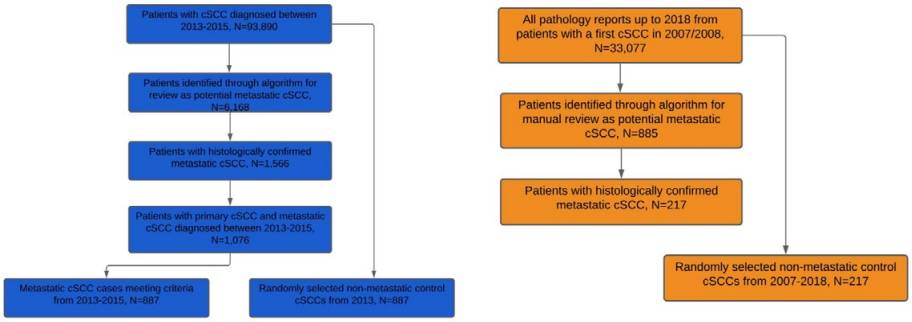
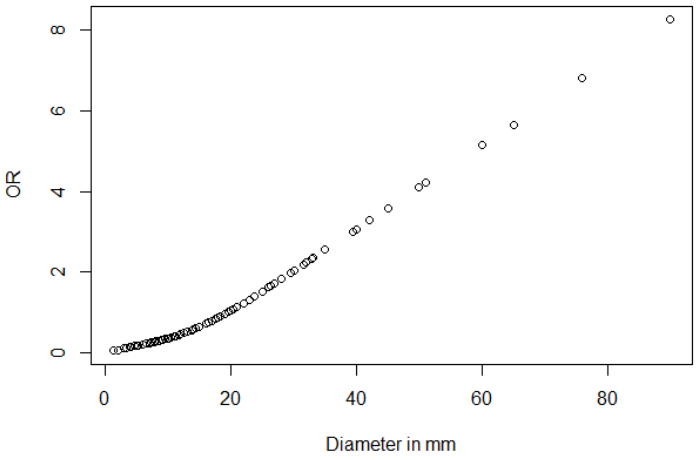
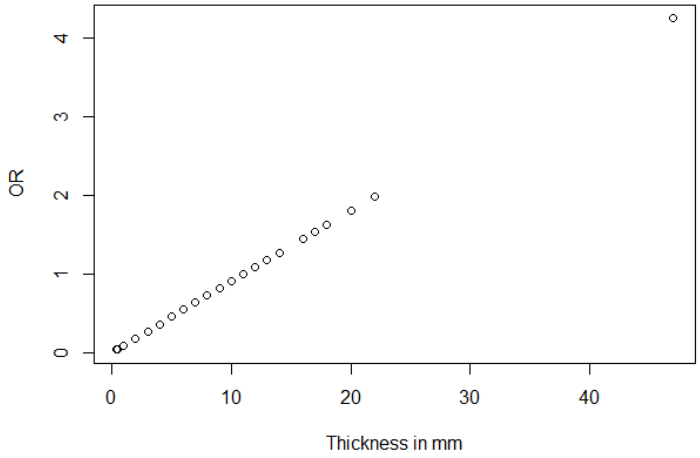
SUPPLEMENTARY MATERIAL



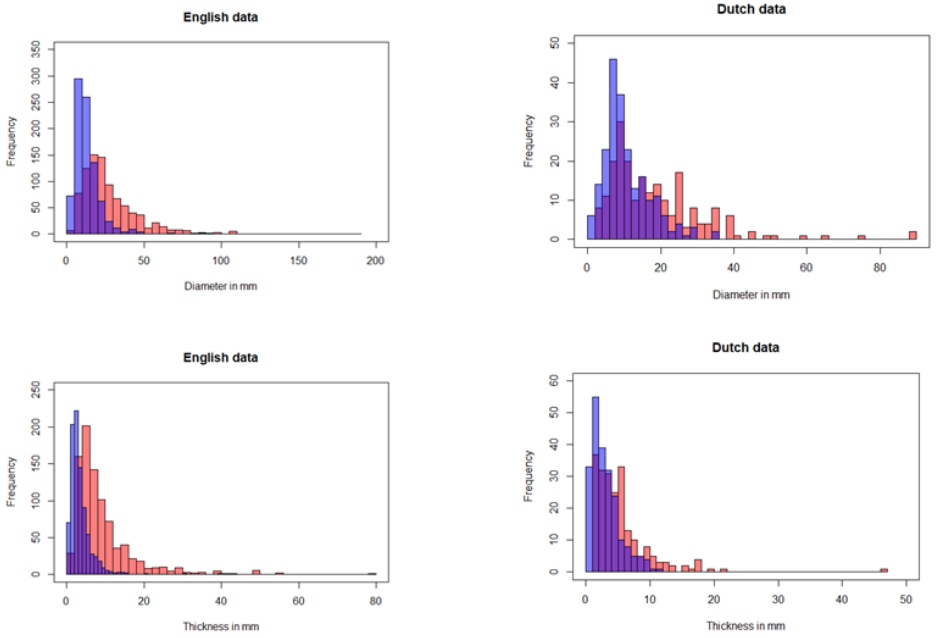
eFigure 1. Flowchart for inclusion of metastatic cases and non-metastatic controls in the English and Dutch data.



eFigure 2. Effect plot of the spline function for diameter with the metastasis outcome in the Dutch data.



eFigure 3. Effect plot of the spline function for thickness with the metastasis outcome in the Dutch data.



eFigure 4. Histograms for diameter and thickness, stratified by cases (pink) and controls (purple) in the English and Dutch data.

eTable 1. Full model including all risk factors in the English data.

Variable	English OR (95% CI)	P-value
Age	0.99 (0.97-1.00)	0.13
Sex		
- **Female**	1.00	
- **Male**	2.50 (1.62-3.85)	<0.001
Previous cSCCs	*Spline*	*0.81*
Immunestatus		
- **Immunocompetent**	1.00	
- **Immunocompromised**	0.78 (0.43-1.40)	0.41
Body site		
- **Trunk & extremities**	1.00	
- **Face**	1.58 (1.02-2.45)	0.04
- **Scalp & neck**	0.73 (0.42-1.27)	0.27
Diameter	*Spline*	*<0.001*
Thickness	*Spline*	*<0.001*
Differentiation		
- **Good/moderate**	1.00	
- **Poor/undifferentiated**	4.46 (2.92-6.80)	<0.001
Tissue involvement		
- **Dermis**	1.00	
- **Subcutaneous fat**	1.67 (1.03-2.73)	0.04
- **Underlying tissue**	4.45 (1.95-10.18)	<0.001
Perineural/lymphovascular invasion		
- **No**	1.00	
- **Yes**	2.18 (1.24-3.84)	0.01
Morphology		
- **None/other**	1.00	
- **Acantholytic/desmoplastic/spindle**	1.44 (0.72-2.88)	0.30

Abbreviations: OR, odds ratio; CI, confidence interval.

eTable 2. Univariable analyses between significantly remaining risk factors in the final model and the metastasis outcome.

Variable	English OR (95% CI)	Dutch OR (95% CI)
Sex		
- **Female**	1.00	1.00
- **Male**	2.01 (1.62-2.48)	1.85 (1.22-2.81)
Body site		
- **Trunk & extremities**	1.00	1.00
- **Face**	1.96 (1.57-2.45)	3.05 (1.87-4.95)
- **Scalp & neck**	1.83 (1.38-2.41)	2.12 (1.06-4.23)
Diameter	*Spline*	*Spline*
Thickness	*Spline*	*Spline*
Differentation		
- **Good/moderate**	1.00	1.00
- **Poor/undifferentiated**	7.56 (5.70-10.03)	3.56 (2.01-6.32)
Tissue involvement		
- **Dermis**	1.00	1.00
- **Subcutaneous fat**	5.87 (4.30-8.03)	3.59 (2.06-6.29)
- **Underlying tissue**	21.88 (12.26-39.05)	11.34 (5.03-25.54)
Perineural/lymphovascular invasion		
- **No**	1.00	1.00
- **Yes**	9.81 (6.54-14.73)	3.91 (2.01-7.61)

Abbreviations: OR, odds ratio; CI, confidence interval.

eTable 3. Odds ratios for metastatic cSCC with diameter and thickness variables following the AJCC8 and BWH criteria in the English data.

Variable[1]	OR (95% CI)
Diameter AJCC8	
- **0.0-19.9 mm**	1.00
- **20-39.9 mm**	2.68 (1.81-3.95)
- **≥40 mm**	7.09 (3.35-15.03)
Thickness AJCC8	
- **0.0-5.99 mm**	1.00
- **≥6.0 mm**	2.14 (1.39-3.30)
Diameter BWH[2]	
- **0.0-19.9 mm**	1.00
- **≥20 mm**	2.42 (1.58-3.71)

[1]Adjusted for all covariates in a multivariable model.
[2]Since BWH has no cut-off criteria for thickness, thickness was included as a continuous variable in multivariable analysis.
Abbreviations: OR, odds ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; mm, millimeter.

eTable 4. Univariable analyses between the categorical diameter and thickness variables and the metastasis outcome in the English and Dutch data.

Variable	English OR (95% CI)	Dutch OR (95% CI)
Diameter		
- **0.0-14.9 mm**	1.00	1.00
- **15.0-29.9 mm**	5.46 (4.06-7.33)	2.50 (1.53-4.06)
- **≥30 mm**	26.68 (17.21-41.35)	16.45 (4.54-59.67)
Thickness		
- **0.0-2.99 mm**	1.00	1.00
- **3.0-7.99 mm**	6.89 (4.75-9.99)	2.62 (1.63-4.21)
- **≥8.0 mm**	45.39 (27.45-75.07)	6.31 (3.20-12.46)

Abbreviations: OR, odds ratio; CI, confidence interval; mm, millimeter.