Development of a clinico-pathological model to estimate the absolute metastasis risk in patients with cutaneous squamous cell carcinoma

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Introduction & Objectives

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer, and it metastasizes in 2-5% of the patients. Clinical staging systems have been developed to stratify patients according to their metastatic risk. However, they do not provide personalized estimates of the absolute metastatic risk, and are insufficient to identify high-risk patients. We developed a model to estimate the probability of metastasis in cSCC patients to support decisions on treatment and surveillance.

Materials & Methods

A nested case-control study was conducted on a well-characterized cohort of 11,137 patients with a histopathologically confirmed first primary cSCC registered in the Netherlands Cancer Registry (NCR), and linked to a nationwide network and registry of histo- and cytopathology (PALGA) for retrieval of subsequent and metastatic cSCCs. Cases who developed metastasis during follow-up were identified (n=195), and matched based on follow-up time and pathology lab to 195 non-metastatic controls. Twenty-two patients with metastasis at baseline were excluded.

A weighted Cox regression model was used to predict the probability of metastasis based on eleven routinely available clinico-pathological variables: sex, age, differentiation grade, number of cSCCs before culprit, tumor diameter, Breslow thickness, presence of perineural (≥1mm) or lymphovascular invasion, tissue involvement, tumor location, morphology type (acantholytic/desmoplastic/spindle versus no/other), and whether the patients had a solid organ transplantation by linkage to the Dutch Organ Transplant Registry or a hematologic malignancy registered by the NCR. Numerical variables were centered. Histopathological characteristics were re-assessed by a dermatopathologist blinded to the outcome. Model predictors were selected using AIC backward selection. Follow-up was truncated at five years. Missing values were imputed with multiple imputation using chained equations. Model performance was assessed using c-index and calibration slope in 100 bootstrapped samples. The calibration slope was used as shrinkage factor of the regression coefficients to improve calibration. Weights for the Cox regression were computed as the inverse of the probability of a patient being sampled from the full cohort, and were used to weigh the performance metrics.

Results

390 cSCC patients were included. Eight out of eleven variables remained in the prediction model (Table 1), including variables that are not used in current staging systems: age, sex, number of cSCCs before culprit and differentiation grade. The model had good discriminative performance (optimism-corrected c-index of 0.81 (95% confidence interval (CI) 0.76-0.85)) and a calibration slope of 0.83 (95% CI 0.64-1.02). Probabilities of metastasis within 5 years can be calculated using the model. For example, the estimated risk probability for a 70-year old male with a 2cm poorly differentiated first cSCC on the face, located in the dermis, without perineural/lymphovascular invasion, is 27%.

Conclusions

The developed clinico-pathological model provides absolute risk predictions for cSCC patients using routinely available risk factors. Once independently validated, the model could be used to predict the individual probability of a patient developing a metastasis within 5 years, and

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possibly guide the management of cSCC patients.

Potential or actual conflicts of interest

Dr.Wakkee participated as speaker/advisory board member/consultant for Sanofi Genzyme, Sunpharma and LEO Pharma. Dr.Bellomo is employed by SkylineDx. The project is co-funded by the PPP Allowance from Health~Holland.

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Keywords

cutaneous squamous cell carcinoma|metastasis|absolute risk prediction model

Attachments

Table 1. Hazard ratios of the prediction model after shrinkage, which can be used to predict risk probabilities within 5 years (baseline survival = 0.972).

Variables	Categories	Hazard ratios (95% Confidence Interval)
Age (in years)		1.03 (1.02-1.05)
Sex	Female	1.00 (reference)
	Male	1.73 (1.23-2.45)
Number of cSCCs before culprit		1.33 (1.28-1.39)
Tumor location	Trunk and extremities	1.00 (reference)
	Scalp/neck	0.54 (0.31-0.93)
	Face	1.32 (0.89-1.95)
Tumor diameter (in cm)		1.76 (1.50-2.07)
Tissue involvement	Dermis	1.00 (reference)
	Subcutaneous fat	1.45 (1.03-2.04)
	Beyond subcutaneous fat	4.21 (2.69-6.59)
Differentiation	Good/moderate	1.00 (reference)
	Poor/undifferentiated	3.89 (2.88-5.26)
Perineural or lymphovascular invasion	Absent	1.00 (reference)
	Present	2.30 (1.53-3.47)

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