

# Personalized follow-up in cutaneous squamous cell carcinoma: integrating a clinicopathological model for absolute metastatic risk into staging systems

Barbara Rentroia-Pacheco, MSc<sup>1</sup>, Lara Pozza MSc<sup>2</sup>, Domenico Bellomo, PhD<sup>2</sup>, Sheril Alex, PhD<sup>2</sup>, Jvalini Dwarkasing PhD<sup>2</sup>, Antien L. Mooyaart, PhD<sup>3</sup>, Loes M. Hollestein, PhD<sup>1,4</sup>, Marlies Wakkee, PhD<sup>1</sup>

<sup>1</sup>Department of Dermatology, Erasmus Medical Center, Rotterdam, The Netherlands <sup>2</sup>SkylineDx B.V., Rotterdam, The Netherlands <sup>3</sup>Department of Pathology, Erasmus University Medical Center, Rotterdam, The Netherlands <sup>4</sup>Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, The Netherlands

## Introduction

Cutaneous squamous cell carcinoma (cSCC) is the 2<sup>nd</sup> most common skin cancer, with a death toll comparable to melanoma, despite its low propensity to metastasize (2%-5%).

Accurate identification of high risk patients remains an unmet need in the field. Therefore, we sought to improve the risk stratification of American Joint Committee on Cancer (AJCC) and the Brigham and Women's Hospital (BWH) staging systems by integrating a recently developed clinicopathological (CP) model predicting absolute metastatic risk.

## Absolute risk model

### Prediction of metastatic risk in patients with cutaneous squamous cell carcinoma (cSCC)

This web-based calculator has been developed by the Skin Cancer Research Group of the Department of Dermatology at the Erasmus MC Cancer Institute in Rotterdam, and validated in an external cohort of cSCC patients, as described in Rentroia-Pacheco et al (2023).

This model has only been developed and validated in cSCC and not in mucosal or genital SCC.

#### Patient characteristics

Age, in years  Sex  Number of prior cSCCs  Tumor location

Age, in years. Patients should be adults (18 years or older)

#### Tumor characteristics

Tumor diameter, in cm  Tissue involvement  Differentiation Grade  Perineural or lymphovascular invasion

Macroscopic tumor diameter, as measured by a pathologist, in centimeters. Decimals are allowed e.g. 2.2

Deepest layer of tissue involvement

Differentiation grade according to the adjusted Broder classification system: good/moderate differentiation 0-75% undifferentiated cells, poor/undifferentiated >75% undifferentiated cells.

Presence of perineural invasion (>=0.1mm) or lymphovascular invasion of any size

Predict

The model is available as a web-based calculator<sup>1</sup>:



## Methods

Nationwide cohort



→ Nested case control cohort (N=390)

Within staging systems low-risk group (AJCC: T1-T2 and BWH: T1-T2a), we tried to discriminate a large fraction of patients with very low metastatic risk from a smaller group with increased risk:

- We computed 5-year metastatic risk with the CP model.
- We binarized the metastatic risk into **CP High-Risk** and **CP Low-Risk**, so as to have a CP Low-Risk, with halved metastatic risk.
- We computed statistics and performance metrics in the intended-use population using weighted metrics, as required by a nested case-control cohort design.

## Results

In the **low-risk group as per AJCC and BWH**, the metastatic risk is about 1%. Within this group:

- **CP Low-Risk patients:**
  - Are 2/3 of the group.
  - Have a very low metastatic risk of about 0.5%.
  - Require a much less intense follow-up regimen.
- **CP High-Risk patients,**
  - Are 1/3 of the group.
  - Have metastatic risk of about 3%.
  - Require regular or more intense follow-up schedules.

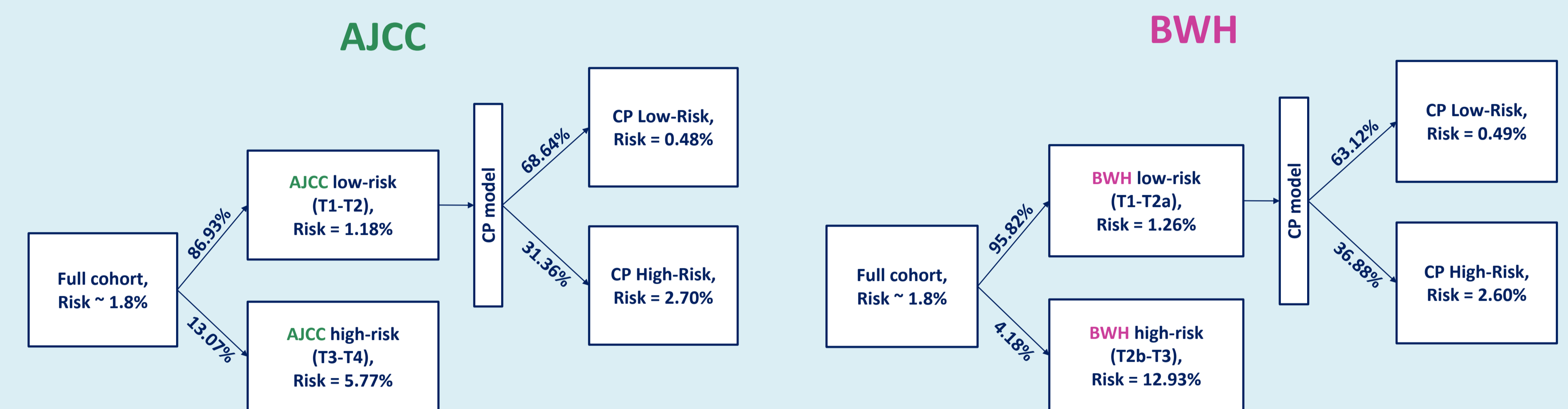


Figure 1 Risk stratification of cSCC patients with the CP model in combination with AJCC and BWH staging systems.

Staging system	NPV	Risk in CP Low-Risk (=100-NPV)	Risk in CP High-Risk (= PPV)	Specificity	Sensitivity	LR+	LR-
AJCC	99.52	0.48	2.70	69.12	71.81	2.33	0.41
BWH	99.51	0.49	2.60	63.61	76.06	2.10	0.38

Negative predictive value (NPV), Positive predictive value (PPV), Likelihood ratio (LR)

Table 1 Performance metrics based on the confusion matrix.

## Conclusion

Our risk model allows for more refined risk stratification within AJCC and BWH low-risk groups, leading to:

- Potentially forgo intensive follow-up regimens in two-thirds of the low-risk patients.
- More personalized decisions about follow-up schedules.
- Improvement in managing healthcare resources, which is very relevant for a cancer with such a high incidence.

## References

1. Rentroia-Pacheco, B., Tokez, S., Bramer, E. M., Venables, Z. C., van de Werken, H. J., Bellomo, D., ... & Wakkee, M. (2023). Personalised decision making to predict absolute metastatic risk in cutaneous squamous cell carcinoma: development and validation of a clinico-pathological model. *EClinicalMedicine*, 63.