Beyond staging systems in cutaneous squamous cell carcinoma: evaluation of two thresholds for a model-estimated metastatic risk

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Category: PS01-21 Risk prediction models for incidence, prognosis, and/or mortality

Background: Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer, therefore causing a death toll comparable to that of melanoma, despite its low propensity to metastasize (2-5%). We recently developed a clinicopathological (CP) model that predicts absolute metastatic risk in cSCC patients. We have recently shown that, in a nationwide Dutch cohort, the model enhances the risk stratification provided by the American Joint Committee on Cancer, eighth edition (AJCC) and the Brigham and Women's Hospital (BWH) staging systems. The current study aims to evaluate the refined risk stratification and designed risk thresholds in an independent, nationwide UK cohort.

Methods: In the Dutch cohort, we defined patients at increased risk within the low-risk group (AJCC: T1-T2, BWH: T1-T2a) as those with an estimated risk above 1%; and in the high-risk group (AJCC: T3-T4, BWH: T2b-T3), as those with a risk above 3.5%. Both risk thresholds were evaluated in the nested case-control (NCC) cohort (n=696), sampled from the nationwide UK cohort (n=31981). The CP model was applied to the NCC cohort and results were binarized as CP Low-Risk or CP High-Risk. Weighted metrics were computed to adjust for the difference in proportion of cases and controls between NCC and nationwide cohorts.

Results: In the low-risk group as per AJCC (T1-T2) and BWH (T1-T2a), the metastatic risk is respectively 0.93% and 1.07%. Within this group, CP High-Risk patients represent respectively 1.69% and 6.11% of the AJCC and BWH groups and have increased metastatic risk of 7.54% in AJCC and 5.36% in BWH. In the high-risk group as per AJCC (T3-T4) and BWH (T2b-T3), the metastatic risk is respectively 7.79% and 13.80%. Within this group, CP High-Risk patients represent respectively 7.42% and 24.40% of the AJCC and BWH groups. They have an increased metastatic risk of 27.92% in AJCC and 24.07% in BWH.

Conclusions: This study validates the designed risk thresholds in an independent nationwide cohort. Differences in performance compared to the Dutch cohort can be explained by the exclusion of patients with multiple missing variables and worse annotation of pathological features in the UK cohort. Additionally, this study confirms that our risk model can enhance cSCC staging systems by a refined risk stratification in both low-risk and high-risk groups. Specifically, the CP High-Risk subgroup within the staging systems' low-risk group might benefit from heightened surveillance and diagnostic

screening, such as lymph node ultrasonography. Similarly, the CP High-Risk subgroup within the staging systems' high-risk group could be considered for intensified surveillance and (adjuvant) treatment. In conclusion, adding the CP model to current cSCC staging systems would enable more personalized decisions about follow-up and treatment, while also facilitating the management of healthcare resources.