Expanding histopathological assessment provides limited prognostic value for metastatic cutaneous squamous cell carcinoma: insights from two nested case-control studies.

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Background: Various refined histopathological factors have been proposed to enhance metastatic risk assessment in patients with cutaneous squamous cell carcinoma (CSCC). Nonetheless, the additional prognostic value of these factors over conventional clinicopathological variables, like invasion depth and differentiation level, are not well-established.

Objective: To evaluate the association between refined histopathological variables and metastasis in CSCC and their value relative to routinely available conventional variables.

Methods: Two nested case-control studies were conducted using data from the Netherlands Cancer Registry and the Dutch Nationwide Pathology Databank (Palga), covering CSCC patients diagnosed between 2007 and 2009 with follow-up until 2021. In the population-based set, 195 primary CSCCs from metastatic patients were matched with 195 non-metastatic controls using incidence density sampling. In the risk-matched set, 250 metastatic cases were matched with 250 non-metastatic controls based on metastatic risk using incidence density sampling. Formalin-fixed, paraffin-embedded tumor blocks from the excisions of both cases and controls were retrieved from the nationwide pathology archives. Pathologists reviewed all retrieved primary CSCCs, evaluating conventional and the following refined histopathological variables: morphological subtype, solar elastosis, peritumoral infiltrate, tumor budding, and mitotic rate. Analyses were conducted using conditional logistic regression.

Results: In the population-based set, multivariable analyses showed no significant associations between refined histopathological variables and metastasis (Table I). In the risk-matched set, severe (OR 0.28; 95%CI 0.09-0.87) and moderate (OR 0.20; 95%CI 0.07-0.56) solar elastosis were negatively associated with metastasis.

Conclusion: The refined histopathological variables morphological subtype, peritumoral infiltrate, tumor budding and mitotic rate do not provide additional prognostic value over conventional risk factors for metastasis in CSCC patients. Further research is needed to clarify the observed negative association with solar elastosis.