

Cutaneous Squamous Cell Carcinoma: Review of the Eighth Edition of the American Joint Committee on Cancer Staging Guidelines, Prognostic Factors, and Histopathologic Variants

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Abstract: Cutaneous squamous cell carcinoma is the second most common form of nonmelanoma skin cancer after basal cell carcinoma and accounts for the majority of nonmelanoma skin cancer-related deaths. In 2017, the American Joint Committee on Cancer revised the staging guidelines of cutaneous squamous cell carcinoma to reflect recent evidence concerning high-risk clinicopathologic features. This update reviews the literature on prognostic features and staging, including the eighth edition of the American Joint Committee on Cancer Staging Manual. A wide range of histopathologic variants of cutaneous squamous cell carcinoma exists, several of which are associated with aggressive behavior. A review of cutaneous squamous cell carcinoma variants, emphasizing diagnostic pitfalls, immunohistochemical findings and prognostic significance, is included. Of note, the eighth edition of the American Joint Committee on Cancer Staging Manual refers to squamous cell carcinoma of the head and neck only.

Key Words: skin, squamous cell carcinoma, AJCC, staging, human papillomavirus, nonmelanoma skin cancer

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Cutaneous squamous cell carcinoma is the second most common cutaneous malignancy, and is frequently associated with chronic sun damage.^{1,2} Approximately 3,500,000 cases of nonmelanoma skin cancer are diagnosed annually in the United States and 20% of them are cutaneous squamous cell carcinomas.³ Cutaneous squamous cell carcinoma is typically a disease of late adulthood; however, children with predisposing genodermatoses including xeroderma pigmentosa and epidermolysis bullosa may also develop this tumor. Cutaneous squamous cell carcinoma affects mainly sun-exposed areas such as the face, scalp, neck, arms, and hands. The majority of the cutaneous squamous cell carcinomas arise in a background of actinic keratosis (Figs. 1A, B). Although cutaneous squamous cell carcinoma occurs predominantly in patients with Fitzgerald skin types I and II, it is the most common skin cancer in dark-skinned patients. Cutaneous squamous cell carcinoma affecting other important locations such as the perianal region, external genitalia, and around the nail

bed appear to be associated with human papillomavirus (HPV).

The current estimated incidence of cutaneous squamous cell carcinoma is 15 to 35/100,000 people per year and is expected to rise 2% to 4% per year owing largely to an aging population and chronic ultraviolet B exposure.^{2,4} Most patients with cutaneous squamous cell carcinoma have an excellent prognosis after surgical clearance. However, there is a subset of cutaneous squamous cell carcinoma that carries increased risk of local recurrence, lymph node metastasis, and disease-specific death. Because of lack of registry data, the exact population-based incidence of poor outcomes is not available. The estimated incidences of lymph node metastasis and disease-specific death are 3.7% to 5.2% and 1.5% to 2.1%, respectively. The number of estimated deaths due to cutaneous squamous cell carcinoma is 3900 to 8800 annually in the United States.⁵ Although the majority are diagnosed in stage I or II, cutaneous squamous cell carcinomas are responsible for the majority of nonmelanoma skin cancer deaths. Several clinical and histologic risk factors are associated with increased risk of local recurrence, lymph node metastasis, and disease-specific death including tumor diameter of 2 cm or larger, invasion of the subcutaneous tissue and beyond, depth of invasion > 6 mm, perineural invasion (especially of large-caliber nerves with diameter of 0.1 mm or more or affecting nerves lying deeper than the dermis), poorly differentiated histology, and location on ear or lip. Recent data show high cure rates for cutaneous squamous cell carcinoma with lymph node metastasis of the head and neck when detected and treated early. Thus, accurate identification of patients with cutaneous squamous cell carcinoma who are at risk for metastasis is beneficial. A limitation of the seventh edition of the American Joint Committee on Cancer (AJCC) seventh staging manual guidelines (AJCC-7) was that T3 and T4 classifications were reserved for tumors with bony invasion, which is rare; therefore the bulk of the poor outcomes occurred in patients with T2 tumors. This made T3 and T4 inconsequential limiting the prognostic utility of the AJCC staging. The changes made in the recently published AJCC eighth edition will hopefully make the 4 tumor stages more distinct, increasing homogeneity, and monotonicity. This will improve the ability to identify the high-risk cutaneous squamous cell carcinomas and consolidate them in the higher stages. The current review is divided in 3 sections, in the first section we examine the prognostic parameters of cutaneous squamous cell carcinoma, although the majority of the studies have been done on cutaneous squamous cell carcinoma of the head and neck, the discussed findings are not limited to cutaneous squamous cell carcinoma of this location. The second section corresponds to a review of changes set forth in the eighth edition of the AJCC staging manual guidelines (AJCC-8). Of note, the guidelines set

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