

## **Cutaneous Squamous Cell Carcinoma Indicators of Biologic Behavior**

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Squamous cell carcinoma, a malignancy of keratinizing epidermal cells, is the second most prevalent form of skin cancer. While most are locally destructive lesions, metastasis does occur in 2 - 5% of all cases. Squamous cell carcinoma may present with a variety of clinical and histologic appearances. These appearances may be used as indicators of biologic behavior and to guide therapy. Anatomic location, tumor size, host immune state, associated conditions, depth of invasion, tumor thickness, histologic grade, perineural invasion have been shown to relate to risk for local recurrence and metastasis.

Squamous cell carcinoma of the lip, ear, genitalia, and perianal skin have a higher risk for metastasis than tumors of other glabrous skin (see Table 1). Rate of metastasis for lip lesions (the vast majority being lower lip tumors) is about 11%. Squamous cell carcinomas less than 1 cm in greatest dimension rarely metastasize. Lesions greater than 2 cm metastasize in % of cases. Immunosuppressed patients have a propensity to develop multiple cutaneous squamous cell carcinomas. This appears to be related to both human papillomavirus infection and ultraviolet light. The multiple tumors also tend to be more aggressive in comparison to lesions in on-immunosuppressed patients. Squamous cell carcinomas arising in association with predisposing conditions such as scars, radiation dermatitis, chronic osteomyelitis, burn scar, xeroderma pigmentosum albinism and discoid lupus erythematosus have an elevated risk for distant metastasis. The rates are 10 to 40%.

Histologic indicators of aggressive behavior include depth of invasion, tumor thickness, histologic grade and presence of perineural invasion (see Table 2). Squamous cell carcinomas may be staged microscopically using the Breslow method usually applied to melanoma. Using this method, Level I, II, and III tumors rarely metastasize. Local nodal metastasis may be expected in up to 20% of Level IV and V tumors. Squamous cell carcinomas extending into skeletal muscle, cartilage or bone have a greater risk for metastasis than those limited to the dermis and subcutaneous fat. Tumor thickness, measuring with an ocular micrometer from the most superficial nucleated tumor cell to the deepest viable tumor cell, is also an accurate predictor of metastasis. Tumors less than 2 mm in

thickness do not metastasize. Lesions 2 to 6 mm thick may recur and metastasize in up to 4.5% of cases. Lesions greater than 6 mm thick metastasize in 15% of cases. The majority of fatal cutaneous squamous cell carcinomas are greater than 10 mm thick. Measured thickness is predictive in lip lesions as well as in tumors of other locations.

Histologic grading of cutaneous squamous cell carcinoma was introduced by Breslow in 1932 (see Table 3). Less than 1% of grade 1 and 2 lesions metastasize. Metastasis occurs in 3.6% of grade 3 lesions and 17% of grade 4 lesions. Well-differentiated squamous cell carcinoma may metastasize in 9.2% of cases and poorly differentiated squamous cell carcinoma in as many as 32%.

Perineural invasion, particularly when present in head and neck squamous cell carcinomas, portends aggressive potential. There is greater local recurrence, risk for cranial nerve and meningeal carcinomatosis, nodal and distant metastasis and death.

Clinical and microscopic staging of cutaneous squamous cell carcinoma is useful in predicting biologic behavior. The majority of lesions are small, superficial, actinic related carcinomas that are locally destructive, but lack risk for distant disease. Local recurrence is a liability, however, in that recurrent lesions have greater potential for aggressive behavior.

**Table 1**

<b>Anatomic Location of Squamous Cell Carcinoma and Risk for Metastasis</b>	
<b>Site</b>	<b>Incidence of Metastasis</b>
Lip	13.7%
Ear	11%
All sites, not otherwise specified	2-5%

**Table 2**

<b>Microscopic Indicators of Metastatic Potential</b>	
Size > 2cm	Poorly differentiated (Broders 3 or 4)

Thickness > 2mm	Perineural invasion
Breslow level IV or V	Immunosuppression
Invasion of muscle, bone, or cartilage	Associated
Anatomic site: Ear, lip, genitalia	Locally recurrent

**Table 3**

<b>Histologic Grading of Cutaneous Squamous Cell Carcinoma</b>		
<b>Broders</b>	<b>UTMCK</b>	<b>Microscopic Appearance</b>
Grade 1	Well differentiated, moderately well differentiated	abundant keratinization, little nuclear anaplasia < 25% undifferentiated cells
Grade 2	Moderately differentiated	50% keratinizing, nuclear anaplasia present < 50% undifferentiated cells
Grade 3	Moderately to poorly differentiated	less than 25% keratinizing, nuclear anaplasia extensive < 75% undifferentiated cells
Grade 4	Poorly differentiated	extensive nuclear anaplasia, little or no keratinization includes spindle cell and undifferentiated carcinomas > 75% undifferentiated cells

**REFERENCES**

Rowe DE, Carroll RJ, Day CL. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. *J Am Acad Dermatol* 1992;26:976-90.

Stein AL, Tahan SR. Histologic correlates of metastasis in primary invasive squamous cell carcinoma of the lip. *J Cutan Pathol* 1994;16-21.

Breuninger H, Black B, Rassner G. Brief scientific reports: microstaging of squamous cell carcinomas. *Am J Cutan Pathol* 1990;94:624-627.

Gregorio CD, Gebbia V, Florena AM, Franco V, Moschella F. Perineural infiltration by cutaneous squamous cell carcinomas of the head and neck. *Anticancer Research* 1995;15:1107-1116.

Johnson TM, Rowe DE, Nelson BR, Swanson NA. Squamous cell carcinoma of the skin (excluding lip and oral mucosa). *J Am Acad Dermatol* 1992;26:467-484.