

Inspection of Deep Tumor Margins for Accurate Cutaneous Squamous Cell Carcinoma Staging

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PRACTICE POINTS

- A proportion of cutaneous squamous cell carcinomas are upgraded from the initial biopsy during Mohs micrographic surgery due to evidence of perineural invasion, bony invasion, or lesser differentiation noted on Mohs stages or debulk analysis.
- Thorough inspection of the deep tumor margins may be required for accurate tumor staging and evaluation of metastatic risk. Cells at the deep margin of the tumor may demonstrate poorer differentiation and/or other higher-risk tumor features than those closer to the surface.
- Tumor staging may be incomplete until the deep margins are assessed to find the most dysplastic and likely clinically relevant cells, which may be missed without evaluation of the debulked tumor.

To the Editor:

Histopathologic analysis of debulk specimens in Mohs micrographic surgery (MMS) may augment identification of high-risk factors in cutaneous squamous cell carcinoma (cSCC), which may warrant tumor upstaging.¹ Intratumor location has not been studied when looking at these high-risk factors. Herein, we report 4 cSCCs initially categorized as well differentiated that were reclassified as moderate to poorly differentiated on analysis of debulk specimens obtained via shave removal.

An 80-year-old man (patient 1) presented with a tender 2-cm erythematous plaque with dried hemorrhagic crusting on the frontal scalp. He had a history of nonmelanoma skin cancers. A biopsy revealed a well-differentiated cSCC, which was upgraded from a T2a tumor to T2b during MMS due to galea involvement. Debulk analysis revealed moderate to poorly differentiated cSCC, with the least-differentiated cells at the deep margin (Figure 1A). Given T2b staging, baseline imaging and radiation therapy were recommended.

A 75-year-old man (patient 2) presented with a 2-cm erythematous plaque on the left vertex scalp with hemorrhagic crusting, yellow scale, and purulent drainage. He had a history of cSCCs. A biopsy revealed well-differentiated invasive cSCC, which was upgraded from a T2a tumor to T2b during MMS due to tumor extension beyond the subcutaneous fat. Examination of the second Mohs stage revealed moderately differentiated cSCC, with the least-differentiated cells at the deep margin, infiltration beyond the subcutaneous fat, and perineural invasion (Figure 1B). Given T2b staging, baseline imaging and radiation therapy were recommended.

An 86-year-old woman (patient 3) presented with a tender 2.4-cm plum-colored nodule on the right lower leg. She had a history of basal cell carcinoma. A biopsy revealed a well-differentiated invasive cSCC staged at T2a. Debulk analysis revealed moderately differentiated cSCC, with the least-differentiated cells

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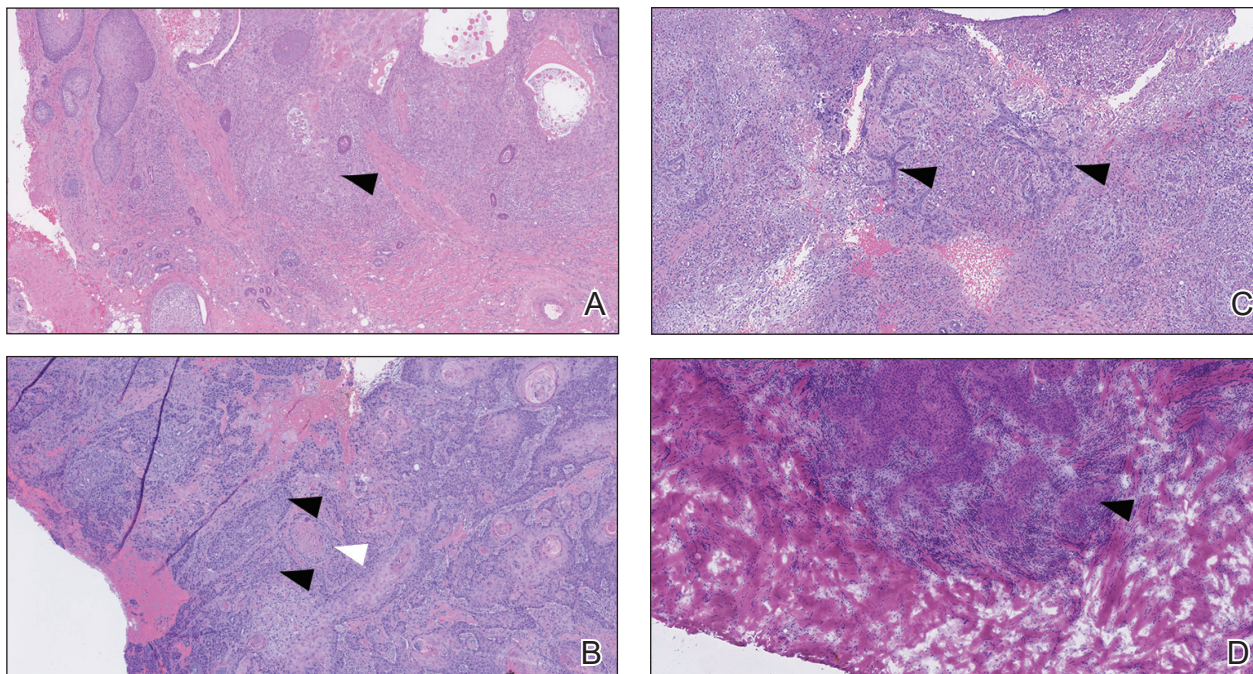


FIGURE 1. A, A deep biopsy revealed a moderately differentiated cutaneous squamous cell carcinoma (cSCC) staged at T2b (patient 1) (H&E, original magnification $\times 50$). B, A moderately differentiated cSCC with perineural invasion staged at T2b (patient 2) (H&E, original magnification $\times 50$). C, A moderately differentiated cSCC staged at T2a (patient 3) (H&E, original magnification $\times 50$). D, A moderately differentiated cSCC staged at T2b (patient 4) (H&E, original magnification $\times 50$). White arrows indicate perineural invasion; black arrows indicate areas of moderate differentiation.

at the deep margin, though the staging remained the same (Figure 1C).

An 82-year-old man (patient 4) presented with a 2.7-cm ulcerated nodule with adjacent scaling on the vertex scalp. He had no history of skin cancer. A biopsy revealed a well-differentiated cSCC (Figure 2) that was upgraded from a T2a tumor to T2b during MMS due to tumor extension beyond the subcutaneous fat. Debulk analysis revealed moderate to poorly differentiated cSCC, with the least-differentiated cells with single-cell extension at the deep margin in the galea (Figure 1D). Given T2b staging, baseline imaging and radiation therapy were recommended.

Tumor differentiation is a factor included in the Brigham and Women's Hospital staging system, and intratumor variability can be clinically relevant for tumor staging.¹ Specifically, cSCCs may exhibit intratumor heterogeneity in which predominantly well-differentiated tumors contain focal areas of poorer differentiation.² This intratumor heterogeneity complicates estimation of tumor risk, as a well-differentiated tumor on biopsy may exhibit poor differentiation at a deeper margin. Our cases highlight that the cells at the deeper margin indeed can show poorer differentiation or other higher-risk tumor features. Thus, the most clinically relevant cells for tumor staging and prognostication may not be visible on initial biopsy, underscoring the utility of close examination of the deep layer of the debulk specimen and Mohs layer for comprehensive staging.

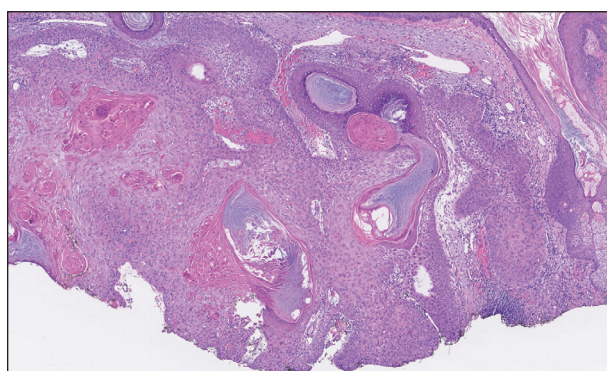


FIGURE 2. The initial biopsy in a patient with an ulcerated nodule with adjacent scaling on the vertex scalp showed a well-differentiated cutaneous squamous cell carcinoma staged at T2a (H&E, original magnification $\times 50$).

Genetic studies have attempted to identify gene expression patterns in cSCCs that predispose to invasion.³ Three of the top 6 genes in this "invasion signature gene set" were matrix metalloproteases; additionally, IL-24 messenger RNA was upregulated in both the cSCC invasion front and in situ cSCCs. IL-24 has been shown to upregulate the expression of matrix metalloprotease 7 in vitro, suggesting that it may influence tumor progression.³ Although gene expression was not included in this series, the identification of genetic variability

in the most poorly differentiated cells residing in the deep margins is of great interest and may reveal mutations contributing to irregular cell morphology and cSCC invasiveness.

Prior studies have indicated that a proportion of cSCCs are histopathologically upgraded from the initial biopsy during MMS due to evidence of perineural invasion, bony invasion, or lesser differentiation noted during MMS stages or debulk analysis.^{1,4} However, the majority of Mohs surgeons report immediately discarding debulk specimens without further evaluation.⁵ Herein, we highlight 4 cSCC cases in which the deep margins of the debulk specimen contained the most dedifferentiated cells. Our findings emphasize the importance of thoroughly examining deep tumor margins for complete staging yet also highlight that identifying cells at these margins may

not change patient management when high-risk criteria are already met.

REFERENCES

1. McIlwee BE, Abidi NY, Ravi M, et al. Utility of debulk specimens during Mohs micrographic surgery for cutaneous squamous cell carcinoma. *Dermatol Surg.* 2021;47:599-604.
2. Ramón y Cajal S, Sesé M, Capdevila C, et al. Clinical implications of intratumor heterogeneity: challenges and opportunities. *J Mol Med.* 2020;98:161-177.
3. Mitsui H, Suárez-Fariñas M, Gulati N, et al. Gene expression profiling of the leading edge of cutaneous squamous cell carcinoma: IL-24-driven MMP-7. *J Invest Dermatol.* 2014;134:1418-1427.
4. Chung E, Hoang S, McEvoy AM, et al. Histopathologic upgrading of cutaneous squamous cell carcinomas during Mohs micrographic surgery: a retrospective cohort study. *J Am Acad Dermatol.* 2021;85:923-930.
5. Alniemi DT, Swanson AM, Lasarev M, et al. Tumor debulking trends for keratinocyte carcinomas among Mohs surgeons. *Dermatol Surg.* 2021;47:1660-1661.