

## Improvements in the Staging of Cutaneous Squamous-Cell Carcinoma in the 7th Edition of the AJCC *Cancer Staging Manual*

Thomas Lardaro, BSc<sup>1</sup>, Sofia M. Shea, MD<sup>1,2</sup>, William Sharfman, MD<sup>1,2,3</sup>, Nanette Liégeois, MD, PhD<sup>1,3,4,6</sup>, and Arthur J. Sober, MD<sup>5</sup>

<sup>1</sup>Johns Hopkins University School of Medicine, Baltimore, MD; <sup>2</sup>Department of Dermatology, Johns Hopkins University, Baltimore, MD; <sup>3</sup>Department of Oncology, Johns Hopkins University, Baltimore, MD; <sup>4</sup>Division of Plastic Surgery, Department of Surgery, Johns Hopkins University, Baltimore, MD; <sup>5</sup>Department of Dermatology, Harvard Medical School, Boston, MA; <sup>6</sup>Department of Otolaryngology, Johns Hopkins Hospital Outpatient Center, Johns Hopkins University, Baltimore, MD

The 7th edition of the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual* includes important improvements to the staging of cutaneous squamous-cell carcinoma (cSCC). In all previous AJCC manuals, cSCC has been staged along with approximately 80 other non-melanoma skin cancers (NMSC). As a result of the diversity in biology and prognosis within the group of NMSC, the previous staging system was irrelevant in staging any particular cutaneous carcinoma with regard to prognosis. The 7th edition features a marked improvement: the NMSC was divided into two chapters. Merkel-cell carcinoma is staged separately in its own chapter, and a new chapter, entitled “Cutaneous Squamous Cell Carcinoma and Other Cutaneous Carcinomas,” was based on evidence-based medicine for cSCC. Other NMSC, excluding Merkel-cell carcinoma, will be staged according to the cSCC guidelines. The development of the cSCC chapter was led by Dr. Nanette Liégeois under the auspice of Dr. Arthur Sober, chair of the NMSC committee.

cSCC poses an important risk to society. In the United States, NMSC is the most frequent cancer. Additionally, the incidence of NMSC has greatly increased since 1960, with some estimates indicating an increased incidence of 3% to 8% per year.<sup>1</sup> cSCC accounts for approximately 20% of all skin cancer deaths.<sup>2</sup> Groups that are at increased risk for developing cSCC include the elderly, the immunosuppressed (especially solid-organ transplant recipients), and

patients with leukemia or lymphoma.<sup>3–5</sup> The 7th edition of the *Cancer Staging Manual* includes a revised evidence-based staging system, which takes into account clinical and histologic features associated with marked mortality. Through the introduction of these changes, surgeons and researchers alike will be better able to ascertain the prognosis and natural history of cSCCs.

There are several notable changes in the 7th edition’s staging of cSCC. The 6th edition of the AJCC *Cancer Staging Manual* did not account for high-risk features. In addition, characteristics such as tumor size >5 cm and extradermal invasion were used as indicators of worse prognosis without strong epidemiological or empirical support. High-risk features now included in the 7th edition are the histologic grade, anatomic site (ear or nonglabrous lip), Clark level  $\geq 4$ , and perineural invasion. The presence of two or more of these high-risk features elevates a T1 tumor to a T2 designation. This change takes into account the tumor characteristics that are likely to predict aggressive behavior and thus have more metastatic potential, irrespective of size. Efforts have also been made in the 7th edition to create greater compatibility between the cSCC staging and the head and neck staging system because most cSCC involve sun-exposed skin, such as the head and neck. These changes include the use of cranial or facial bone involvement and invasion of the skull base or axial skeleton as criteria for the T3 or T4 designation, respectively.

Strict tumor, node, metastasis system criteria preclude the inclusion of clinical risk factors into the staging system. Because data suggest that immunosuppression correlates with worse prognosis, its inclusion as a risk factor was considered by the NMSC task force. Organ transplant

recipients develop cSCC 65 times more frequently compared to age-matched controls.<sup>6</sup> The cSCCs in this population seem to be more aggressive, with an increased tendency to recur and/or metastasize. Boffetta and colleagues pointed out that focusing on size of tumor in immunocompromised patients might be misleading because small tumors can behave aggressively.<sup>7</sup> Although immunosuppression is not incorporated into the staging system, centers are encouraged to collect data on patients' immune status.

The characterization of nodal metastases has also been revised in the 7th edition. In the 6th edition, nodal disease was scored as either present (N1) or absent (N0). The 7th edition categorizes nodal metastases as N0–N3 by using both the size and number of involved nodes. Mounting evidence demonstrates that increased nodal burden correlates with decreased survival.<sup>8</sup> Studies also suggest that patients with increased nodal burden may benefit from more aggressive therapy.<sup>9</sup> Finally, the 7th edition classification of distant metastases remains in the same binary form of “not present” (M0) or “present” (M1).

As a result of the demographics of our aging population and the increased number of transplant patients who are living longer lives, the morbidity and mortality of cSCC is likely to increase over the next several decades. It will be of great importance to predict the prognosis of cSCC to ensure that adequate treatment options are used for the benefit of the patient. The 7th edition staging of cSCC in the *AJCC Cancer Staging Manual* provides tumor-specific staging features supported by the current base of evidence. The recognition of these high-risk factors will permit the further elucidation of the pathological mechanisms underlying the disease process and will encourage coordinated

and consistent collection of data that will be the basis of future improvements.

**ACKNOWLEDGMENT** Dr. Nanette J. Liégeois is supported with a Career Development Award from the Dermatology Foundation. Dr. Nanette J. Liégeois is president and founder of Meridian Skin Care Limited.

## REFERENCES

1. Diepgen TL, Mahler V. The epidemiology of skin cancer. *Br J Dermatol*. 2002;146(Suppl 61):1–6.
2. Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. *J Am Acad Dermatol*. 1992;26:976–90.
3. Ulrich C, Schmook T, Sachse MM, et al. Comparative epidemiology and pathogenic factors for nonmelanoma skin cancer in organ transplant patients. *Dermatol Surg*. 2004;30:622–7.
4. Ramsay HM, Fryer AA, Hawley CM, et al. Factors associated with nonmelanoma skin cancer following renal transplantation in Queensland, Australia. *J Am Acad Dermatol*. 2003;49:397–406.
5. Veness MJ, Quinn DI, Ong CS, et al. Aggressive cutaneous malignancies following cardiothoracic transplantation: the Australian experience. *Cancer*. 1999;85:1758–64.
6. Jensen P, Hansen S, Moller B, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Dermatol*. 1999;40:177–86.
7. Boffetta P, Gridley G, Lindelof B. Cancer risk in a population-based cohort of patients hospitalized for psoriasis in Sweden. *J Invest Dermatol*. 2001;117:1531–7.
8. Andruchow JL, Veness MJ, Morgan GJ, et al. Implications for clinical staging of metastatic cutaneous squamous carcinoma of the head and neck based on a multicenter study of treatment outcomes. *Cancer*. 2006;106:1078–83.
9. Audet N, Palme CE, Gullane PJ, et al. Cutaneous metastatic squamous cell carcinoma to the parotid gland: analysis and outcome. *Head Neck*. 2004;26:727–32.