

GUEST EDITORIAL

Merkel Cell Carcinoma: If No Breslow, Then What?

MICHELLE L. HEATH, MD¹ AND PAUL NGHIEM, MD, PhD^{2*}¹Department of Medicine, Division of Dermatology, University of Washington, Seattle, Washington²Fred Hutchinson Cancer Research Center, Department of Medicine, Division of Dermatology, University of Washington, Seattle, Washington

Merkel cell carcinoma (MCC) is a skin tumor of neuroendocrine origin with a mortality of 33%, the highest of any cutaneous malignancy. Within the United States the estimated annual incidence is increasing and is estimated at 0.44 per 100,000 persons, resulting in roughly 1,000 new cases per year [1]. Several factors may be contributing to this trend, including changes in the major risk factors for this disease: the increasing age of the general population, higher rates of immunosuppression, and increasing sun exposure. Additional likely contributors to the trend include improved detection and reporting. While reported rates have tripled between 1986 and 2001, MCC remains approximately 50-fold less common than melanoma [1]. This rarity has hampered our ability to study this disease systematically. To date there are no controlled trials to assess treatment and outcome. Further obscuring matters is the lack of uniform agreement on staging and treatment. While its high mortality and increasing incidence have brought greater attention to MCC recently, our ability to accurately predict prognosis based on histology remains limited.

Evidence to date supports sentinel lymph node biopsy (SLNB) as the best prognostic indicator. Allen et al. [2] found a significant 5-year disease-specific survival difference between patients clinically staged as node-negative (75% survival) and those pathologically node-negative (97%) by SLNB ($P=0.009$). Further supporting the role of SLNB, Gupta et al. [3] found the 3-year recurrence rate three times higher in patients with a positive SLNB (60%) as compared to those with a negative biopsy (20%) ($P=0.03$). While it is thus clear that SLNB provides important prognostic information, it is certainly not an ideal indicator. In the Allen series 3% of those with a negative biopsy went on to die of MCC and in the Gupta series 20% had recurrence within 3 years. Additionally, SLNB is not performed on all patients. Indeed, technical difficulties may arise that can thwart a successful node biopsy. This is particularly a problem in the head and neck region (the most common

site for MCC) where the facial nerve and parotid anatomy often complicate the procedure. Furthermore, for patients in whom a wide surgical excision has been performed, the ability to identify the true sentinel lymph node is often compromised by disruption of the relevant draining lymphatics. Given the above, it would be very helpful to have independent pathologic predictors.

MCC has been likened to melanoma on several fronts: both are cutaneous neoplasms with aggressive biologic behavior and are associated with sun exposure and advancing patient age. The role of Breslow depth as a prognostic indicator for melanoma is well established. However, for MCC a reproducible histologic prognostic indicator has not emerged in the literature.

In this issue of the *Journal of Surgical Oncology*, Goldberg et al. evaluated the role of histologic depth as a potential prognostic indicator of disease-free and overall survival for patients with MCC. Paraffin-embedded sections were evaluated for tumor thickness and the charts retrospectively reviewed for pertinent clinical data on 60 MCC patients. No correlation was found between tumor thickness and disease-free or overall survival in patients lacking nodal involvement, arguing that "Breslow depth" will not become a useful independent predictor for MCC as it has for melanoma.

Numerous parameters have thus far been evaluated for MCC in the search for a histologic prognostic indicator. Overall tumor size (clinical diameter) was reported by several authors as having significant prognostic capabilities; however, larger studies have failed to find this association [2,3]. Growth patterns, the associated lymphocytic inflammation, cell size, mitotic activity, necrosis, perineural invasion, and a wide array of

*Correspondence to: Paul Nghiem, MD, PhD, University of Washington Medical Center at South Lake Union, 815 Mercer St, Seattle, WA 98109. Fax: 206-221-4364. E-mail: pnghiem@u.washington.edu

Received 6 September 2006; Accepted 6 October 2006

DOI 10.1002/jso.20726

Published online in Wiley InterScience (www.interscience.wiley.com).

immunohistochemical protein expression are among other parameters that have been evaluated and either not found to have a significant association or contradictory findings are described in the literature [4–7].

In terms of tumor depth as related to prognosis, publications preceding this most recent by Goldberg et al. have produced conflicting results. Mott et al. [5] evaluated 25 patients and found invasion into the subcutaneous fat to be significantly associated with poor disease outcome as defined by death from disease or the presence of metastatic disease ($P = 0.005$). In the largest series, Skelton et al. [7] reviewed 132 cases (with survival analysis on 85) and reported the depth of invasion was associated with a worse survival; however, statistical significance was not achieved. Contrasting these two reports are the findings of Llombart et al. [4] who failed to find tumor thickness as an independent predictor of reduced disease-free survival in multivariate analysis of 20 MCC patients. More recently, Sandel et al. [6] evaluated tumor depth and size in 37 patients and failed to find a correlation with overall survival. They reported a trend between depth of invasion and local recurrence ($P = 0.07$); however, there was no correlation with regional recurrence or distant metastasis. Thus, the recent contribution by Goldberg et al. in this issue lends support to the growing body of evidence that tumor depth lacks significant independent prognostic capability for MCC.

In addition to examining histologic tumor depth, Goldberg et al. reviewed clinical tumor diameter as related to survival and did not find that large primary tumors (≥ 2 cm) were associated with a poorer prognosis than tumors < 2 cm. Goldberg et al. used the four-stage system of the American Joint Committee on Cancer (AJCC) which distinguishes stage I (< 2 cm) and stage II (≥ 2 cm). This system was not specifically designed for MCC and is used for a wide range of non-melanoma skin cancers. While tumor size has been found to be a significant prognostic indicator by some authors [2], this finding has not been consistent in the literature. An alternative staging method outlined by Yiengpruksawan et al. implements a three-stage system classifying patients as localized (stage I, with IA < 2 cm and IB

≥ 2 cm), nodal (stage II), or distant metastatic disease (stage III) [8]. The lack of prognostic significance of tumor size in local disease as found by Goldberg et al. further supports this simplified staging system.

At present our ability to predict prognosis in patients with this deadly disease is frustratingly limited with no histologic prognostic indicator having been reproducible between cohorts. While prior studies evaluating pathologic predictors are small and thus often underpowered to detect modest differences, the lack of uniform trends among the studies suggests that even with larger numbers the prognostic significance of a finding (if later validated in larger studies) would likely be small. As mRNA expression analysis and other techniques are developed, we may uncover new methods for predicting the biologic behavior and optimal therapy of individual tumors. Until then, however, disease staging with nodal evaluation by SLNB (for clinically localized disease) remains the most important factor in prognosis and management for MCC.

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