



## **Clinical Significance of Microscopic Metastasis to Sentinel Lymph Nodes in Patients with Malignant Melanoma**

Jennifer G. Pryor, MD

CAP Residents Forum Delegate

Regional lymph node dissection improves survival in melanoma patients with nodal disease but is associated with unnecessary morbidity when used in all patients with melanoma.<sup>1</sup> Sentinel lymph node (SLN) biopsy, which is less invasive than regional lymph node dissection,<sup>2</sup> accurately predicts the status of the lymph node basin and pathologically identifies patients who do not require further treatment.<sup>3</sup> SLN biopsy can potentially improve patient survival and enable clinicians to predict prognosis, plan treatment regimens, and potentially limit disease.<sup>4</sup> Approximately twenty percent of clinically node negative melanoma patients have occult (microscopic) nodal disease,<sup>2</sup> and 15-20% of SLN positive patients will have additional metastases in non-sentinel nodes.<sup>3,5</sup> SLN biopsy followed by immediate completion lymph node dissection (CLND) in patients with microscopic nodal disease has been reported to improve survival.<sup>6</sup>

SLN biopsy has become the standard of care in the staging of melanomas  $\geq 1$  mm thick. Patients with pathologic Stage 0 (in-situ) and Stage IA (<1mm thick nonulcerated) melanomas do not require pathologic evaluation of their lymph nodes.<sup>7</sup> A positive SLN should be followed by CLND, at least in patients whose melanomas are 1.2–3.5 mm thick.<sup>6</sup> Some data suggest that patients with small metastases (<0.1 mm) or isolated immunohistochemically positive cells are unlikely to benefit from CLND and should be treated as SLN negative for staging purposes.<sup>8</sup> However, there is contradictory evidence that these patients in fact have a significantly worse long-term prognosis.<sup>9</sup> Use of histologic characteristics of the SLN micrometastasis, such as tumor burden or location, may be used to predict the likelihood of micrometastases in non-sentinel nodes and thus help avoid CLND, but it is still in its infancy. Similarly, while molecular assays can potentially detect sub-microscopic metastases, their reliable application in a predictive fashion has not been established. Until further data is available, conservative management with CLND, regardless of quantitative sentinel node tumor burden, seems warranted.<sup>10,11</sup>

Pathologists play a critical role in staging of patients with melanoma. There are significant differences in outcome when patients without clinically apparent nodal disease are staged pathologically.<sup>12,13,14</sup> Staging is performed using the AJCC Staging System for Melanoma,<sup>7</sup> in which the number of positive lymph nodes is

an important prognostic indicator.<sup>15</sup> Also of prognostic importance is whether the metastases are clinically occult (microscopic) or clinically apparent (macroscopic), discovered by palpation or radiographic studies.<sup>7</sup> Pathologists typically use hematoxylin and eosin (H&E) stained sections, augmented by immunohistochemistry to facilitate identification of micrometastases. Isolated immunohistochemically positive tumor cells must be distinguished from nodal nevus cells, macrophages, and antigen-presenting interdigitating dendritic cells; this is best achieved through the use of more than one melanocytic marker.

In summary, there is some evidence to indicate that patients with small metastases (<0.1 mm) or isolated immunohistochemically positive cells have a worse long-term prognosis, and CLND in patients with microscopic SLN disease may improve survival. Important goals for pathologists include finding a reliable method for the rapid identification of microscopic SLN metastases and exploring alternative methods such as fine needle aspiration for nodal staging of melanoma patients. Further research on these topics is needed in 2009, and pathologists are positioned to play a critical role in the development of these methodologies.

## References

1. Cascinelli N, Morabito A, Santinami M, et al. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. *Lancet*. 1998;351(9105):793-796.
2. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg*. 1992;127(4):392-399.
3. Cascinelli N, Bombardieri E, Bufalino R, et al. Sentinel and nonsentinel node status in stage IB and II melanoma patients: two-step prognostic indicators of survival. *J Clin Oncol*. 2006; 24(27): 4464-4471.
4. Gutzmer R, Al Ghazal M, Geerlings H, Kapp A. Sentinel node biopsy in melanoma delays recurrence but does not change melanoma-related survival: a retrospective analysis of 673 patients. *Br J Dermatol*. 2005;153(6): 1137-1141.
5. McMasters KM, Wong SL, Edwards MJ, et al. Frequency of nonsentinel lymph node metastasis in melanoma. *Ann Surg Oncol*. 2002;9(2):137-141.
6. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *New Engl J Med*. 2006;355(13):1307-1317.
7. Greene FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual*. 6<sup>th</sup> ed. New York, NY: Lippincott-Raven Publishers; 2002.

8. Satzger I, Völker B, Meier A, et al. Prognostic significance of isolated HMB45 or Melan A positive cells in Melanoma sentinel lymph nodes. *Am J Surg Pathol.* 2007;31(8): 1175-1180.
9. Scheri RP, Essner R, Turner RR, Ye X, Morton DL. Isolated tumor cells in the sentinel node affect long-term prognosis of patients with melanoma. *Ann Surg Oncol.* 2007;14(10):2861-2866.
10. Amersi F, Morton DL. The role of sentinel lymph node biopsy in the management of melanoma. *Adv Surg.* 2007; 41: 241-256.
11. Scolyer RA, Murali R, Gershenwald JE, Cochran AJ, Thompson JF. Clinical relevance of melanoma micrometastases in sentinel nodes: too early to tell. *Ann Oncol.* 2007;18(4): 806-808.
12. Balch CM, Soong SJ, Atkins MB, et al. An evidence-based staging system for cutaneous melanoma. *CA Cancer J Clin.* 2004;54(3):131-149.
13. Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol.* 2001;19(16):3635-3648.
14. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol.* 2001;19(16):3622-3634.
15. Buzaid AC, Tinoco LA, Jendiroba D, et al. Prognostic value of size of lymph node metastases in patients with cutaneous melanoma. *J Clin Oncol.* 1995;13(9): 2361-2368.