

EDITORIAL

The Challenge of Defining Guidelines for Sentinel Lymph Node Biopsy in Patients with Thin Primary Cutaneous Melanomas

Jeffrey E. Gershenwald, MD¹, Daniel G. Coit, MD², Vernon K. Sondak, MD^{3,4}, and John F. Thompson, MD⁵

¹Departments of Surgical Oncology and Cancer Biology, The University of Texas MD Anderson Cancer Center, Houston, TX; ²Memorial Sloan-Kettering Cancer Center, New York, NY; ³Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL; ⁴Departments of Oncologic Sciences and Surgery, University of South Florida, Tampa, FL; ⁵Melanoma Institute Australia and the University of Sydney, Sydney, NSW, Australia

The technique of lymphatic mapping and sentinel lymph node (SLN) biopsy was pioneered by Dr. Donald Morton of the John Wayne Cancer Institute as a minimally invasive surgical staging technique to identify patients with cutaneous melanoma who harbor occult regional node disease (i.e., microscopic nodal metastasis) and who may therefore benefit from lymphadenectomy.¹ Based on the simple concept that afferent lymphatic vessels originating from the site of primary melanomas drain to specific regional lymph nodes—the SLNs—and that the histological status of these nodes reflects the status of the remainder of the regional node basin, this approach has revolutionized the management of “at-risk” patients with cutaneous melanoma during the past two decades. It allows detection of nodal disease below the discovery threshold of any available nonpathological techniques, including contemporary imaging modalities. The independent prognostic significance of SLN status has been well established in numerous studies, and accumulating evidence provides strong support for early identification and treatment of patients with melanoma metastatic to a SLN.^{2,3} The improved staging afforded by SLN biopsy also has been beneficial for stratifying patients eligible for clinical trials.⁴ SLN biopsy is currently recommended in the management guidelines for clinically localized primary cutaneous melanoma in the United States (issued by the National Comprehensive Cancer Network [NCCN])⁵ and in management guidelines currently used in many other countries around the world.

Publication of the American Society of Clinical Oncology (ASCO)/Society of Surgical Oncology (SSO) Joint Clinical Practice Guidelines on SLN biopsy for melanoma adds support for the use of SLN biopsy from two of the most respected oncology treatment organizations in the world.^{6,7} Production of the guidelines was a collaborative effort involving a multidisciplinary Guideline Development Panel, including medical oncologists, surgical oncologists, other clinicians, and nonclinicians. The panel’s stringently evidence-based approach (in contradistinction to the consensus-based approach used by the NCCN and many national and international guidelines-development bodies) provides a degree of objectivity, but it also limits the body of data from which conclusions can be made. This necessarily led to the omission of several important, high-quality studies that are widely cited by melanoma surgeons and other clinicians that did not meet the prespecified criteria for this formal guidelines development exercise. For example, studies that explored the risk of a positive SLN but did not include follow-up data were excluded from consideration. This represents a particularly problematic constraint for studies of SLN biopsy in patients with thin melanomas, where follow-up of a decade or more is required to assess the prognostic impact of regional nodal staging.⁸ In view of these issues, this invited editorial focuses particularly on the role of SLN biopsy in patients with thin melanomas. It was prompted, at least in part, by the recognition that the very stringent—but arguably somewhat arbitrary—criteria for defining what constituted allowable studies for inclusion in the data set may have limited the Guideline Development Panel’s ability to produce “state of the art,” contemporary recommendations.

The evidence-based approach used by the Guideline Development Panel also placed constraints on the strength of the recommendations that it was able to make. For

guidelines to be broadly applicable, well-defined operational definitions of key guideline descriptors, including terms like “is indicated,” “should be considered,” “should be discussed,” and “may be recommended”—are necessary to achieve the intended impact on clinical practice and behavior. Without such definitions, the stringent evidence basis of the guidelines may fail to translate seamlessly into clinical practice. As authors of this editorial, we believe that this is particularly germane to the ASCO/SSO guidelines regarding SLN biopsy for patients with thin melanomas. This is of great practical relevance, because the majority of patients who present with primary cutaneous melanomas today have thin tumors. Therefore, including SLN biopsy, the management of some of these patients has a potentially large impact on the resources required to treat patients with early-stage melanomas.

The current AJCC staging system defines “thin” (T1) cutaneous melanomas as invasive primary tumors ≤ 1.00 mm in Breslow thickness. The T1 category is subdivided into T1a and T1b based on the absence or presence, respectively, of ulceration and/or mitotic activity (the latter criterion assessed using the dermal “hot spot” approach and defined as at least 1 mitosis per millimeter squared).^{9–11} We agree with the ASCO/SSO guidelines that “available evidence does not support routine SLN biopsy for patients with melanomas that are T1 or < 1 mm Breslow thickness, although it may be considered in selected high-risk cases.” Because there is no current consensus among melanoma experts as to what constitute the appropriate selection criteria for patients with “high-risk” T1 melanomas, and recognizing the limitations of the evidence allowable for consideration in the ASCO/SSO guidelines development process, it is inevitable that only a relatively vague statement could be made. It is our goal to supplement the statement made in the guideline document, recognizing that even among the four authors of this editorial, practice patterns differ in selecting T1 patients for SLN biopsy.

What then is the evidence that we can cite that the Guidelines Development Panel could not consider? Pooled series have clearly demonstrated that the overall probability of finding a positive SLN among all patients with melanomas ≤ 1 mm who were selected to undergo SLNB is approximately 5%. 1) Among patients whose primary tumor is < 0.76 mm in thickness, the overall probability of finding a positive SLN is very low (approximately 2–4%, or less), regardless of whether the tumor is T1a or T1b.¹² Given the overall large fraction of patients who present with thin melanomas, coupled with the small risk of potential morbidity associated with the SLN biopsy procedure and the unfavorable cost-per-positive-SLN-identified, SLN biopsy should be considered in these patients only if there is a strong indication of increased

risk. The challenge is that there is little evidence to define what confers an increased risk of SLN metastasis in this subpopulation (apart from the presence of a significant residual visible component of the melanoma, implying that its Breslow thickness is likely to have been underestimated). 2) In patients whose primary tumor is between 0.76–1.00 mm, the probability of a positive SLN increases into the 6–11% range; within this cohort, patients with T1b melanomas (ulcerated or with a mitotic rate $\geq 1/\text{mm}^2$) are even more likely to have a positive SLN.^{8,13–15} 3) There is strong evidence that “younger” patients are more likely to have a positive SLN, although available data do not adequately define what age serves as a clinically appropriate cutoff. 4) There is little convincing evidence that patients with thin melanomas who have Clark level IV invasion are more likely to have a positive SLN. Based on currently available data, some melanoma surgeons advocate the use of SLN biopsy for selected patients with T1 melanomas 0.76–1.00 mm thick, albeit with different criteria employed to select specific patients with tumors in that range.

Once the *probability* of a positive SLN among patients with thin melanomas has been accurately defined, still to be established is what constitutes the *threshold* probability to recommend SLN biopsy. Importantly, this involves consideration of the likelihood of finding a positive SLN, the risk of the procedure (including, in some cases, the use of general anesthesia for patients in whom local anesthesia would be adequate if only a wide excision of the primary site was to be performed), as well as the likely benefits that will accrue to the patient from the knowledge of their SLN status. In this regard, the relatively long time horizon before the prognostic impact of a positive SLN in patients with T1 melanomas becomes manifest also must be taken into account. Because SLN positivity is more likely in younger patients, and because younger patients clearly have a longer anticipated lifespan during which to realize a potential benefit, an additional implication is that “younger” patients with T1 melanomas may be better candidates for SLN biopsy than “older” patients who are otherwise considered to be at the same level of risk of harboring occult regional nodal metastasis.^{16,17} However, again, neither evidence nor consensus can yet definitively inform us how young is “young.”

There is now general consensus and a large body of evidence supporting the position that SLN biopsy is indicated for patients with melanomas ≥ 1 mm thick; in the absence of contraindications (e.g., significant comorbidities), this procedure is generally recommended for such patients. In contrast, no overall consensus has been reached about which patients with thin melanomas should be offered SLN biopsy, and indications continue to evolve.¹⁸ We believe that surgeons who care for patients with clinically localized invasive melanomas of any thickness

should discuss the concept of SLN biopsy with all of them. The goal of that discussion, however, should sometimes be to articulate clearly why SLN biopsy is not recommended. Our duty as surgeons is to understand the likely natural history, evidence-based indications, contraindications, patient preferences (e.g., aversion to risk), and special circumstances, if any, and integrate this body of knowledge to synthesize individualized recommendations for each patient. Given the current state of the art, we believe that a rational result of this process is a recommendation for SLN biopsy for many patients with melanomas 0.76-1.00 mm in thickness, but not for the overwhelming majority of patients with melanomas <0.76 mm in thickness.

Disclosures and Financial Support Dr. Gershenwald is a consultant for Navidea. Dr. Sondak is a paid consultant for Merck and Navidea. None for Dr. Coit. Dr. Thompson is a consultant for GSK, Roche, and Provectus.

REFERENCES

- Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg*. 1992;127:392-99.
- Gershenwald JE, Thompson W, Mansfield PF, Lee JE, Colome MI, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol*. 1999;17:976-83.
- Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Elashoff R, et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med*. 2006;355:1307-17.
- Eggermont AM, Suci S, Santinami M, Testori A, Kruit WH, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. *Lancet*. 2008;372:117-26.
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): melanoma. Version v1.2013, 2012.
- Wong SL, Balch CM, Hurley P, Agarwala SS, Akhurst TJ, et al. Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Joint Clinical Practice Guideline. *J Clin Oncol*. 2012. doi:10.1200/JCO.2011.40.3519.
- Wong SL, Balch CM, Hurley P, Agarwala SS, Akhurst TJ, et al. Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Joint Clinical Practice Guideline. *Ann Surg Oncol*. 2012. doi:10.1245/s10434-012-2475-3.
- Wright BE, Scheri RP, Ye X, Faries MB, Turner RR, et al. Importance of sentinel lymph node biopsy in patients with thin melanoma. *Arch Surg*. 2008;143:892-9 (Discussion 899-900).
- Balch CM. Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, et al (editors). *AJCC cancer staging manual*. 7th edn. New York, Springer; 2009.
- Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009;27:6199-206.
- Thompson JF, Soong SJ, Balch CM, Gershenwald JE, Ding S, et al. Prognostic significance of mitotic rate in localized primary cutaneous melanoma: an analysis of patients in the multi-institutional American Joint Committee on Cancer melanoma staging database. *J Clin Oncol*. 2011;29:2199-205.
- Andtbacka RH, Gershenwald JE. Role of sentinel lymph node biopsy in patients with thin melanoma. *J Natl Compr Canc Netw*. 2009;7:308-17.
- Murali R, Scolyer RA, Thompson JF. Can we better identify thin cutaneous melanomas that are likely to metastasize and cause death? *Ann Surg Oncol*. [Epub ahead of print July 10, 2012].
- Han D, Yu D, Zhao X, Marzban SS, Messina JL, et al. Sentinel node biopsy is indicated for thin melanomas ≥ 0.76 mm. *Ann Surg Oncol* [Epub ahead of print July 6, 2012].
- Caudle AS, Ross MI, Prieto VG, Warneke CL, Lee JE, et al. Mitotic rate predicts sentinel lymph node involvement in melanoma: impact of the 7th edition AJCC melanoma staging system. *Ann Surg Oncol*. 2010;17(suppl 1):S8.
- Paek SC, Griffith KA, Johnson TM, Sondak VK, Wong SL, et al. The impact of factors beyond Breslow depth on predicting sentinel lymph node positivity in melanoma. *Cancer*. 2007;109:100-8.
- Sondak VK, Taylor JM, Sabel MS, Wang Y, Lowe L, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity: lessons learned from the generation of a probabilistic model. *Ann Surg Oncol*. 2004;11:247-58.
- Lawson EH, Gibbons MM, Ko CY. Appropriate use of surgical procedures for patients with cancer. *Surg Oncol Clin North Am*. 2012;21:479-86.