Sentinel node biopsy and standard of care for melanoma

Charles M. Balch, MD,[a,b] Donald L. Morton, MD,[c] Jeffrey E. Gershenwald, MD,[b,d] Kelly M. McMasters, MD, PhD,[e] Omgo E. Nieweg, MD, PhD,[f] Barry Powell, MD,[g] Merrick I. Ross, MD,[d] Vernon K. Sondak, MD,[h] and John F. Thompson, MD[i,j]

Baltimore, Maryland; Chicago, Illinois; Santa Monica, California; Houston, Texas; Louisville, Kentucky; Amsterdam, The Netherlands; London, United Kingdom; Tampa, Florida; and Sydney, Australia

An international panel was convened by the organizing committee of the International Sentinel Node (SN) Society (ISNS) at their meeting in Sydney, Australia, on February 21, 2008, to address questions about SN biopsy (SNB) for melanoma. The panelists subsequently wrote this consensus statement, based on their interpretation of current evidence, as a guide to clinical treatment of patients with clinically localized melanoma. The panel comprised a cross section of expert melanoma surgeons who have contributed data and leadership to investigations of SNB.

From the Departments of Surgery, Oncology, and Dermatology, Johns Hopkins Medical Center, Baltimore[a]; Melanoma Staging Committee, American Joint Committee on Cancer, Chicago, Illinois[b]; Melanoma Program, John Wayne Cancer Institute at Saint John's Health Center, Santa Monica[c]; Departments of Surgical Oncology and Cancer Biology, University of Texas MD Anderson Cancer Center, Houston, Texas[d]; Department of Surgery, University of Louisville[e]; Division of Surgical Oncology, Netherlands Cancer Institute[f]; Plastic and Reconstructive Surgery, St George's Hospital, London[g]; Division of Cutaneous Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa[h]; Sydney Melanoma Unit[i]; and Department of Surgery, The University of Sydney.[j]

Dr McMasters is Chair of the Sunbelt Melanoma Trial.

The Multicenter Selective Lymphadenectomy Trials (MSLT-I and MSLT-II) mentioned in this report are supported by the National Cancer Institute (CA29605).

Disclosure: Drs Balch, McMasters, Sondak, Gershenwald, and Ross received financial support in the past 5 years from Schering Inc for speaking and research grants regarding adjuvant therapy. Drs Morton, Nieweg, Powell, and Thompson have no conflicts of interest to declare.

Reprint requests: Charles M. Balch, MD, Johns Hopkins Medical Institution, 600 N Wolfe St, Osler 624, Baltimore, MD. E-mail: balchch@jhmi.edu.

J Am Acad Dermatol 2009;60:872-5.

0190-9622/$36.00

doi:10.1016/j.jaad.2008.09.067

Abbreviations used:

AJCC:	American Joint Committee on Cancer
ISNS:	International Sentinel Node Society
MSLT:	Multicenter Selective Lymphadenectomy Trial
SN:	sentinel node
SNB:	sentinel node biopsy

IS SNB A STAGING AND/OR A THERAPEUTIC PROCEDURE?

The panel was in unanimous agreement that SNB (including preoperative lymphoscintigraphy and intraoperative lymphatic mapping) represents a valuable staging procedure. Panel members stated that the SN concept of sequential, orderly progression through regional afferent lymphatics is validated by the absence of metastases in "downstream" lymph nodes during long-term follow-up after SNB. Hematogenous spread cannot be ruled out, but the relatively low frequency of distant metastases in patients with tumor-negative SN indicates that this route of metastasis is far less common.

The panel agreed that SNB should be discussed with and recommended to patients when at least one of the following indications is present: (1) the risk of clinically occult nodal metastases is sufficient to justify the procedure (approximately $\geq 10\%$); (2) the prognostic information from SNB would be of value to the patient and the treating physicians; (3) the tumor status of the SN would be useful in guiding decisions regarding completion lymphadenectomy and adjuvant therapy; (4) nodal staging information is important for entry into clinical trials in which the patient is interested; and/or (5) the morbidity and risks of SNB are acceptable to the physician and the patient.[1-3]

The panel concurred that it is not necessary to demonstrate a survival advantage for SNB (as compared with wide local excision of the primary

melanoma without SNB) before recommending this procedure. They further noted that SNB is valuable because it is a minimally invasive procedure to stage the regional lymph nodes with little morbidity.[3,4]

WHAT ARE THE INDICATIONS FOR SNB?

The panel was in unanimous agreement that SNB should be discussed with and offered to all patients with primary melanomas equal to or greater than 1.0 mm in thickness and clinically normal regional lymph nodes by physical examination when the criteria described above are met.

Most of the panelists would also discuss and offer SNB to patients whose melanomas are not thicker than 1.0 mm but have characteristics that increase the likelihood of regional node micrometastasis. Although unanimous consensus was not reached for all criteria, most panelists would consider recommending the procedure for patients with T1 melanomas with primary tumor ulceration, a mitotic rate greater than or equal to 1/mm^2, and/or Clark level IV/V invasion—especially if tumor thickness exceeds 0.75 mm. In fact, some of the panelists would use this tumor thickness as a sole criterion for SNB. Ulceration, mitotic rate, and Clark level would be especially relevant in patients who have no significant comorbidity, who are younger than 40 to 45 years,[5] or whose primary tumor depth is uncertain because of tumor-positive deep margins in the biopsy specimen.

Data for patients with intermediate-thickness (1.2-3.5 mm) primary melanomas from the first Multicenter Selective Lymphadenectomy Trial (MSLT-I), a randomized prospective surgical trial updated at the ISNS meeting, did not show a significant difference in overall melanoma-related survival but continued to show improved disease-free survival in patients who underwent SNB compared with those who had nodal observation; thus, there was a 26% reduction in the relative risk of recurrence (hazard ratio 0.74; 95% confidence interval 0.59-0.93; P = .009), which was durable for at least 10 years.[4]

FOR WHOM IS THE INFORMATION FROM SNB USEFUL?

Patients

The panelists emphasized that most patients with melanoma want to know their prognosis as precisely as possible. Because the presence or absence of nodal micrometastasis is the single most significant determinant of survival, patients desire this information to plan their lives, to be considered for new therapies under evaluation in clinical trials, and to make an informed decision about completion lymphadenectomy and adjuvant therapy with currently available agents.

SNB improves disease-free survival,[4] but detractors will argue that it may only reduce regional nodal recurrence. However, from a patient's perspective, a recurrence in the regional lymph nodes is as distressing as a recurrence elsewhere, and well to be avoided.[6] Another contrary opinion has held that unless SNB improves overall survival, it should not be performed.[7] However the panel did not believe that information about a minimally invasive, minimally morbid staging procedure should be withheld simply because the procedure does not improve overall survival. The burden of therapeutic efficacy is not imposed on computed tomography, magnetic resonance imaging, positron emission tomography, or other components of the staging assessment for cancer; why then should SNB be required to improve overall survival?[1,2,4,8]

Melanoma physicians

The panelists agreed that the information from SNB is of particular staging value to identify patients with nodal micrometastases. Breslow thickness and other features of the primary melanoma are not the only prognostic characteristics used for accurate predictions of metastatic risk and survival outcome. Information based on SN status is also valuable for counseling these patients about the need for completion lymphadenectomy to improve regional disease control, reduce operative morbidity (as compared with the morbidity associated with possibly more radical regional surgery and often radiation therapy for palpable nodal recurrence), reduce the relative risk of recurrence by 26%, and potentially improve survival if nodal metastases are present. In addition, the information provided by a tumor-positive SN can be used to counsel patients regarding enrollment into melanoma clinical trials, and it can serve as the basis for discussing a screening and follow-up regimen based on risk for subsequent development of metastases. Conversely, patients whose SN is negative for tumor can be reassured that their prognosis is relatively improved; these patients are less likely to require adjuvant treatments and/or frequent follow-up.

Clinical investigators

The panelists agreed that most current and virtually all future melanoma clinical trials will require pathologic nodal staging of disease before study entry. Data from the American Joint Committee on Cancer (AJCC)/Union Internationale Contre le Cancer melanoma staging database showed that the range of 5-year survival for patients with nodal metastases varied dramatically (23%-87%) based on the thickness and ulceration status of the primary