Sentinel node biopsy and standard of care for melanoma: A re-evaluation of the evidence

Matthew H. Kanzler, MD
Stanford and San Jose, California

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Despite continued improvements in diagnostic and prognostic tools for malignant melanoma, significant therapeutic advances continue to elude researchers. Early recognition and prompt primary excision remain the only therapies proven to affect overall survival in these patients to date. Initial optimism over new therapeutic interventions for melanoma has unfortunately always been short-lived. Randomized prospective trials frequently fail to confirm initial enthusiasm of new therapeutic interventions.

When faced with mounting evidence from prospective trials that electively removing regional lymph nodes from all patients with cutaneous melanoma did not influence overall survival (as it did in certain other malignancies), surgeons hypothesized that a potential therapeutic benefit might be missed in prospective studies because of the dilutional effect of those patients not expected to benefit from elective nodal removal because they did not possess microscopic nodal metastases in the first place. Thus was born the concept of the sentinel node biopsy (SNB) procedure, whereby patients with microscopic lymph node metastases who *might* benefit from complete nodal dissection could be identified by a relatively noninvasive procedure, while sparing those patients without microscopic disease the morbidity frequently associated with complete nodal dissections.

Because of the theoretical appeal of SNB, coupled with the intrinsic need for physicians to "do something" for patients with potentially fatal diseases when no other viable therapies existed, SNB gained widespread acceptance by surgeons and melanoma experts before completion of necessary prospective studies necessary to validate the theoretical benefit of SNB in melanoma. In the May *Journal*, a commentary entitled "Sentinel node biopsy and standard of care for melanoma" was presented by Balch et al[1] as an "interpretation of current evidence" regarding SNB as interpreted by a "cross section of expert melanoma surgeons."

It has long been the tradition of the *Journal* to publish multiple viewpoints on controversial topics. Few topics qualify for "controversial" as much as SNB for melanoma. A careful review of the commentary by Balch et al[1] reveals several truths, but also multiple opinions not supported by scientific evidence. "Standard of care" consensus statements are typically published when there is a lack of evidence to guide clinical practices. The purpose of this commentary is to re-examine the current evidence (see Table I), and provide alternate interpretations for some of conclusions presented in the commentary by Balch et al.[1]

IS SNB A STAGING AND/OR THERAPEUTIC PROCEDURE?

The authors correctly concluded that SNB is a staging procedure, not a therapeutic procedure.[1] The landmark Multicenter Selective Lymphadenectomy Trial (MSLT)-I study[2] evaluated overall survival for 1269 patients with intermediate-thickness (1.2-3.5 mm) cutaneous melanomas. Patients were prospectively randomized into one of two groups: (1) patients who underwent immediate SNB, followed by complete nodal dissection only if the SNB specimen was positive; or (2) an observation group, where complete nodal dissection was undertaken only if clinically palpable nodes developed during follow-up. After a median follow-up of 59.5 months, no difference in overall survival was seen between the two groups. Although these results have been touted as "interim," the data are already mature to

From the Departments of Dermatology at Stanford University School of Medicine and Santa Clara Valley Medical Center.
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Correspondence to: Matthew H. Kanzler, MD, Valley Specialty Center, Suite 510, 751 S Bascom Ave, San Jose, CA 95128. E-mail: Matthew.Kanzler@Stanford.edu.
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5 years, making significant changes in outcomes unlikely with further follow-up.

Unfortunately, statistically inappropriate secondary end points were also reported by the MSLT-I authors,[2] which overshadowed the negative outcome of this important study. The authors' suggestion that early removal of microscopic nodal metastases might improve survival (as compared with removing nodes when they become clinically palpable) has subsequently been shown to be a result of inappropriate subset analyses by the authors.[3,4] The differences in survival seen merely confirmed the previously known fact that patients with macroscopic nodal disease have a poorer prognosis than those with microscopic disease.

In the recent *Journal* commentary, Balch et al[1] made a logical recommendation that SNB should be discussed with patients whose risk of harboring clinically occult nodal disease is 10% or greater. However, the panel went further, and stated that SNB should be recommended for patients in whom "the tumor status of the SN would be useful in guiding discussions regarding completion lymphadenectomy and adjuvant therapy."[1] This criterion would be rational if complete lymphadenectomy and adjuvant therapy were known to be effective in the treatment of melanoma. Unfortunately, the current evidence shows quite the opposite.

Every major prospective study evaluating lymphadenectomies for patients without clinical evidence of nodal disease has failed to show a survival advantage for this procedure in patients with melanoma.[5-8] This includes multicentered World Health Organization Melanoma Group trials of patients with extremity lesions[5] (553 patients) or trunk lesions[6] (252 patients), and an Intergroup Melanoma Surgical Program trial[8] (740 patients) reported by the same lead author as the MSLT-I. In addition, a recent 16-center comparative study involving 298 patients with melanoma and positive SNB specimen found that patients had similar survival whether a complete lymphadenectomy was performed immediately after SNB, or was delayed until clinically palpable nodes developed. [9] The ongoing MSLT-II is addressing the need for completion lymphadenectomy in a prospective fashion. However, until this study is completed, the best data available to date show that lymphadenectomies in the absence of palpable disease (either with or without SNB procedures) do not improve the survival of patients with melanoma. Thus, the choice to undergo SNB for prognostic data, but to avoid completion lymphadenectomies (with potential associated morbidities) regardless of the SNB status is actually supported by current clinical data, whereas recommendations to complete lymphadenectomies for all SNB-positive patients is based on "unanimous" endorsement by the panel of Balch et al.[1]

The use of sentinel node status to guide discussion of adjuvant therapy is dependant on proof that an effective agent currently exists. The only currently approved adjuvant therapy for treatment of melanoma, interferon, was initially approved by the Food and Drug Administration after data from one study were published (Eastern Cooperative Oncology Group 1684).[10] However, the overall survival advantage initially seen from adjuvant interferon in this study was lost after longer follow-up.[11] In addition, meta-analysis of multiple interferon trials has failed to show improvement in overall survival in patients with melanoma,[12] and data from M.D. Anderson Cancer Center (Houston, TX) showed that interferon use is not cost-effective in micronodal disease (ie, those patients identified by SNB).[13] The few months of additional disease-free survival afforded patients treated by interferon is outweighed by the severe toxicity of this therapy. The "nail in the coffin" with regard to interferon use in SNB-positive patients, however, came with the long-awaited completion of the Sunbelt Melanoma Trial. The results of this trial showed that interferon given to patients with melanoma and positive SNB specimens does not improve the overall survival or disease-free survival in these patients.[14]

Balch et al[1] also stated in their commentary that SNB should be recommended to patients because the procedure is necessary for entry into clinical trials in which the patient might be interested. There is no doubt that patients with positive sentinel nodes are at an increased risk for recurrence, and having a positive SNB specimen definitely should qualify patients for investigational trials. However, it is a travesty that being SNB positive is currently a *requirement* for entry into these important studies. Sentinel node status is only one indicator of prognosis. It is ridiculous to think that a patient with a 4-mm ulcerated melanoma has a good prognosis, merely because their SNB specimen is negative. Several patients are being denied access to important clinical studies, based solely on one predictor of survival (SNB status). All patients with high-risk melanomas should be eligible for these clinical trials, and patients already known to be at high risk for recurrence should not be forced to undergo a SNB procedure just to qualify for an investigational study.

WHAT ARE THE INDICATIONS FOR SNB?

The panel was unanimous that SNB should be offered to all patients with melanomas 1 mm or greater in thickness, and most panelists also would offer SNB to patients with melanomas thinner than