

The role of sentinel lymph node biopsy for melanoma: Evidence assessment

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Three decades after the first clinical trial of elective lymph node dissection (ELND) was initiated, the value and acceptance of sentinel lymph node (SLN) biopsy (SLNB) for patients with clinically localized melanoma remains a controversial issue with broad disparity in practice within the specialty of dermatology.¹⁻⁵ On opposing sides of the argument are real and theoretic benefits of SLNB that have been advocated juxtaposed against reasonable and justifiable concerns that have been raised by critics. Many questions remain unanswered and future trial results may or may not support reasons for performing SLNB today. The commonly cited sometimes heated current debate is interesting in itself, considering the fact that the majority of patients with melanoma are given a diagnosis of thin primary tumors or already have clinically evident metastases and, hence, do not fall within the current guidelines for consideration of SLNB.^{1,6}

New evidence often invalidates previously accepted therapy and replaces it with better and safer treatments. The optimal practice of medicine requires the fluid integration of clinical expertise with the best available levels of evidence and the patient's personal preferences and circumstances. Unfortunately in the evidence-based era, highest-level evidence is still lacking for the majority of disease states. Physicians need to be aware of the current best available evidence, how to judge levels

Abbreviations used:

ASCO:	American Society of Clinical Oncology
CLND:	complete lymph node dissection
ELND:	elective lymph node dissection
MSLT:	Multicenter Sentinel Lymphadenectomy Trial
NLM:	National Library of Medicine
SLN:	sentinel lymph node
SLNB:	sentinel lymph node biopsy
WHO:	World Health Organization
WLE:	wide local excision

of evidence, and formulate their interpretation of data into practice.

The purpose of this review is to present the extensive available SLNB data, which are found by and large outside the core dermatology literature. It is appreciated that variable interpretation of existing evidence is certain, and final interpretations and opinions may respectfully differ from one physician to another.

METHODS

Available data, including interim results of the prospective randomized Multicenter Sentinel Lymphadenectomy Trial (MSLT)-I as publicly presented and made available on the Internet, were reviewed to determine whether the evidence supports the use of SLNB in any subset of patients with melanoma.⁷ The search included 1198 articles identified by a melanoma sentinel node search in the National Institutes of Health National Library of Medicine (NLM) (last date performed June, 23, 2005) with bibliographic resources including MEDLINE/PUBMED and the NLM catalog extending from 1983 to 2005 (<http://www.nlm.nih.gov>). Additional searches were performed in PUBMED with a total of approximately 300 additional articles reviewed (<http://ncbi.nlm.nih.gov/entrez/query.fcgi>).

A standard hierarchy of evidence was used to evaluate and choose studies to review based primarily on the strength of study end points combined with the strength of study design. Hierarchy of

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evidence from best to worst includes: (1) randomized clinical trials, ranked in order as (a) randomized double-blind, or (b) randomized nonblinded; (2) observational studies and published reports, ranked in order as (a) longitudinal (cohort) studies, (b) case-control studies/cross-sectional studies, (c) case series, or (d) case reports; and (3) prevailing expert opinion and clinical experience as documented in (a) review articles or book chapters, or (b) the authors' expertise. Systematic meta-analysis may add strength of evidence. The results of this evidentiary review are presented as a series of questions addressed by the relevant available evidence.

DOES THE AVAILABLE EVIDENCE SUPPORT THE SENTINEL NODE HYPOTHESIS?

The sentinel node hypothesis and the selective approach to complete lymph node dissection (CLND) was formally introduced in the early 1990s as a minimally invasive procedure to stage the entire nodal basin and, thus, identify those who could potentially benefit from CLND and spare those with a negative SLNB the morbidity associated with CLND.^{8,9} Metastasis to lymph nodes is a complex process involving many interrelated biochemical, mechanical, and molecular events.¹⁰ The SLN concept is predicated on the theory that an orderly progression of cancer cells occurs in the initial stage of the metastasis within the lymphatic system. Proponents believe that this occurs in a significant proportion of patients, although it is also recognized that direct hematogenous metastasis may occur in some without SLN metastasis. The first lymph node to which cancer cells metastasize through the lymphatics is termed the SLN. Thus, according to the hypothesis, a tumor-negative SLN can predict with high confidence the absence of metastatic disease in the rest of the primary draining nodal basin.²

Strong evidence in favor of the hypothesis that the SLN really is the first draining node is based on a strong correlation between the pathologic status of the SLN and that of the rest of the nodal basin in prospective trials and single institution and pooled data reviews, and the reproducible correlation between SLN status and overall disease-specific outcome.^{7,11-23} Evidence exists to support the belief that SLNB accurately identifies the SLN in patients with primary melanoma.^{2,14,24} The combination of preoperative lymphoscintigraphy, intraoperative gamma probe interrogation, and intraoperative injection of vital blue dye consistently provides the highest success rate in accurately identifying the SLN. The evidence does not exclude the possibility that use of preoperative lymphoscintigraphy and

intraoperative gamma probe interrogation alone with omission of dye may also be as accurate as the use of all 3 localization methods.^{13,19,25-28}

A false-negative finding, that is the presence of histologically or clinically identified metastasis in non-SLNs in patients with a negative SLN, challenges the validity of the sentinel node hypothesis. Current evidence suggests 3 main causes of false-negative findings: technical failure, pathologic failure, and biologic failure.^{16,18,29} A technical failure can be caused by inexperience, as available evidence strongly suggests a learning curve must take place before the SLN can be reliably identified.⁷ Even experienced surgeons, however, have false-negative results. Available data are conflicting regarding whether SLNB after a wide excision is associated with a higher likelihood of false-negative results, but published data and expert opinion suggest that after extensive excision, flap reconstruction, or both the false-negative rate of SLNB is increased.^{1,30,31} However, the existence of failures when the procedure is either performed by inexperienced surgeons or performed after excessively wide excision is not incompatible with the validity of the sentinel node hypothesis.

A pathologic failure may be caused by lack of sensitivity of current histopathology methods to identify nodal metastases that are in fact present. Available evidence strongly suggests that serial sectioning and immunohistochemistry, if hematoxylin-eosin staining is negative, identifies a higher percentage of positive sentinel nodes, and likely reduces pathologic false-negative cases.³²⁻³⁴ Evidence is less conclusive regarding how extensive the sampling of the sentinel node should be to achieve an optimum balance between cost, labor intensity, and outcome. Available evidence does not support making any clinical decisions based on molecular techniques such as reverse-transcriptase polymerase chain reaction outside of prospective clinical trials.^{13,35}

A biologic failure may occur when lymphatics are obstructed by melanoma cells and can also occur if an inadequate initial excision is performed, leaving cells at or near the primary site that acquire the capability to disseminate secondarily through lymphatic channels into nodes other than the original SLN. The evidence indicates that these types of failure are uncommon with an experienced multidisciplinary approach consisting of nuclear medicine, surgery, and pathology, but are inevitable in some cases.¹⁸

In addition, through the knowledge gained from development and experience with the SLNB procedure, the concepts of aberrant lymphatic drainage

pathways to unexpected nodal basins and interval nodes (also known as ectopic, intercalated, or in-transit nodes) located between the primary site and the expected regional nodal basin have been elucidated.^{14,36-39} In our centers, at least, this has changed how physicians search for clinically detectable nodal disease, and has provided further strong support for the validity of the sentinel node hypothesis by explaining hitherto unrecognized patterns of melanoma metastasis, often falsely attributed to hematogenous dissemination in the past.

DOES SLNB ACCURATELY PREDICT OUTCOME?

The available evidence overwhelmingly supports SLN status as the most powerful independent factor predicting survival and indicates that SLNB provides the highest sensitivity and specificity of any nodal staging test available today.^{1,2,14,40-48} Accurate staging is widely accepted as the basis for counseling, therapeutic decision making, and prognostication in melanoma. Prognostic information is often invaluable and helps the vast majority of patients in an informed decision-making process. Some contend that metastasis to the regional lymph nodes is always associated with tumor dissemination beyond the nodes with a likely or even invariably fatal outcome. Clinical evidence does not support this notion, which is contradicted by prospective clinical trials demonstrating a significant percentage of long-term survivors with stage III disease in clinical trials and in any busy melanoma practice.^{17,49-53}

DOES SLNB RESULT IN IMPROVED REGIONAL DISEASE CONTROL?

The evidence that SLNB followed by immediate CLND results in better regional control than delayed CLND is indirect. No study has yet been completed that would directly answer this question, and no comparative high-level data exist in terms of regional failure after nodal dissection between these groups. The prospective, randomized multinational MSLT-I trial will help answer this question. However, almost 3 decades of evidence exists regarding the regional failure rate after delayed CLND and immediate CLND (ELND or after a positive SLNB).^{11,13,16,29,50-59} The rates of nodal relapse reported are in the range of 0% to 10% for CLND after a positive SLNB or ELND, and 9% to 36% after CLND for gross disease depending on the amount of gross disease (as high as 63% with bulky disease), number of positive nodes, and the status of extracapsular spread.^{11,29,51-65} Regional control does not appear to be compromised by SLNB.^{50,54} Gershenwald et al⁵⁴ reported a nodal recurrence rate of 10% in the positive SLNB/CLND

basin and none were the only site of recurrence, similar to ELND trials. Expert opinion among surgical oncologists predominantly indicates that performing a delayed CLND for clinically evident disease versus an immediate CLND for microscopic disease identified by a SLNB taken as a whole differs significantly with respect to surgical complexity and resulting morbidity.⁵⁰ In our own clinical practices, we have seen far fewer regional relapses and less morbidity from CLND among patients undergoing CLND after positive SLNB than among those who present with clinically evident nodal disease. Uncontrolled regional disease is recognized as a significant source of melanoma-related morbidity and can have a major negative impact on quality of life.^{11,58}

DOES SLNB IMPROVE SURVIVAL?

The strongest case for the routine use of SLNB would be made by the demonstration of a benefit in terms of survival for all patients subjected to the procedure. No conclusive or high-level evidence exists that a positive SLNB followed by immediate CLND improves overall survival in patients with melanoma. However, some available lower-level evidence does suggest a potential subset survival benefit.^{7,11,40,50,66-72}

Currently, it is generally accepted that ELND is not associated with a demonstrated improvement in overall survival compared with delayed node dissection at the time of clinically evident nodal recurrence. However, approximately 80% of patients entered into the initial melanoma ELND trials do not have nodal metastasis and will survive, leaving only approximately 20% of the overall group who may benefit. Survival end point differences between randomized groups are, thus, impossible to prove without many more patients in each randomized study arm than done in any ELND trial, especially if a relatively small subset does benefit. The majority of randomized controlled ELND trials did not include preoperative lymphoscintigraphy, which may also impact the overall survival results between the study arms. A potential outcome benefit for early therapeutic lymph node dissection was suggested in a randomized trial of ELND versus observation conducted by the World Health Organization (WHO).⁷⁰ In this trial, 240 patients with melanoma greater than 1.5 mm were randomized to ELND versus observation. No overall survival benefit was noted, but the group with positive nodes in the ELND (immediate CLND) arm had a 48% 5-year survival compared with the group with positive nodes in the observation arm (delayed CLND), who had a 27% 5-year survival ($P = .04$). This type of post hoc analysis of prospective

study data must be interpreted with caution, and can at best only be considered suggestive.

A single institution study compared survival between matched (but not randomized) groups of patients undergoing immediate CLND after a positive SLNB versus delayed CLND after clinical nodal disease recurrence.¹⁷ A significant improved survival in the positive SLNB with immediate CLND group versus delayed CLND of nodal metastases group was demonstrated with 5-, 10-, and 15-year survival of 73%, 69%, and 69% versus 51%, 37%, and 32%, respectively ($P \leq .001$). Even in the observation group that developed palpable nodal disease, therapeutic CLND was associated with long-term disease-free survival in a significant proportion, with 32% of these patients alive at 15 years and many of these likely cured of their disease.

Based on the large body of prospectively collected data, survival for patients with regional nodal disease is recognized to be based on the number of metastatic nodes, tumor burden within the node (macroscopic vs microscopic), and ulceration status of the primary melanoma.^{40,41} Survival for 1429 patients with lymph node metastases, subgrouped by presenting clinical stage, calculated from onset of the primary melanoma diagnosis to minimize lead-time bias, demonstrated a significant overall survival benefit for microscopic (clinically node negative, pathologically positive, $n = 825$) versus macroscopic (clinically node positive, pathologically positive, $n = 604$) detection ($P < .0001$).

Based on the available evidence, potential subset survival benefit for subclinical detection of nodal disease followed by immediate CLND exists. The MSLT-I is the only current prospective randomized trial designed to address the survival benefit of SLNB.^{7,24}

MSLT-I: Interim results

The first public presentation of interim results of the MSLT-I took place at the International Sentinel Node Society Conference in Los Angeles, Calif, on December 6, 2004. Subsequently, updated data with somewhat longer follow-up were presented at the American Society of Clinical Oncology (ASCO) Meeting in Orlando, Fla, on May 14, 2005.⁷ The MSLT-I, with a median follow-up of 59.5 months, involves 2001 patients enrolled (accrual now complete) from 18 centers worldwide, publicly reported but not published in a peer-reviewed journal. Eligible patients included those with primary cutaneous melanoma Breslow thickness of 1.0 mm or more, Clark level IV or higher, with clinically negative nodes, who were randomized in a 60:40 ratio to wide local excision (WLE) and SLNB versus

WLE alone. Patients with a positive SLNB in the WLE/SLNB arm underwent immediate CLND. Patients in the WLE-only arm underwent delayed CLND after clinical detection of nodal metastases.

At the first presentation in Los Angeles, Calif, in 2004, the 5-year melanoma-specific survival within the WLE/SLNB arm was 88% for patients with a negative SLNB versus 71% for patients with a positive SLNB. This significant difference provides strong, high-level evidence for the prognostic benefit of SLNB. This survival difference was maintained after 7 years, as presented at ASCO. The 7-year melanoma-specific survival for patients who were SLN positive with melanoma 1.2- to 3.5-mm thick in the WLE/SLNB arm who underwent immediate CLND was 69% versus 48% for patients in the WLE-only arm undergoing delayed CLND when nodal metastasis became clinically evident ($P = .0034$, relative risk 0.53, 95% confidence interval 0.33, 0.84). This interim evidence strongly suggests that in a subset of patients with occult SLN metastasis, immediate CLND prolongs survival compared with delayed CLND when SLN metastasis become clinically evident.

Several other interesting results can be found in the available data. In the WLE/SLNB group, 19.8% had a positive SLN. In the WLE-only group, 20.3% experienced a lymph node basin recurrence. Similarly, in the WHO prospective ELND trial, which did not involve serial sectioning and immunohistochemistry for the nodes and did not use lymphoscintigraphy to direct the ELND, the percentage of patients who developed regional node metastases as the first site of recurrence in the observation arm was 30.5% as compared with 22% found to harbor microscopic metastases in the ELND arm.^{70,73} The findings argue strongly that most if not all lymph node metastases identifiable histopathologically have the potential to develop into clinically recognizable tumors.

Significant immunologic down-regulation has been reported to occur in SLNs with metastatic deposits from melanoma and many other cancer types.⁷⁴ A relatively large body of data provides evidence of cytokine-mediated SLN immunosuppression associated with primary melanoma.⁷⁴⁻⁸⁴ Melanoma SLNs show a significant decrease in T cell-rich paracortical areas and a profound down-regulation of interdigitating antigen-presenting dendritic cells, even in the absence of SLN metastasis.^{74,75} The local cytokine environment has a significant impact on maturation and function of dendritic cells, which favors immunosuppressive dendritic cells and SLN immune malfunction.^{82,83} Taken together, these results support the hypothesis that the primary melanoma interacts with the SLN as an

immunologic unit to create a local immunosuppression that favors melanoma metastasis and growth. Additional evidence in support of this hypothesis has been reported.⁷⁶ Primed Melan-A/MART-1-specific CD8 T cells that reside and accumulate at high frequency in metastatic lymph nodes have been shown to be functionally tolerant to tumor progression in the local microenvironment whereas those that circulate in the blood maintain strong cytotoxic functions.⁷⁶ Manipulation of the local cytokine microenvironment may be able to reverse the local immune dysfunction.^{75,84}

With respect to tumor burden, the average number of total involved nodes after CLND in the SLNB arm was 1.6 compared with 3.4 after delayed CLND in the observation arm. Only 5% with a positive SLNB had 4 or more positive nodes after immediate CLND compared with 27% after delayed CLND in the observation arm. This suggests a clinical benefit if tumor burden correlates with survival, regional control, or both.

The final point of interest in the MSLT-I analysis found that 7.4% of patients with a negative SLNB failed in the regional lymph node basin. Previous studies have demonstrated that the false-negative rate for SLNB is relatively low but present.^{13,24,85} The false-negative rate in 2784 patients with a median follow-up of 18 months in the sunbelt randomized trial was 1.5% on the head and neck, and 0.5% on the trunk and extremities.¹³ The false-negative rate in MSLT-I was highest for melanomas located on the head and neck, and was lowest during later study time points presumably because of increasing procedural experience. The false-negative rate for surgeons performing 25 or fewer cases was 10.3%, versus 5.2% for surgeons performing greater than 25 cases ($P = .01$).

IS THE MORBIDITY OF SLNB JUSTIFIED IN THE ABSENCE OF A PROVEN SURVIVAL BENEFIT?

Reported rates of wound complications after CLND for advanced regional disease are high, even in centers of excellence. The overall reported rates of wound morbidity, infection, lymphedema, and delayed healing in the axilla are between 35% and 51%, and 25% to 90% in the inguinal region, thought to increase with tumor burden.^{13,58} Realizing that definitive comparisons are impossible between studies, postoperative complications after SLNB are observed in about 5% in comparison with 36% after ELND.^{11,13,59}

SLNB is not without morbidity. Results of the largest reported prospective randomized trial involving 79 centers with more than 3600 patients

undergoing SLNB found an overall 4.6% complication rate, most of which were minor versus a 23.2% complication rate after CLND in the setting of a positive SLNB.¹³ Complications after SLNB included hematoma/seroma (2.31%), minor wound infection (1.08%), lymphedema (0.66%), wound separation (0.24%), pulmonary complication (0.14%), sensory nerve injury (0.14%), hemorrhage (0.09%), thrombophlebitis (0.09%), deep vein thrombosis (0.09%), motor nerve injury (0.09%), and others (0.42%) including one allergic reaction to blue dye.

Some reports have suggested the possibility of increased risk of local or in-transit recurrence after SLNB.⁸⁶⁻⁸⁸ One large series obtained by pooling the results of two prospectively collected melanoma databases (MD Anderson, Houston, Texas, and Sydney Melanoma Unit, Australia) concluded that the overall incidence of in-transit metastases in patients undergoing SLNB is low and does not seem to have increased since the introduction of the SLNB technique.⁸⁸ By multivariate analysis, in-transit recurrence was predicted by Breslow depth, ulceration, and positive SLN status. The local or in-transit recurrence rate in MSLT-I was 8% in the WLE/SLNB arm versus 9% in the WLE-only arm, providing strong evidence that SLNB is not associated with an increased risk of in transit metastasis.

OTHER ASPECTS OF SENTINEL NODE BIOPSY

Although no randomized trial evidence exists, many series and reports support the use of SLNB for melanoma on the head and neck, vulva and eyelid, in pediatric patients, and during pregnancy.^{12,13,89-95} Radiopharmaceuticals at dosages used for SLNB carry negligible risk and are not contraindicated in pregnancy. Because of the risk of a rare but potentially catastrophic event of anaphylaxis to vital blue dye in patients who are pregnant, use of radiocolloid alone for SLNB in pregnancy is used at our institutions.⁹² No current evidence supports omission of a CLND after a positive SLNB.⁹⁶⁻¹⁰⁴ After a positive SLNB, 15% to 21% of patients have evidence of positive non-SLN metastases after CLND. This likely represents an underestimate because these nodes are neither serial sectioned nor stained with immunohistochemistry. An analysis of the evidence regarding the use of postsurgical systemic adjuvant therapy is beyond the scope of this report.¹⁰⁵ The available evidence overwhelmingly supports the use of SLNB to identify patients who may be candidates for adjuvant therapy and/or as an entry and stratification criterion for adjuvant therapy clinical trials.

CONCLUSION

Future trial results, research, and discovery will certainly impact the role of SLNB in the management of melanoma and provide evidence to ultimately determine the scope and limits of the procedure.¹⁰⁶⁻¹⁰⁹ While we await the results of clinical and basic research to advance the field, the current evidence supports the use of SLNB in the management of melanoma.

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ECZEMA HERPETICUM PATIENTS NEEDED FOR REFERRAL

The *Atopic Dermatitis and Vaccinia Network (ADV N)*, a consortium of 5 medical centers, is charged with developing and implementing a plan to reduce the risk of eczema vaccinatum (a potentially life-threatening complication of smallpox vaccine immunization). ADVN is conducting a study to elucidate the mechanism predisposing patients with atopic dermatitis (AD) to eczema vaccinatum. As smallpox vaccinations are currently not conducted, we will compare the genetic make-up of subjects with eczema herpeticum (EH) compared to AD subjects without EH.

The consortium is seeking:

Persons 1-80 years old with AD and a positive lab test for herpes simplex (PCR, immunofluorescence, culture, or Tzanck prep) and who self-report as either **African American** or **Caucasian**.

If you know patients with a history of eczema herpeticum, please ask them to contact one of the participating centers or direct them to our Web site (www.atopicderm.org)

Participating Centers:

- National Jewish Medical and Research Center, Denver, CO
PI: Donald Leung, MD, PhD, 303-398-1067
- Oregon Health and Science University, Portland, OR
PI: Jon Hanifin, 503-494-2121
- University of California at San Diego, San Diego, CA
PIs: Rich Gallo, MD, PhD and Tissa Hata, MD, 858-657-8390
- Children's Hospital, Boston, MA
PI: Lynda Schneider, MD, 617-355-6127
- Johns Hopkins Asthma and Allergy Center, Baltimore, MD
PIs: Lisa Beck, MD, and Kathleen Barnes, PhD, 410-550-4763

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