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

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

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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Funding sources: None.
Conflicts of interest: None identified.
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J Am Acad Dermatol 2006;54:19-27.
Published online December 5, 2005.
0190-9622/$32.00

doi:10.1016/j.jaad.2005.09.029

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