EVIDENCE-BASED PRINCIPLES & “SENTINEL” LYMPH NODE BIOPSIES FOR MELANOMA

Mark R. Wick, M.D.

From the Department of Pathology, University of Virginia Health System, Charlottesville, Virginia

Contact information for Dr. Wick-- Room 3020 University Hospital, University of Virginia Health System, 1215 Lee Street, Charlottesville, VA 22908-0214 (Telephone 434-924-9038; E-mail—mrw9c@virginia.edu)
Evidence-based medicine (EBM) has emerged as a distinct discipline in the past 2 decades. It is in many ways a new model, which alters the traditional authority-based paradigm of medical practice (1). EBM depends on the use of logic, randomized trials, and statistical analysis to separate data-based concepts and procedures from purely-empirical or observational ones. Periodic analysis and meta-analysis of medical concepts is also an important element of the process. Lastly, EBM places an emphasis on systematic dissemination of information, so that current evidence-based concepts can effectively reach clinical practice. Allied areas of procedural development are those of medical decision analysis (MDA), represented by mathematical techniques that are predicated on Bayesian probability theory, and epistemological medicine. Their respective goals are to provide objective, probabilistic underpinnings for medical decisions, and to determine the best method(s) for integrating variables into a particular theory or model (2).

These facets of current medicine are, perhaps, more familiar to laboratory-based physicians than they are to other specialists. Indeed, the authors of this review recently took a verbal poll of colleagues to ask how many of them felt that the practice of pathology was EBM-based. Almost without exception, they answered that query affirmatively. Nevertheless, one could seriously question that impression after an objective assessment of detailed approaches to common problems in laboratory medicine. Are pathologists, in fact, as evidence-based as we believe?

### Empiricism & the Practice of Pathology

Much of pathology—and medicine—is still based on empiricism, simply defined as an approach based on observation and experience. That is certainly not a bad thing in and of itself, and, in fact, empiricism is often the most efficacious means of clinical problem-solving. Internists can make the diagnosis of congestive heart failure accurately based on symptom complexes and physical findings. Similarly, pathologists can recognize and stage invasive colon carcinoma with a combination of naked-eye inspection and an examination of standard microscopic sections stained with hematoxylin and eosin (H&E). Indeed, empiricism is a kind of evidence-based approach to science if it is done correctly by observers with sufficient training and knowledge. Each physician’s education is integrated with experience in an ongoing fashion, refining and adding to his or her cognitive “database” to modify and improve approaches to particular problems. That process has always been defined as the “art” of medical practice, but it has undeniably factual underpinnings.

The difficulty with a solely empirical approach to medical practice is that it allows unneeded variation and inefficiency to persist. If no attempt is made to codify procedures and processes, predicking them on MDA and epistemology, some practitioners may achieve the right “answer” but only through a circuitous route. One must return to the basic elements of EBM-based questions in order to avoid that pitfall. Those are—“Is the evidence valid?” “Is the evidence important?” “Can the evidence be applied to individual cases reliably?” “How likely are particular outcomes over time?” “How precise are prognostic or predictive estimates?” and “Are the patients being studied similar to those seen in ‘real-life’ situations?” (1).

Like any other specialty, pathology is subject to the continuation of thought-processes and procedures that are not supported by EBM data. This is true despite the data-intensive nature of our specialty and its historical emphasis on analytic thought. The following material specifically addresses information pertaining to “sentinel lymph node biopsy” for malignant melanoma and other tumors, and controversial issues attached to that technique.
Concepts Concerning Tumor Metastasis & Procedures Associated with Them

One of the most misunderstood facets of tumor biology is that which concerns the mechanisms and nature of metastasis. Interestingly—and somewhat surprisingly—that statement is equally true whether one considers physicians or laypersons as the “interpreters” of metastasis. Laypeople struggle with the concept that neoplasms can begin their growth in one organ and then involve others, often mistakenly espousing the idea that the lesions are each independent of one another. On the other hand, all physicians grasp the principles of local tumor growth into lymphovascular spaces and the dissemination of neoplastic cells in circulation. However, the great majority of them also wrongly believe that there is an inviolable topographical aspect to this process in regard to certain tumors. For example, it is thought by many people that carcinomas and melanomas invariably involve regional lymph nodes in a linear fashion before spreading to other visceral sites (3); hence, a currently-popular procedure has arisen known as the “sentinel lymph node biopsy” (SLNB) (4,5). In that method, dyes or radioactive tracers are injected into the tissue surrounding the primary tumor, and the lymph node with the highest concentration of those markers is felt to be that through which lymphatic fluid and tumor cells first pass in drainage from the lesional site (6). Theoretically, if no neoplastic cells are seen microscopically in the SLNB, it is assumed that no metastases exist in the “downstream” lymph nodes or in the viscera (7). The “sentinel” node biopsy procedure has been widely used in patients with cutaneous melanoma and in others with breast carcinoma (8-10); nonetheless, it has also been extrapolated to many other sites and tumors as well (11). Both prognostic and therapeutic value has been ascribed to this operation (3), and various technological approaches have been applied to the pathologic evaluation of SLNB beyond H&E examination (12). Those include such modalities of study as immunohistology and the polymerase chain reaction, using antibodies and nucleic acid primers related to tumor-selective molecules. In that context, it has been presumed that even a few tumor cells in the node (which will likely be invisible in conventionally-stained sections) would markedly change the prognosis of the patient for the worse (13).

The “sentinel node concept” has been embraced widely by many surgeons and oncologists. Nevertheless, how does it stand up to scrutiny in the setting of EBM and MDA? First, one may consider the contention that SLNB “interrupts” a programmatic sequence of metastasis which is felt to involve node groups in a linear fashion. Is that concept valid? Biological-clinical data would suggest that it is not. Metastasis of any neoplasm is most properly viewed as a systemic process ab initio, and lymph node involvement is simply a marker for it (14-21). Carlson (22) and others (23-25) have shown that distant metastasis often occurs well before initial clinical recognition of cutaneous melanoma or carcinoma of the breast. Hence, it appears that malignant tumors which have acquired a metastasizing phenotype will express that potentiality virtually immediately, rather than having to attain a “critical mass” or size to do so. Of course, tumor size does relate to clonal evolution and accrual of genetic mutations, but it does so only imperfectly. The latter statement has generous support from publications on “thin” melanomas that metastasize widely (26,27) and small breast carcinomas that do likewise, particularly in men (28,29). The general behavior of small-cell neuroendocrine carcinoma represents another exemplary paradigm (17,30).

An unfortunate truth is that many physicians embrace a naïve model of metastasis. Rather than being simply a mechanical embolization process, as conceptualized by many people, metastasis involves the loss or acquisition of critical cellular growth-modulating proteins; invasion of the tumor across the basement membranes of lymphatics or blood vessels or both; embolic spread to another tissue or organ; neovascularization; and growth and survival in a “foreign” tissue-milieu (18-21,31-33). The last of those requirements
largely centers on the ability of the neoplastic cells to evade, exist in symbiosis with, or overcome immune surveillance by the host (34).

Much has been made of the correlation between “local” growth and recurrence of malignancies and the risk of distant disease, with the implication being that the first leads to the second sequentially (35). That construction is likewise flawed. It is more correct to say that robust local growth of a neoplasm simply reflects a metastasizing phenotype, and that the progression of clinically-obvious distant metastases occurs concurrently with locoregional proliferation. As an extension of that model, one can consider the meaning of “micrometastases” in lymph nodes. In patients with melanoma (36) and several other tumors, micrometastatic nodal implants do not equate with a significantly-worsened prognosis as compared with truly node-negative cases. That observation likely represents a defective ability for micrometastasizing lesions to proliferate actively and autonomously, and it does not mean that similar micrometastatic implants in viscera are absent. The latter tumor colonies merely lack the ability to flourish.

Another commonly-held fallacy is that lymph nodal growth of a tumor must invariably involve a “sentinel” site first, before other nodes in a regional “basin” are affected. It has been shown clearly that a proportion of patients with melanoma (37) or breast carcinoma (38) will have histologically-negative SLNBs with tumor-positive nodes in the remaining basin; neoplastic nodal implants are not always “linear.”

How does this information translate into the realm of MDA? First, it impugns the validity of claims that SLNB by itself does, or can, have any real impact on long-term survival in a causal fashion (39-41). Returning to a statement made earlier in this discussion, macrometastatic involvement of sentinel nodes is most properly regarded only as a marker for a metastasis-capable neoplasm with a vigorous capacity to grow in distant sites. If effective systemic antineoplastic therapy is available, it would definitely be indicated under such circumstances. On the other hand, if efficacious treatment is not obtainable, there is no reason to administer any. Those statements are particularly apropos to metastatic breast carcinoma and melanoma, respectively. Salutary effects are achievable with chemotherapy in selected patients with disseminated mammary cancer (42), whereas no adjuvant treatment has yet been shown unequivocally to extend the lives of persons with metastatic melanoma (43,44).

Yet another issue in this specific area of discussion is whether histologically-positive SLNBs must prompt a complete excision of the involved node group. That question was specifically considered by Fisher et al. 25 years ago in reference to breast carcinoma (45). Patients in that study were randomized to mastectomy with or without locoregional irradiation, but without lymphadenectomy, even if the nodes were tumor-positive. There was no difference in the incidence of subsequent distant metastasis in either group. That observation led Fisher and colleagues to conclude that “the findings provide further insight into the biologic significance of the positive lymph node and confirm our prior contention that positive regional lymph nodes are indicators of a host-tumor relationship which permits the development of metastases... they are not important sources of distant disease.” Gray and coworkers (38) have recently studied a group of women with breast cancer and micrometastatically-involved axillary SLNBs found with immunohistology. They found that all of those patients were free of additional nodal disease in followup, and suggested that microscopic implants of breast carcinoma in sentinel lymph nodes—as detected with adjuvant pathologic studies alone—did not mandate formal nodal dissection. Survival benefit, or lack thereof, has become a hotly-debated topic in reference to basin-lymphadenectomies for melanoma patients with positive SLNBs (46,47). Several retrospective and prospective surgical trials have shown no effect on overall survival by
lymph node dissection (48-52), but some current investigators continue to hold views to the contrary (3,53). Again, predicated on the biological premises presented above, there is no logical reason to expect that removal of regional lymph nodes would somehow prevent distant visceral disease.

How does this information translate into pragmatic approaches for pathologists? First, their role as medical peer-educators requires that a scientifically-sound doctrine be applied to clinical questions concerning metastases of malignant tumors, in lymph nodes or other sites. Advancement of reliable canon will sometimes meet with resistance, but should be pursued nonetheless. Secondly, if surgeons nevertheless choose to perform SLNBs in the face of opposing evidence, a sensible approach to their pathologic evaluation should be undertaken. Some authors have suggested that several technology-intensive methods should be used routinely in examining sentinel nodes (12). However, the recommendation on this topic (and the only society-based one of which the authors are aware) made by the Association of Directors of Anatomic & Surgical Pathology (54) states that “more than one [H&E-stained] section [should] be performed on each block in these cases, if the node or nodes are not positive grossly or at intraoperative pathologic consultation.... It is....also unclear whether immunostains add clinically relevant information and whether they may be substituted for additional H&E-stained sections.” We believe that the same can be said regarding use of the polymerase chain reaction for tumor-related markers; indeed, all non-H&E stain-based pathologic examinations of SLNBs are currently developmental rather than standard. Our present approach is to submit the entire lymph node, cut at 1 mm. levels, and examine microscopic serial-sections of each stained with H&E in the examination of SLNB specimens.

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EVIDENCE-BASED PRINCIPLES AS APPLIED TO THE SENTINEL LYMPH NODE BIOPSY TECHNIQUE FOR MELANOMA

Mark R. Wick, MD
University of Virginia Medical Center
Charlottesville, Virginia, USA
Framing EBM Questions: Specific Elements

- Classical Evidence-Based Questions:
  - Is the evidence valid and reproducible?
  - Is the evidence important?
  - Can it be applied to individuals reliably?
  - How likely are the outcomes over time?
  - How precise are the prognostic estimates?
  - Are the study patients similar to those seen in “real life”?
Dermatology Times®
Special Report
MELANOMA
The Traditional “Model” of Metastasis

• The time-honored concept of metastasis is that carcinomas and melanomas *invariably* involve lymph nodes first, *in continuity* with the primary tumor, and *then* proceed to distant sites. The regional lymph nodes are actually regarded as the “seeds” of systemic disease by some observers.

• This “growth-in-line” construction is overly-simplistic, ignoring the capacity of tumor cells to cross blood vessel walls, the role of host immunity, and the interplay of tumor cells and influences of various visceral environments.

• In fact, based on modern information on tumor biology, lymph nodal metastasis should be regarded *as* a reflection of *systemic disease*—at least when it is present in macroscopic form—and the patient treated accordingly (by medical oncological means) *if* such therapy is available and efficacious.

• The “sentinel node” paradigm— at least as it relates to subsequent regional lymphadenectomy— is called into serious question by this sequence of arguments.
Required Steps for Metastasis of Melanoma

(From Fidler I-- http://www.moffitt.org/moffittapps/ccj/v2n5/article3.html)
Competing Models of Cutaneous Melanoma Metastasis
Findings from 1665 women with primary breast cancer, treated at 34 NSABP institutions in Canada and the United States, have failed to demonstrate that patients with medial-central tumors had a greater probability of developing distant metastases or dying than did those with lateral tumors despite the greater incidence of internal mammary (IM) node involvement when tumors are medial-central in location. A comparison of patients with similar clinical nodal status and tumor location who were treated either by radical mastectomy (RM) or by total mastectomy plus radiation therapy (TM + RT) failed to indicate that radiation of IM nodes reduced the probability of distant treatment failure (TF) or mortality. When findings from patients having equivalent clinical nodal status and tumor location treated by TM alone or TM + RT were compared, it was found that the addition of RT failed to alter the probability of the occurrence of a distant TF or of death. This was despite the fact that in the nonradiated group two putative sources of further tumor spread, i.e., positive axillary and IM nodes, were left unremoved and untreated. The findings provide further insight into the biologic significance of the positive lymph node and confirm our prior contention that **positive regional lymph nodes are indicators of a host-tumor relationship which permits the development of metastases and they are not important sources of distant disease.**
Macroscopically-Obvious Lymph Nodal Metastasis of Melanoma: Marker or Source of Additional Disease?
Nodal “Macrometastasis” of Melanoma:” Marker or Source of Additional Disease?
Wide Excision for Melanoma, To Clear “In Continuity” Lymphatics

Chest Radiograph from Patient with Melanoma Of Left Shoulder, Treated with Forequarter Amputation
SLNB For Melanoma 2008– Questions or Conclusions, or Both?
The “Pro” Argument
(With Deference to Dr. Cochran)
Sentinel-Node Biopsy or Nodal Observation in Melanoma

Donald L. Morton, M.D., John F. Thompson, M.D., Alistair J. Cochran, M.D., Nicolas Mezzillo, M.D., Robert Elashoff, Ph.D., Richard Essner, M.D., Omer E. Nieweg, M.D., Ph.D., Daniel F. Roses, M.D., Harald J. Hoekstra, M.D., Ph.D., Constantine P. Karakousis, M.D., Ph.D., Douglas S. Reintgen, M.D., Brendon J. Coventry, M.D., Edwin C. Glass, M.D., and He-Jing Wang, M.D., for the MSLT Group*.

ABSTRACT

BACKGROUND
We evaluated the contribution of sentinel-node biopsy to outcomes in patients with newly diagnosed melanoma.

METHODS
Patients with a primary cutaneous melanoma were randomly assigned to wide excision and postoperative observation of regional lymph nodes with lymphadenectomy if nodal relapse occurred, or to wide excision and sentinel-node biopsy with immediate lymphadenectomy if nodal micrometastases were detected on biopsy.

RESULTS
Among 1269 patients with an intermediate-thickness primary melanoma, the mean (SE) estimated 5-year disease-free survival rate for the population was 78.38 (1.6)% in the biopsy group and 73.1 (2.1)% in the observation group (hazard ratio for death, 0.74; 95% confidence interval [CI], 0.59 to 0.93; P=0.009). Five-year melanoma-specific survival rates were similar in the two groups (87.1±1.3% and 86.6±2.1%, respectively). In the biopsy group, the presence of metastases in the sentinel node was the most important prognostic factor; the 5-year survival rate was 72.3±4.6% among patients with tumor-positive sentinel nodes and 90.2±1.3% among those with tumor-negative sentinel nodes (hazard ratio for death, 2.48; 95% CI, 1.54 to 3.98; P=0.001). The incidence of sentinel-node micrometastases was 16.0% (122 of 764 patients), and the rate of nodal relapse in the observation group was 15.6% (78 of 500 patients). The corresponding mean number of tumor-involved nodes was 1.4 in the biopsy group and 3.3 in the observation group (P=0.001). Indicating disease progression during observation. Among patients with nodal metastases, the 5-year survival rate was higher among those who underwent immediate lymphadenectomy than among those in whom lymphadenectomy was delayed (72.3±4.6% vs. 52.4±4.5%; hazard ratio for death, 0.51; 95% CI, 0.32 to 0.81; P=0.004).

CONCLUSIONS
The staging of intermediate-thickness (1.2 to 3.5 mm) primary melanomas according to the results of sentinel-node biopsy provides important prognostic information and identifies patients with nodal metastases whose survival can be prolonged by immediate lymphadenectomy. (ClinicalTrials.gov number, NCT00575496.)

From the Departments of Surgical Oncology (D.L.M., R.E.), and Biostatistics (R.E., H.J.W.), John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, CA; the Sydney Melanoma Unit, Royal Prince Alfred Hospital, Camperdown, NSW, Australia (J.C.); the Department of Pathology and Laboratory Medicine, University of California at Los Angeles, Los Angeles (A.J.C.); the Department of Surgical Oncology, National Cancer Institute, Naples, Italy (N.M.); the Department of Biostatistics, University of California at Los Angeles, Los Angeles (R.E., H.J.W.); the Department of Surgery, Netherlands Cancer Institute, Amsterdam (O.E.N.); the Department of Surgery, New York University School of Medicine, New York (D.F.R.); the Department of Surgical Oncology, University Medical Center Groningen and Groningen University, Groningen, the Netherlands (H.J.H.); the Department of Surgery, Millard Fillmore Hospital, Buffalo, NY (C.P.K.); the Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL (D.S.R.); the Department of Surgery, Royal Adelaide Hospital, Adelaide, SA, Australia (B.J.C.); and the Department of Nuclear Medicine, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles (E.C.G.). Address reprint requests to Dr. Morton at the John Wayne Cancer Institute at Saint John's Health Center, 2000 Santa Monica Blvd., Santa Monica, CA 90404, or at mortondj@jwci.org.

*Members of the Multicenter Selective Lymphadenectomy Trial (MSLT) Group are listed in the Appendix.

The results of the study by Morton et al. convincingly show that sentinel node biopsy is a standard of care staging procedure and is justified in patients with melanoma with tumor thicknesses of 1.2 to 3.5 mm who have a sufficient risk of nodal metastasis.
The Opposing Argument
Two hundred and fifty-nine patients with malignant melanoma have been reviewed. One hundred and fifty of these were determinate. A primary excision and dissection in continuity of the tumor, the intervening lymphatics, and the regional lymph nodes achieved a 5-year survival free of disease for 67.5% of the patients. When the nodes were clinically negative but microscopically positive, 45% survived. An elective node dissection offers no better prognosis than does a therapeutic dissection and is not indicated in the primary treatment of malignant melanoma.
From September, 1967, to January, 1974, a clinical trial was carried out by the WHO Melanoma Group to evaluate the efficacy of elective lymph-node dissection in the treatment of malignant melanoma of the extremities with clinically uninvolved regional lymph nodes. Treatment was prospectively randomized: 267 patients to excision of primary melanoma and immediate regional-lymph-node dissection and 286 to excision of primary melanoma and regional-lymph-node dissection at the time of appearance of metastases. The statistical analysis showed no difference in survival between the two groups of patients, regardless of how the data were analyzed (according to sex, site of origin, maximum diameter of primary tumor or Clark's level or Breslow's thickness).

*Elective lymph-node dissection in malignant melanoma of the limbs does not improve the prognosis and is not recommended when patients can be followed at intervals of three months.*
A prospective randomized study was initiated at our institution in 1972 to determine the efficacy of routine elective lymphadenectomy in localized (stage I) melanoma. Included in the study were 171 patients, 62 of whom had no lymphadenectomy, 55 of whom had delayed lymphadenectomy, and 54 of whom had immediate lymphadenectomy. No significant difference was found among the three treatment groups with respect to survival or metastasis-free survival. Multifactorial analysis indicated that the level of invasion and the thickness of the lesion were the most important prognostic factors, followed by age (60 years or older), site (legs), and tumor type (nodular). A prognostic index based on these variables was highly predictive of metastasis or death. Even when this score was considered, no significant variation was noted among the three treatment groups. More subsequent complications of melanoma, however, occurred in the group with no lymphadenectomy--36 in this group but only 19 in each of the other treatment groups. This finding was not statistically significant but does indicate that a few additional problems may be associated with leaving regional nodes intact. Further studies are needed, and indeed are being conducted, to determine whether elective lymphadenectomy improves survival sufficiently to offset the costs and the complications associated with this approach.
How Does Sentinel Node Biopsy for Melanoma Measure Up in the Context of EBM?

- It is, by definition, a precursor of formal lymphadenectomy (FL) if the SLN is positive; FL still has not been shown to improve overall long-term survival in melanoma cases.

- ***There is no effective adjuvant therapy for melanoma to treat “microscopic” disease***

- The effectiveness of SLN as a prognostic technique is uncertain in an “n of 1” setting, and therefore counseling patients on their eventual individual outcomes should not depend only upon the results of this procedure.
Additional Confounding Issues

• Does it make sense to apply special techniques for the detection of “micrometastases,” if the long-term prognostic meaning of those is still uncertain? (‘If something is not worth doing, it is not worth doing well’ [Dr. Gene Siegal, 2000])

• How does one deal with the relatively common finding of nodal nevus rests? Can these always be distinguished from metastatic melanoma reliably?

• There have been no prospective studies comparing serial sectioning and H&E staining vs. IHC that have shown any clear benefit of the latter procedure in studying SLNB
Nodal “Micrometastasis” of Melanoma
Nodal “Micrometastasis” of Melanoma: Immunostaining for Melan-A/MART-1
Van Akkooi ACJ, de Wilt JHW, Verhoef C, et al.: Clinical relevance of melanoma micrometastases (<0.1 mm) in sentinel nodes: are these nodes to be considered negative? *Ann Oncol* 2006; 17: 1578-1585

……On multivariate analysis the SN tumor burden was the most important prognostic factor for DFS (*P* = 0.005) and OS (*P* = 0.03). Distant metastasis-free survival was identical (91%) to the 5-yr OS of SN negative patients, the estimated 5-yr OS was 100% for these patients and additional non-SN positivity was not observed. Therefore, our data suggest that patients with sub-micrometastases (<0.1 mm) in the SN may be judged as SN-negative, as non-stage III, and are highly unlikely to benefit from CLND, which we no longer recommend.
Nodal Melanocytic Nevus “Rests”– Not Always So Easily Recognized!
Do We Know the Frequency with Which Occult Single Nevocytes are Present in Otherwise Normal Lymph Nodes?

Quite simply…… NO.
Does SLNB Actually Detect *ALL* Intranodal Metastases of Melanoma?

“The detection of melanoma cell deposits in only 7 of 22 false-negative SLNs suggests that mechanisms other than failure of histopathologic examination may contribute to the failure of the SLN biopsy technique in some patients.”
What About “Atypical” (Biologically Uncertain) Melanocytic Lesions—Will They Benefit Diagnostically from SLNB?

- The incidence of benign nevocytic inclusions is simply not known in relation to cases of Spitz nevus, cellular blue nevus, Reed’s nevus, etc., nor is it known whether or not benign melanocytes in SLNB in such cases look like “ordinary” nevocytic rests

- The result is compound confusion
Sentinel lymph node biopsy in patients with “atypical Spitz tumors.” A report on 12 cases

Carmelo Urso MD\textsuperscript{a,}\textsuperscript{*}, Lorenzo Borgognoni MD\textsuperscript{b}, Calogero Saieva MD\textsuperscript{c}, Gerardo Ferrara MD\textsuperscript{d}, Galliano Tinacci MD\textsuperscript{a}, Brunero Begliomini MD\textsuperscript{e}, Umberto M. Reali MD\textsuperscript{b}

\textsuperscript{a}Department of Anatomic Pathology, Dermatopathology Section, S. M. Annunziata Hospital, Florence, Italy
\textsuperscript{b}Plastic Surgery Unit, Regional Melanoma Referral Center, Tuscan Tumor Institute (ITT), S. M. Annunziata Hospital, Florence, Italy
\textsuperscript{c}Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Center (CSPO), Scientific Institute of Tuscany, Florence, Italy
\textsuperscript{d}Department of Anatomic Pathology, G. Runno General Hospital, Benevento, Italy
\textsuperscript{e}Department of Anatomic Pathology, Misericordia e Dolce Hospital, Prato, Italy

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The pragmatic management of ASMT is to label them descriptively and treat them surgically whenever possible, as if they were melanomas, while at the same time admitting that we cannot predict the biologic properties of each and every one of them. Importantly, this paradigm does not include sentinel node biopsy. **Compounding uncertainty with more uncertainty is never a good idea.**

(MRW–July 2006)
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<th>Primary Cutaneous Lesion</th>
<th>Lymph Node Biopsy</th>
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On the Cover

What Do These Cells Prove?

Philip E. LeBoit, MD

“To some, everything— a sure diagnosis of melanoma... to me, nothing.”

PEL, August 2003
Conclusions According to MRW

- Although SLNB & ELND have not yet been proven to affect overall long-term survival of melanoma patients, their slight but measurable benefit on short-term survival (≤ 5 yrs) may be reason enough to recommend the procedure in properly-selected cases.

- There is no proven reason, other than expediency, to perform routine special studies (IHL; MP) on SLNB for melanoma. In fact, these very procedures often raise questions to which answers are not currently available. I recommend serially sectioning SLNBs grossly & completely at 2 mm intervals and obtaining 3 histologic levels of each interval.
Conclusions of MRW (continued)

• “Micrometastases” of melanoma are defined differently by different people, but it appears clear that a few intranodal melanocytes are not actionable, vis-à-vis the need for lymphadenectomy. I endorse van Akkooi’s conclusion that implants of <0.1 mm fall into the same category (pragmatically equaling stage 0).

• SLNB has no role in the diagnosis of biologically-indeterminate melanocytic tumors of the skin. There is no data base from which to make meaningful or scientifically-valid conclusions on such a practice.

• SLNB has become “standard of care” de facto, but it is only properly used for vertical growth phase tumors between 1.2 mm and 3.5 mm in depth. Surgeons who perform the procedure in a “blanket” fashion are misapplying the available data on SLNB and its potential benefits.