Sentinel lymph node biopsy for melanoma was introduced in the early 1990s as a minimally invasive method of identifying and pathologically staging regional lymph node basins in patients with clinical stage I/II melanoma. Numerous large trials have demonstrated that sentinel lymph node evaluation has utility in improving accuracy of prognostication and for risk stratifying patients into appropriate groups for clinical trials. However, there remains a great deal of controversy regarding the therapeutic role of removal of the remainder of locoregional lymph nodes should metastatic cells be identified in the sentinel node. This CME article will outline a brief history of the sentinel node concept before reviewing updates in surgical technique, histopathologic evaluation of nodal tissue, and cost effectiveness of sentinel node biopsy. (J Am Acad Dermatol 2010;62:723-34.)

Learning objectives:
After completing this learning activity, participants should be able to describe the concept of sentinel lymph node biopsy, to discuss the risks and benefits associated with this procedure, and to summarize the role of sentinel lymph node biopsy in management of patients with melanoma.

Key words: melanoma; sentinel lymph node biopsy.

Over the past few years, there has been a great deal of research and debate focused on determining the optimal diagnostic, prognostic, and therapeutic strategies for cutaneous melanoma. Sentinel lymph node biopsy (SLNB) has emerged as a highly valuable prognostic tool. The presence or absence of melanoma cells in lymph nodes draining the primary tumor site is the strongest predictor of both overall survival and risk of recurrence. An excellent comprehensive review of the theory and development of SLNB, and the technical aspects of its performance, was provided by Perrot et al in 2003. This topic was revisited in a well balanced and thorough 2006 review by Johnson et al. The present article will briefly review many of the seminal concepts behind evaluation of the sentinel lymph node (SLN), but will focus mainly on the most recent studies and discussions regarding the role of SLNB in the management of melanoma since the last review by Johnson et al, which was performed more than 4 years ago. Our review will be in the format previously used by Johnson et al, and it will provide updated data for the topics that they outlined. Our goal is to provide a balanced and updated review of the literature, with discussion of the varying and sometimes conflicting opinions regarding the prognostic and therapeutic utility of SLNB.

Abbreviations used:

- ELND: elective lymph node dissection
- HMB-45: human melanoma black 45
- IHC: immunohistochemical staining
- MART-1: melanoma antigen recognized by T-cells
- Melan-A: melanocyte antigen
- MSLT-1: Multicenter Selective Lymphadenectomy Trial 1
- RT-PCR: reverse transcriptase polymerase chain reaction
- SLN: sentinel lymph node
- SLNB: sentinel lymph node biopsy
HYPOTHESES REGARDING ROUTES OF METASTASIS OF CUTANEOUS MELANOMA

Key points

• Different hypotheses exist regarding the further spread of melanoma cells once present in the lymph node.

• These different hypotheses explain why surgical treatment of locoregional lymph nodes may or may not improve overall survival.

Much of the controversy regarding the potential therapeutic benefit of surgical treatment of locoregional lymph nodes basins in patients with melanoma stems from differing hypotheses regarding the path that tumor cells take as they metastasize. In the late 19th and early 20th centuries, Halsted introduced the “tumor-node-blood” concept, hypothesizing that breast cancer cells metastasize from the primary tumor site via the lymphatics, after which systemic dissemination could occur via both the lymphatics and the bloodstream. Today, it is generally agreed upon that metastasis of melanoma cells can occur via lymphatic, hematogenous, or combined routes. However, there is disagreement about the behavior of the metastasizing cells once they reach the regional lymph nodes. Depending on the theory that one believes, different interpretations regarding SLN positivity are made. Some believe that metastases first travel to the SLN and incubate for an indeterminate period of time before spreading to other nodes, the bloodstream, and subsequently to distant sites. Others believe the presence of cells in a SLN is merely a marker for a given tumor’s metastatic capability, a positive sentinel node indicating systemic spread of melanoma cells. Medalie and Ackerman argued that “Nodes are not traps or dams, but filters; they have been shown to allow passage of fluid, air, erythrocytes, lymphocytes, bacteria, and intact neoplastic cells into the efferent lymphatics and into the rest of the vascular system.”

These clinicians argue that systemic spread has already occurred once there are enough metastatic cells to be histologically detectable in a lymph node. Whether this systemic spread becomes clinically meaningful or evident depends on an individual tumor’s biology and that patient’s ability to mount an effective antitumor immune response.

In Grichnik’s recent letter to the editor in the Journal of Investigative Dermatology, another interesting hypothesis has been raised regarding the spread of melanoma and why removal of the lymph nodes in a basin in which a positive SLN has been found has not improved survival in patients with melanoma. A summary of his hypothesis is as follows: it has been shown that the subcapsular sinus channel system, which drains the afferent lymphatics, contains a number of intermediate channels that can directly connect the efferent and afferent lymphatics. Given that melanoma is a genetically heterogeneous disease with different populations of malignant cells within a given tumor, there may exist a subpopulation of melanoma stem cells that do not express markers that home them to the lymph node, allowing them to pass directly from afferent lymphatics to efferent lymphatics and into the vascular system to disseminate systemically. The cells that are found in the lymph nodes may represent another subpopulation of tumor cells that do include markers that allow for adherence and retention within the sentinel node. An example of this is CCR7, a marker that has been associated with lymph node homing of melanoma cells but which has been shown to be heterogeneously expressed within a given tumor. In his letter, Grichnik states that this hypothesis requires further testing, and that SLNB will continue to be important for proper prognostication as we continue to develop a better understanding of the complex melanoma tumor biology.

Of note, there have also been insights into the potential for certain cell adhesion molecules to be used as specific indicators of prognosis. Through the use of microarray, the expression of melanoma cell adhesion molecule (MCAM) in a primary melanoma was shown to be a highly specific prognostic marker for predicting outcome in a retrospective study evaluating 72 patients. In another study, the expression of CEACAM1 was also shown to be an independent factor for the risk of metastasis that had better predictive value than Breslow thickness. In the future, these markers may serve to improve prognostic accuracy or serve as a potential therapeutic target.

Given that we are currently unable to prognosticate accurately or tailor treatment based on each tumor's...
genetic profile and each individual’s immune response to a given tumor, we continue to rely on the best available methods of prognosis and potential treatment of melanoma, which are based on evaluation of the primary tumor’s characteristics and, in melanomas deemed “high risk,” evaluation of local lymph nodes and subsequent decision-making algorithms based on positivity or negativity of the sentinel node.

**HOW DID SENTINEL LYMPH NODE BIOPSY BECOME AN ACCEPTED STANDARD FOR EVALUATION OF THE LOCAL NODAL BASIN OVER ELECTIVE LYMPH NODE DISSECTION?**

**Key point**

- SLNB is less invasive and more sensitive than elective lymph node dissection for the detection of micrometastases in the locoregional lymph node basin

Before the advent of SLNB, elective regional nodal dissection (ELND) was used to stage regional lymph nodes for patients with melanoma at Breslow depths of 0.75 to 4.0 mm. ELND involved the removal of lymph nodes surrounding a primary melanoma based on anatomic maps of predicted lymphatic drainage. The origins of ELND date back to the late 1800s, when Snow, an English surgeon, suggested that melanomas first traveled to a lymph node before disseminating systemically. He believed that early removal of the local lymph node basin might cure patients that had no clinically palpable nodes. ELND prevailed as an accepted therapeutic option for melanomas for much of the 20th century, despite considerable controversy and only retrospective evidence showing a modest survival benefit. ELND is no longer performed for the following reasons:

1. No prospective randomized trial has shown an overall survival benefit, even in patients with intermediate thickness (0.76–4.0 mm) melanomas;
2. Nodal staging after ELND is relatively inaccurate because of the limitations in sensitivity imposed by the time and cost associated with histopathologically evaluating up to 30+ lymph nodes in a given basin;
3. ELND is often associated with significant short- and long-term morbidity. Postoperative complications, including wound infections, seromas, and hematomas, occur in up to 39% of patients. In addition, chronic lymphedema and paresthesias can occur in up to 10% of patients undergoing ELND;
4. Only 20% of patients with intermediate thickness melanomas have any nodal involvement, indicating that 80% of patients would undergo the procedure unnecessarily; and
5. With often ambiguous and unpredictable drainage patterns, the incorrect basin may be dissected.

**DOES THE AVAILABLE EVIDENCE SUPPORT THE SENTINEL NODE CONCEPT?**

**Key points**

- The SLN is defined as the node whose afferent lymphatic channel is the first to receive lymph from the site of the primary melanoma
- The sentinel node concept for melanoma was first developed in the early 1990s by Morton et al

Compared to ELND, SLNB has been developed as a more prognostically accurate, less morbid approach of evaluating the lymphatic basin to which tumor cells may drain. In 1990, Morton, an American surgeon, initially presented the concept of the SLNB for melanoma at the annual meeting of the Society of Surgical Oncology. Based on previous investigations that showed that early stage regional metastasis first occurs in the lymph nodes that drain the tumor and surrounding skin, Morton defined the “sentinel node” as the node whose afferent lymphatic channel is the first to receive lymph from the site of the primary melanoma—an important distinction that is based on functionality rather than anatomy (Fig 1). The SLNB concept is based on the assumption that melanoma metastasizes in an orderly fashion from primary tumor site to the SLN and then to the rest of the regional lymphatic basin. This is believed to occur in a significant number of cases, although hematogenous metastasis can occur before or without lymph node involvement in some patients. According to Morton's theory, the SLN was hypothesized to serve as an accurate marker for likelihood of involvement of the rest of the regional nodal basin. Therefore, if the SLN was found to be negative for tumor cells, then one could be reasonably confident that the rest of the primary draining nodal basin was free of metastatic disease.

Evidence to support that the surgically identified and presumed SLN is actually the first node of metastasis comes from numerous studies mentioned in the following section, where SLN identification was assessed by comparing the status of the presumed sentinel node with that of the remainder of the regional lymphatic basin.
DOES SENTINEL LYMPH NODE BIOPSY ACCURATELY IDENTIFY THE SENTINEL LYMPH NODE?

Key points

- Identification of the SLN is most commonly accomplished by injection of both radioactive colloid (pre- and intraoperatively) and blue dye (intraoperatively) around the primary tumor.

- A learning curve of 30 to 55 cases is required for a surgeon to acquire the necessary skill to reliably perform the procedure.

SLN detection commonly involves the use of preoperative cutaneous lymphoscintigraphy using radioactive colloid, most commonly labeled with technetium-99m. After injection around the primary tumor site, sequential radiographic images display the lymphatic drainage patterns and help in identifying the sentinel node.
the radioactive tracer as it is taken up by the surrounding lymphatic channels and transported to tumor-draining regional nodal basin(s), identifying the basin(s) at highest risk for metastasis. Intraoperatively, the SLN(s) are localized by use of a gamma probe to measure levels of radioactivity from the preoperatively injected radiocolloid, and then by visual identification of blue dye, which is injected around the primary tumor site with subsequent uptake in the afferent lymphatics and SLN(s). Numerous single-institution studies have evaluated the accuracy of pre- and intraoperative SLN detection using peritumoral intradermal injection of isosulfan blue dye alone, intradermal injection of technetium-99m-labeled sulfur colloid alone, or a combination of both. The reported SLN identification rate ranged from 82% to 100%, as assessed by comparing the status of the presumed SLN’s status with that of the remainder of the regional lymphatic basin (Table I). It has been shown that surgeons performing this technique need a minimum of 30 to 55 cases before achieving optimal accuracy of this technique while minimizing false negative results and dissected basin relapse.

The first large randomized trial to demonstrate the accuracy of lymphatic mapping/SLNB technique was the first Multicenter Selective Lymphadenectomy Trial (MSLT-1), an international randomized prospective trial. The third interim analysis of MSLT-1 clearly showed that when performed by an experienced team composed of nuclear medicine, surgical oncologists, and pathologists, lymphatic mapping/SLNB is a safe, accurate, and low-morbidity method of identifying patients with nodal metastases. Their data showed that the overall rate of SLN identification was 95.3% (1352 of 1419), as indicated by the presence of both isosulfan blue dye and radioisotope in a given node or nodes. In addition, the incidence of dissected basin relapse was 6.3% (59 of 944 initially SLN-negative patients) at a median follow-up of 6 years, which suggests a high rate of accurate SLN identification. Therefore, the procedure is widely accepted as being accurate in staging the regional nodal basin. As a result of these studies, a combination of both blue dye and radiocolloid is now widely considered the standard for accurate detection of the SLN in patients with clinically negative nodes.

HISTOPATHOLOGIC EVALUATION OF THE SENTINEL LYMPH NODE

Key points

- **SLNB allows for intensive histopathologic evaluation of a limited number of involved lymph nodes**
- **The use of immunohistochemical evaluation of lymph nodes has greatly improved the sensitivity of detection of micrometastases compared to hematoxylin–eosin stain alone**

Histopathologic staging of SLN has important prognostic implications for patients, because several major studies have shown that involvement of the SLN is strongly associated with a negative disease outcome. Accurate pathologic staging of SLN is extremely important because it has important prognostic implications and it allows the patient to be risk stratified into relatively homogenous groups for clinical trials of adjuvant therapy. However, finding the optimal pathologic protocol for assessment of SLN is an area of active research, and so far no approach has been universally adopted.

Before the advent of lymphatic mapping/SLNB, pathologists would receive the contents of an entire lymph node basin after an ELND, which, at times, had up to 20 to 30 or more lymph nodes in addition to adipose and other tissue. After gross examination of as many nodes as could be identified, standard pathologic examination involved serial sectioning every 3- to 4-mm interval of nodal tissue or one representative 3-μm section followed by hematoxylin–eosin (H&E) staining and inspection under a microscope. It has been estimated that with this

### Table I. Clinical trials of lymphatic mapping and sentinel lymph node biopsy for melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of patients</th>
<th>No. of basins</th>
<th>CLND</th>
<th>SLN identification rate (%)</th>
<th>Positive SLNB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morton31</td>
<td>1992</td>
<td>223</td>
<td>237</td>
<td>Y</td>
<td>82</td>
<td>22</td>
</tr>
<tr>
<td>Reintgen32</td>
<td>1994</td>
<td>42</td>
<td>42</td>
<td>Y</td>
<td>100</td>
<td>19</td>
</tr>
<tr>
<td>Krag33</td>
<td>1995</td>
<td>121</td>
<td>121</td>
<td>Y</td>
<td>98</td>
<td>12</td>
</tr>
<tr>
<td>Thompson33</td>
<td>1995</td>
<td>118</td>
<td>120</td>
<td>Y</td>
<td>87</td>
<td>21</td>
</tr>
<tr>
<td>Morton36</td>
<td>2005</td>
<td>72</td>
<td>79</td>
<td>Y</td>
<td>90</td>
<td>15</td>
</tr>
</tbody>
</table>

Modified from Amersi and Morton.

CLND, Complete lymph node dissection; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; Y, yes.
superficial analysis, less than 1% of lymph node tissue was assessed for metastases.\textsuperscript{23} This incomplete analysis of the lymph nodes led to a number of false negative results of these ELNDs.\textsuperscript{39} The advent of lymphatic mapping/SLNB has made the histopathologic identification of metastasis within nodes much more sensitive by cutting down the number of nodes that need to be investigated to only one, or at most a few, thereby allowing for more intensive analysis of the material.\textsuperscript{40}

Historically, routine histology with H&E staining has been the method of choice for identifying metastatic disease in SLNs. This technique can identify micrometastatic disease in an estimated 15% to 20% of SLNB procedures.\textsuperscript{41,42} However, several studies have shown that the use of only routine histologic H&E examination of lymph nodes underestimates the presence of micrometastatic disease and may miss up to 12% of true positive nodes.\textsuperscript{43,47} Immunohistochemical staining (immunohistochemistry [IHC]) improves sensitivity by detecting clusters or even single metastatic melanoma cells easily overlooked by H&E staining alone. Studies have shown that the use of IHC increases the detection rate of metastatic melanoma by 40%,\textsuperscript{45,48} and the current predominant view is that it increases the detection of positive SLNs by 10% to 34%.\textsuperscript{49,51}

The three most commonly used markers for IHC of melanoma are S-100, HMB-45, and Melan A/MART 1. Currently, S-100 remains the most sensitive marker for detection of melanoma, while HMB-45 and Melan A/MART 1 are used more for their specificity. Given the variable sensitivity and specificity of each marker, a combination of these markers is preferred for the evaluation of nodal specimens.\textsuperscript{51}

Reverse transcriptase polymerase chain reaction (RT-PCR) has emerged as a potential molecular staging tool used to identify patients with histologically missed micrometastatic disease. This technique relies on detection of distinct mRNA expressed by melanoma cells, such as tyrosinase, MAGE-3, MART-1, gp100, and other markers.\textsuperscript{42,52-54} Despite the increased sensitivity, RT-PCR can also give false positive results, which have been attributed to the presence of benign melanocytic nevus cells (capsular nevi) found in the capsule of lymph nodes. Reports have indicated that capsular melanocytic nevus cells can occasionally be found in superficial lymph nodes.\textsuperscript{55} These benign capsular nevus cells express tyrosinase, thereby giving positive RT-PCR results—even in the absence of melanoma.\textsuperscript{41} False positive results can also come from melanophages that have engulfed melanoma tumor cells and have traveled to the lymph node.\textsuperscript{56,57} To circumvent this problem, researchers have tried the use of multi-marker RT-PCR targeting not only tyrosinase but also MART-1, MAGE-3, and/or gp100 mRNAs. The use of two or more melanoma markers for RT-PCR does increase accuracy and specificity of detection of metastasis.\textsuperscript{56,58,59} The clinical relevance of this enhanced ability to detect micrometastases by RT-PCR is still under investigation. Initial results from 30-month follow-up of the Sunbelt Melanoma Trial did not show any difference in disease-free or overall survival in RT-PCR—positive and —negative patients,\textsuperscript{60} but a subsequent metanalysis that included this trial suggested that RT-PCR may have valuable prognostic use.\textsuperscript{61} This technique appears to hold promise, but is currently undergoing further refinement to enhance specificity. Consequently, the current American Joint Committee on Cancer (AJCC) guidelines state that more study data with longer follow-up are needed before they start recommending its use.

### Table II. Comparison of 5-year overall survival based on Breslow thickness and sentinel lymph node status in 209 clinically stage I/II patients

<table>
<thead>
<tr>
<th>Breslow thickness (mm)</th>
<th>5-year OS rate based on Breslow thickness alone (%)</th>
<th>AJCC 5-year OS based on Breslow thickness in nonulcerated primary tumor (for comparison), (%)</th>
<th>5-year OS for all SLN-negative patients, classified by Breslow thickness</th>
<th>5-year OS for all SLN-positive patients, classified by Breslow thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-1.0 (n = 63)</td>
<td>100</td>
<td>97 (T1A)</td>
<td>100 (n = 59)</td>
<td>100 (n = 4)</td>
</tr>
<tr>
<td>1.0-2.0 (n = 91)</td>
<td>93</td>
<td>91 (T2A)</td>
<td>95 (n = 75)</td>
<td>87 (n = 15)</td>
</tr>
<tr>
<td>2.0-4.0 (n = 44)</td>
<td>64</td>
<td>75 (T3A)</td>
<td>76 (n = 29)</td>
<td>40 (n = 15)</td>
</tr>
<tr>
<td>&gt;4.0 (n = 11)</td>
<td>63</td>
<td>71 (T4A)</td>
<td>60 (n = 5)</td>
<td>67 (n = 6)</td>
</tr>
</tbody>
</table>

Data from Vuylsteke et al.\textsuperscript{62} AJCC, American Joint Committee on Cancer; OS, overall survival; SLN, sentinel lymph node.
metastasis by standard H&E staining. In their recommendation, they stated that only after H&E confirmation should a SLN be defined positive for metastasis. However, recognizing the widespread availability and reliability of IHC, and the ability of this method to detect nodal metastases at a level of <0.1 mm tumors, the AJCC has revised their guidelines. The 2009 AJCC Staging System for cutaneous melanoma states that a SLN can be defined positive by detection of micrometastasis by either H&E staining or by IHC staining of melanoma-associated markers.

WHAT ARE THE CAUSES OF FALSE NEGATIVE SENTINAL LYMPH NODE BIOPSY AND WHAT CAN BE DONE TO REDUCE THIS RATE?

Key points

- **False negative is defined as same-basin recurrence among patients with an initial tumor-negative SLN**
- **Preventable false negative SLNBs occur as a result of deficiencies of nuclear medicine, surgical technique, or pathologic evaluation**

Currently, the “false negative rate” is defined as the rate of same-basin recurrence among patients with a tumor-negative SLN. By convention, in order to be considered false negative, the first melanoma recurrence has to be in the sampled node basin. With this new definition and longer follow-up periods for patients with an initially negative SLNB, the false negative rate has been reported to be as high as 15% to 25.

There are three known major causes of false negative SLNB procedure: technical failure, biologic failure, and pathologic failure. A recent study by Karim et al closely investigated 33 patients (from a total of 2426 patients who underwent SLNB) with false negative SLNBs to try to identify the exact cause of false negative results. They concluded that false negatives occur because of deficiencies in nuclear medicine, surgery, or pathology. The results of this study confirm an already known observation: that the experience of each of the team’s components is important in identification of SLN, and that the nodal recurrence rate can be significantly reduced if all the team members are sufficiently trained and experienced with the procedure. The rate of technical failure can also increase if the SLNB procedure is performed after extensive excision and/or flap reconstruction at the primary tumor site. There is evidence to show that the technical failure rate can be reduced if an experienced surgeon performs the procedure. However, like many surgical procedures, there will always be a low level of technical failure rate which should be acceptable, and failure rate should not challenge the validity of the SLN hypothesis.

A biologic failure may occur when lymphatics are obstructed by melanoma cells, which can lead to rerouting of lymph flow. This would lead to inability to detect and retrieve the true SLN. In addition, the rare presence of aberrant lymphatic drainage pathways and in-transit nodes can also lead to biologic failure.

Pathologic failure is caused by the inability of current histopathologic method to detect micrometastatic disease that might be present in the SLN. It has been shown that use of serial sectioning and IHC can increase the detection rate of micrometastases and therefore reduce the number of pathologic false negatives, although the clinical significance of micrometastases detected by extended sampling is still being studied.

RT-PCR, a much more sensitive technique than histologic analysis, is currently being studied as a staging tool for identifying patients with histologically missed micrometastatic disease. While routine H&E is capable of detecting one melanoma cell in $10^4$ lymphocytes, IHC enhances this detection to one melanoma cell in $10^5$ lymphocytes. More strikingly, RT-PCR can identify one melanoma cell in a background of $10^6$ to $10^7$ normal cells. The clinical significance of this enhanced ability to detect micrometastasis by RT-PCR is still under investigation. Some studies suggest that this technique can provide important prognostic information, asserting that micrometastatic disease in the SLN of melanoma patients missed by routine histology but detected by RT-PCR may be clinically relevant disease. However, there is no consensus on the prognostic role of RT-PCR in upstaging of disease.

As discussed earlier, a recently published meta-analysis systematically reviewed the available data on the prognostic role of RT-PCR status in the SLN(s) of patients with melanoma. The metaanalysis pooled the results of 22 published studies, including the Sunbelt Melanoma Trial, which analyzed 4019 patients who had undergone SLNB for clinical stage I and II melanoma. They analyzed correlation of PCR status with TNM staging, disease recurrence rates, and survival. Although the available evidence was somewhat conflicting, the overall conclusion was that RT-PCR status of SLN appears to represent significant metarisk for both disease-free and overall survival. It was also concluded that RT-PCR has
clinically valuable prognostic power, suggesting that micrometastases missed by routine histology in the SLN(s) is indeed clinically relevant. However, the authors caution that the available evidence is not yet sufficient to consider using PCR status in the therapeutic decision making process, stating that although the results are promising, more research needs to be performed.

**DOES SENTINEL LYMPH NODE BIOPSY ACCURATELY PREDICT PROGNOSIS?**

**Key points**

- **SLN status is currently the most sensitive and specific staging tool available**
- **Ultrasound is currently not a better alternative prognostic tool compared to SLNB**

A large body of evidence supports the notion that SLNB is the most sensitive and specific staging tool available today, and that SLN status is the most important prognostic factor for disease-free and overall survival. In a multivariate Cox model, the sentinel node status had a higher prognostic predictive value (Hazard ratio, 2.42; 95% CI, 1.52-3.87) than Breslow thickness, Clark level, ulceration, age, or gender. To our knowledge, there is only one nonrandomized retrospective study of 309 patients that failed to show the prognostic significance of SLN status. However, this single negative study had a follow-up period of only 22 months, and the results contrasted with numerous other similar small retrospective studies with similar follow-up periods.

The MSLT-I trial confirmed the prognostic importance of SLN status, again showing that SLN status is the most statistically significant predictor of survival for clinically localized (stage I/II) intermediate thickness melanoma, with the potential to provide more accurate information for a given patient than demographic (gender) or histopathologic factors of the primary tumor (Breslow depth or ulceration). The 5-year disease-free survival for patients with positive SLN status was 72.3%, compared to 90.2% in those with negative SLN status.

Some have argued that despite these data, there is currently no indisputable proof that all positive SLNs, especially ones with micrometastatic disease, will progress to clinically relevant disease. Those in favor of this view state that in certain patients, micrometastatic deposits of melanoma within the SLN(s) will remain dormant or will be destroyed by the immune system, therefore never developing into clinically relevant metastases. In this small percentage of patients, the positive SLN will not be prognostically relevant, and will in fact be what has been termed a “prognostic false positive” SLN. However, others have proposed an alternate view to this concept of a false positive SLN, providing evidence that removal of SLN(s) may be adequately therapeutic in certain situations where micrometastatic deposits are below a certain size or capsular invasion threshold. However, because there is currently no method of evaluating the eventual fate of a given micrometastatic deposit in a given patient, further research is needed in this area before we can accurately and consistently identify the small percentage of patients with positive SLNBs who will not progress to clinically relevant disease.

Some have argued that although SLN status is statistically more significant as a predictor of overall survival, there may not be enough clinically useful difference of SLN status over Breslow thickness in ability to predict melanoma-specific death, given their similar P values (P < .001 for SLN status vs P = .002 for Breslow depth) and hazard ratios (hazard ratios of 2.48 [1.54-3.98] for SLN status vs 1.66 [1.20-2.30] for Breslow depth). However, in a small study of 209 patients by Vuytsteke et al, although there was comparable prognostic accuracy of SLN status and Breslow depth for melanomas from <2 mm and >4 mm, there was a significant improvement in prognostic accuracy for intermediate thickness melanomas (2-4 mm) when using SLN status instead of Breslow thickness (Table II).

In light of these data, it has been argued that SLN status may only have additional prognostic use in the subgroup of melanomas with Breslow thickness from 2 to 4 mm. What this argument does not take into account is the prognostic importance of additional positive nodes if the sentinel node is positive. In addition to the information provided by Breslow thickness, prognosis for patients with melanoma varies significantly based on the number of positive nodes, whether they are clinically palpable, and ulceration of the primary tumor. To show an extreme example of this difference, patients with a non-ulcerated primary tumor and a single, microscopically positive node have a 5-year survival rate of 69%. Alternatively, patients with an ulcerated primary tumor and ≥4 clinically positive nodes have an average 5-year survival rate of 13%. However, as will be discussed in detail in part II of this series, the morbidity and unproven therapeutic use of complete lymph node dissection (CLND) must be weighed against the benefit of this additional prognostic use, especially considering that only 20% of patients with a positive SLNB have involvement of other nodes. MSLT-II, which will also be extensively discussed in part II of this series, is currently enrolling patients to specifically evaluate the potential therapeutic benefit of CLND after positive SLNB.
The use of ultrasound (US) has been suggested as an alternative to SLNB. However, is the sensitivity of this technique high enough to replace SLNB? In a small 2003 study, Rossi et al enrolled 125 patients with >1 mm thick melanoma and performed preoperative US on all patients scheduled for SLNB. If concerning features for metastasis were detected in any lymph nodes in the target basin by US, a fine-needle aspiration (FNA) was performed for more detailed analysis. The results of this study revealed that preoperative US, combined with FNA, was only able to identify approximately one-third of patients with positive SLNB. Although the specificity of this technique was 100% in this study, the sensitivity was only 39% (12 of 31 patients), leading to a false negative rate of 61%. This is believed to mainly be caused by the inability of US to identify tumor deposits <2 mm in diameter. The investigators of this study argue that rather than an alternative prognostic tool to SLNB, preoperative US combined with FNA could allow about 10% of patients with positive FNA to proceed directly to a full nodal dissection rather than undergo and SLNB followed by a CLND. However, given the technique’s very low sensitivity, US is currently not comparable to SLNB for prognostic purposes.

**IS THERE ANY PSYCHOLOGICAL BENEFIT OF KNOWLEDGE OF SENTINEL LYMPH NODE STATUS?**

**Key points**
- Very limited data are available regarding the psychological impact of knowledge of nodal status
- Patient preferences regarding knowledge of sentinel node status should be discussed carefully before the procedure

As physicians, we often assume that patients uniformly assign a high value to information regarding prognosis. Surprisingly, there are very limited data regarding the psychological impact of undergoing SLNB or of subsequent knowledge of SLN status. A small study published in 2002 by Rayatt et al surveyed 98 patients before and after undergoing SLNB for stage I/II melanoma. Patients were asked a number of questions regarding their pre- and postoperative concerns, what benefits they perceived to derive from the procedure, and how the procedure and subsequent result impacted their psychological well being. The authors concluded that, independent of SLN status, the two main psychological benefits afforded by SLNB included peace of mind and planning for the future. The authors also added that these benefits were not necessarily translatable to improvement in quality of life or a reduction in stress, and the percentage of patients reporting “feeling cured,” “feeling reassured disease had not spread,” and “feeling well looked after” significantly decreased from the initial 6-month follow-up to the last scheduled follow-up at 18 months. Regardless of SLN status, 97% of patients reported being “glad” they had the procedure. This study was limited by having a small sample size, and with even fewer patients at the 18-month follow-up. In a subsequent editorial, the authors assert that the small and transient psychological benefit shown in this study is not an adequate stand-alone justification for SLNB.

Previous studies evaluating patient preferences with use of interferon as adjuvant therapy have shown that a large percentage of patients with melanoma are willing to undergo a moderately to severely morbid treatment for a small potential increase in odds of survival. However, in this study, there were also a significant percentage of patients that preferred a higher risk of recurrence over toxic treatments, suggesting that the risks and benefits of any potentially morbid procedure should be carefully analyzed on an individual basis.

The difference in individual patient preferences and values highlighted by both of these studies shows the importance of careful and thorough informed consent. These results also suggest a possible role of postdiagnosis psychological evaluation of patients to better understand their preferences regarding knowledge of nodal status.

**COST/BENEFIT OF NODAL ANALYSIS**

**Key points**
- The cost of performing SLNB in the United States ranges from $7,000 to $15,000 per patient
- Limited available data on cost effectiveness of this procedure suggests that it may be cost effective for melanomas >1 mm in thickness

As physicians, one of our goals is to provide the optimal care for each patient, often with little regard to cost. However, from a societal perspective, the cost of performing SLNB—and the subsequent CLND—should be considered. The cost to perform SLNB, including physician care, medications, dyes, operating room, and pathology costs, has been estimated to be from $7000 to $15,000 per patient. This compares to an average cost of approximately $1500 for wide local excision alone. Agnese et al determined that for melanomas <1.2 mm, SLNB is not cost-effective, because the cost per life saved ranged from $627,000 to $931,000. In summary, the cost of performing SLNB is not cost-effective for most melanoma patients. However, if the melanoma is >1 mm in thickness, SLNB may be cost-effective, and the costs of performing SLNB may be justified.
addition, given the lack of proven survival benefit, some would argue that the costs and potential morbidity associated with CLND in patients with positive SLN (operative plus postoperative complication management) might be high enough to be considered unjustifiable, given that it is unnecessary in at least 80% of those patients.

Until recently, no studies had evaluated the cost effectiveness of SLNB in intermediate melanomas. Morton et al. developed a Markov model to simulate the natural history of melanoma progression in patients with primary melanomas > 1 mm. This study calculated health outcomes in terms of survival (life years saved), and quality-adjusted life years (QALYs). They found that over a simulated 20-year period, SLNB versus wide excision alone led to 0.31 life years saved and 0.44 QALYs, which equaled an extra 5.2 months in full health for only a slight increase in cost over wide local excision alone. It must be stated, however, that this study based its model on certain controversial interpretations of MSLT-1, including a slightly higher 5-year disease-free survival (78% vs 73%), and the 20% survival benefit found in the post hoc analysis of patients undergoing immediate CLND versus patients found to have clinically palpable nodes. Perhaps with different inputs into the model, the conclusions of this study may have been different.

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