Controversies in the Management of Regional Nodes in Melanoma

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Key Words
Melanoma, lymph node dissection, sentinel lymph node biopsy

Abstract
The surgical management of the regional lymph node basin of melanoma has undergone significant changes in the past 2 decades, most of which have been guided by prospective randomized trials. Historically, routine elective lymph node dissection was recommended for the management of melanoma regardless of clinical nodal involvement. Subsequent randomized trials failed to show a clear benefit for all patients, and sentinel lymph node (SLN) biopsy emerged as an alternative. Although the prognostic value of SLN biopsy in intermediate-thickness melanoma is well accepted, its value for patients with thin and thick lesions is debated. The therapeutic advantage of removing an involved SLN, and the need for a completion lymph node dissection after the identification of a positive SLN, are areas of continued controversy. This article discusses these issues in the management of the regional lymph node basin in patients with melanoma. (JNCCN 2012;10:414–421)

SLN Biopsy

The SLN hypothesis dictates that the first draining lymph node from a tumor, the sentinel lymph node, has the highest risk of harboring clinically occult metastases. This principle was first introduced for carcinoma of the parotid and penis. Morton et al. then adapted this model for melanoma. In the operating room, the SLNs are identified using guidance from the gamma probe and visual confirmation of blue dye, which is injected around the primary lesion at surgery. This combination has been shown to improve the detection of melanoma metastasis, with an overall detection rate of more than 96%.

Who Needs an SLN Biopsy?

The risk of a positive SLN increases with tumor thickness, mitotic rate, and the presence of ulceration. Large studies also supported the increasing risk associated with ulceration, high mitotic rate, lymphovascular invasion, young age, and absence of regression. All of these factors must be evaluated when considering SLN biopsy, many of which can be individualized through the use of a nomogram. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Melanoma recommend that practitioners discuss SLN biopsy with all patients with a melanoma greater than 1 mm in thickness (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). The detection of lymph node metastasis through SLN biopsy stratifies a group of patients with worse survival compared with node-negative patients.
Although the prognostic value of SLN biopsy is clear, the potential therapeutic benefit remains uncertain. The Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1) study compared outcomes after wide local excision (WLE) and therapeutic lymph node dissection if clinical nodal recurrence developed versus outcomes after WLE and SLN biopsy, with completion lymphadenectomy if microscopic SLN involvement was discovered.\textsuperscript{16} MSLT-1 again confirmed the prognostic value of SLN biopsy, with a 5-year melanoma-specific survival rate of 72\% in patients with a positive SLN and 90\% among those with tumor-negative SLNs ($P < .001$). The study also showed improved disease-specific survival; however, this was largely due to lower nodal basin failures after SLN biopsy. Overall, no overall survival advantage was observed when comparing patients randomized to WLE and SLN biopsy and those who underwent WLE alone.

In a retrospective subset analysis of all node-positive patients, improved survival was observed in patients with a positive SLN compared with those who developed clinically positive nodes on the observation arm (72\% vs. 52\%, $P = .004$). The incidence of SLN micrometastases was 16\%, and the rate of relapse in regional nodes in the observation group was nearly identical (15.6\%), suggesting a natural progression of subclinical micrometastatic disease to clinically relevant lymphadenopathy. The mean number of tumor-involved nodes at lymphadenectomy was 1.4 in the SLN biopsy group and 3.3 in the nodal observation group that experienced recurrence ($P < .001$), suggesting disease progression during the period of observation.

Although the results of MSLT-1 confirmed the power of SLN biopsy in intermediate-thickness melanoma (1.2–3.5 mm), numerous controversies arose over its therapeutic potential. The inclusion of nodal recurrences in the calculation of disease-free survival has been criticized. In patients with intermediate-thickness melanoma, the most common site of first recurrence is the regional lymph node basin, and therefore a disease-free survival advantage in the SLN biopsy arm is expected. Arguments have also been raised against the postrandomization subgroup analysis, comparing patients with microscopic nodal disease with those with macroscopic disease, which was not a primary outcome of the study.\textsuperscript{17} However, it was impossible to know pre-operatively who would experience recurrence in the nodes, and therefore impossible to randomize these groups at the outset. The lack of overall survival difference may be confounded by the low incidence of positive nodes; only 16\% of patients could have benefited from a lymph node dissection.

Also of concern is that the false-negatives were not included in the calculations of the 20\% difference.\textsuperscript{17} Although the authors of MSLT-1 assumed that all positive SLNs would eventually progress to a clinically positive node, because the rate of nodal metastases in the observation group was 15.6\% and the rate of positive sentinel nodes was 16\%, this comparison does not include the false-negatives, and therefore the rates are not necessarily the same.\textsuperscript{17} It is conceivable that a significant survival difference may emerge on longer follow-up in subsequent planned analyses.

The question of whether the SLN biopsy procedure could influence the development of in-transit metastasis has been raised. Retrospective data correlated removal of the SLNs with an altered pattern of subsequent recurrence and increased incidence of in-transit recurrences.\textsuperscript{18,19} In response, numerous studies, including 2 large single-center series, have refuted an association between patterns of recurrence and SLN biopsy.\textsuperscript{20,21} These series show that the incidence of in-transit is low and most likely dictated by primary tumor biology rather than by treatment variables.

Considerable debate exists on the efficacy of SLN biopsy in patients with thin ($\leq 1$ mm) or thick ($\geq 4$ mm) primaries. The role of SLN biopsy in thin melanomas has been discussed extensively by Andtbacka and Gershenwald.\textsuperscript{22} The incidence of nodal metastasis is low with thin melanoma and, other than increasing tumor thickness and mitotic rate, the prognostic factors are poor. Recently, the largest analysis of mitotic rate demonstrated its independent prognostic value,\textsuperscript{11} and it replaced Clark level in the staging of thin melanomas.\textsuperscript{1} Accordingly, any patient with a thin melanoma with increasing thickness and/or mitosis greater than or equal to 1 has a worse melanoma-specific survival, and SLN biopsy should be discussed, with the caveat that the prognostic value of SLN in this situation may be less.\textsuperscript{23,24}

Overall, this population has an excellent prognosis, and the risks and benefits of the procedure and the cost must be considered and discussed in the absence...
of clear therapeutic benefit.\(^{24,25}\) The total cost to perform an SLN biopsy ranges from $7,000 to $15,000 per patient compared with an average cost of $1,500 for a WLE alone.\(^{24,26}\)

The prognostic significance of nodal staging for thick primaries (≥ 4 mm) has also been questioned because of the high risk of metastatic disease in these patients.\(^{27}\) Only approximately half of all patients diagnosed with thick melanoma will be alive in 10 years.\(^1\) Most studies have shown SLN status to be independently prognostic (Table 1).\(^{28–31}\) Patients with thick melanoma, however, have a higher false-negative rate, which is likely a consequence of the higher incidence of pathologic adverse features, such as lymphovascular invasion and ulceration.\(^{31}\) Based on several supportive retrospective reviews, SLN biopsy is recommended for patients with thick primaries and clinically negative regional nodes.

The role of SLN biopsy also remains unclear in cases of in-transit lesions and microscopic satellitosis. Satellitosis is strongly associated with SLN-positive rates greater than 70%, regional nodal involvement, and poor survival.\(^{32–34}\) In-transit metastases have also been associated with high SLN positivity rates.\(^{33}\) Both scenarios are associated with a high risk of distant metastasis, and by definition are stage III disease; therefore the role of a staging SLN biopsy may be irrelevant.

### The Role of Ultrasound as a Means to Interrogate the SLN

Ultrasound is an emerging technology that could provide an attractive alternative to surgical interrogation of lymph nodes. The procedure is relatively inexpensive, safe, and well tolerated. However, whether ultrasound can detect metastasis as effectively as surgical removal of lymph nodes is unclear. Studies have examined ultrasound in combination with guided fine-needle aspiration cytology in the setting of SLN biopsy. A prospective evaluation of ultrasonographic criteria found a sensitivity of 82% and a positive predictive value of 52%.\(^{36}\) This experience, however, has not been consistent across groups.\(^{37}\) Other studies have reported sensitivity rates of approximately 30%, with a cutoff value of detecting metastatic lesions of approximately 4.5 mm.\(^{38,39}\) The discrepancy among reports may be from differences in operator experience, learning curve, ultrasound technology, or where the sentinel node is identified on preoperative lymphoscintigraphy (targeted ultrasound) versus nontargeted ultrasound, with which the entire lymph node basin is screened for suspicious changes.\(^{40}\) In a recently published abstract, ultrasound data were extracted for all patients enrolled in MSLT-II from 2004 to 2010 and compared with the pathologic assessment of the SLN.\(^{41}\) Ultrasound had a true-positive rate of only 1.6%, yielding a sensitivity of 8% for the preopera-

### Table 1 Prognostic Value of Sentinel Lymph Node in Thick (> 4 mm) Melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>SLN % Positive</th>
<th>Survival SLN−</th>
<th>Survival SLN+</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gershenwald et al.,(^{30}) 2000</td>
<td>131</td>
<td>39</td>
<td>82% 3-y DFS</td>
<td>58% 3-y DFS</td>
<td>&lt; .03</td>
</tr>
<tr>
<td>Ferrone et al.,(^{28}) 2002</td>
<td>126</td>
<td>30</td>
<td>56% 5-y RFS</td>
<td>32% 5-y RFS</td>
<td>.0008</td>
</tr>
<tr>
<td>Carlson et al.,(^{29}) 2003</td>
<td>114</td>
<td>33</td>
<td>82% 3-y OS</td>
<td>57% 3-y OS</td>
<td>.006</td>
</tr>
<tr>
<td>Jacobs et al.,(^{32}) 2004</td>
<td>43</td>
<td>44</td>
<td>53-mo DFS</td>
<td>44-mo DFS</td>
<td>.02</td>
</tr>
<tr>
<td>Caraco et al.,(^{33}) 2004</td>
<td>62</td>
<td>NR</td>
<td>55% 3-y OS</td>
<td>55% 3-y OS</td>
<td>NS</td>
</tr>
<tr>
<td>Gutzmer et al.,(^{29}) 2008</td>
<td>152</td>
<td>49</td>
<td>68% 5-y OS</td>
<td>53% 5-y OS</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Scoggins et al.,(^{31}) 2010</td>
<td>240</td>
<td>41.7</td>
<td>55.5-mo median OS</td>
<td>43-mo median OS</td>
<td>.004</td>
</tr>
<tr>
<td>Meguerditchian et al.,(^{36}) 2011</td>
<td>91</td>
<td>53</td>
<td>111-mo median OS</td>
<td>41-mo median OS</td>
<td>.006</td>
</tr>
</tbody>
</table>

Abbreviations: DFS, disease-free survival; NR, not reported; NS, not significant; OS, overall survival; RFS, relapse-free survival; SLN, sentinel lymph node.
tive detection of positive SLNs. SLN biopsy remains the most accurate means of regional node staging in patients with melanoma.

How Should SLNs Be Analyzed?

The role of frozen section in melanoma has been controversial, because studies have shown a reduced ability to detect SLN metastasis on frozen section42–44 and a potential to waste valuable portions of the SLN.45 Advocates of frozen section have argued a low false-negative rate and the ability to spare patients an additional anesthesia.46,47 Newer techniques, such as imprint cytology, have suggested a role for intraoperative analysis, without the limitations of traditional frozen section analysis.48 These techniques, however, remain unproven, and the consensus of the American College of Pathology and the International Sentinel Lymph Node Society is to not perform a frozen section.49

The technique of histologic evaluation of the SLN includes a period of fixation, bisection through the longest meridian, and a variable number of hematoxylin-eosin (H&E)–stained sections from each half.50 Many studies have shown that immunohistochemistry with antibodies against HMB-45 and MART-1 can increase the detection of melanoma.51,52 A study of extensive sectioning in conjunction with immunohistochemistry showed that detection of SLN positivity can be increased through staining (H&E, S-100, HMB-45) 3 sections from 3 levels at 250-µm intervals.53 Follow-up of patients with sentinel nodes analyzed in this manner showed improved recurrence-free and disease-specific survivals compared with patients whose nodes were analyzed in a conventional manner. Debate remains regarding the relevance of more sensitive techniques, such as reverse transcriptase-polymerase chain reaction (RT-PCR), to detect melanoma-specific genes. Using this technique, up to 25% to 50% of H&E-negative SLNs are positive on RT-PCR.54,55 Although Takeuchi et al.56 showed a very poor survival with the multimarker PCR–positive group, approximately that of patients with clinical stage III disease, long-term follow-up from the Sunbelt Melanoma Trial and Memorial Sloan-Kettering Cancer Center have not confirmed a prognostic difference in patients who are PCR-positive compared with those who are PCR-negative.57,58 Little evidence currently exists that increasing sensitivity of metastatic detection has physiologic relevance.

Which Patients Need a Complete Lymph Node Dissection?

Complete lymph node dissection (CLND) after a positive SLN biopsy is the current standard approach. However, whether this procedure is necessary in everyone is highly debated. Furthermore, despite the guideline, great disparity exists in the number of patients who actually undergo a CLND.59 A recent review of the National Cancer Data Base showed that only 50% of patients with a positive SLN biopsy underwent CLND.60

The rationale for performing a CLND includes improved staging, better local control, and the capacity to do a less-morbid procedure at detection of microscopic disease. At CLND, 15% to 20% of specimens will harbor disease seen on routine H&E staining, and this accurately stages patients. In the Sunbelt Melanoma trial, the rate of recurrence in the regional lymph node basin after CLND in SLN-positive patients was exceedingly low.61 Furthermore, the morbidity of early CLND may be less than when palpable lymphadenopathy is present. In a recently published analysis of MSLT-1, an increase in lymphedema and hospital stay was observed for patients undergoing a delayed CLND.62 The increased risk of complications likely reflects the morbidity associated with surgery in the setting of increased tumor burden. In addition, the information gained from a CLND is prognostic, because a positive nonsentinel lymph node (NSLN) is the most important predictor of survival among patients with a positive SLN.63–65

Further supporting the debate on the need for CLND are the results of highly selected retrospective studies that have not shown a significant difference in survival for patients undergoing nodal observation. A multi-institutional study collected data on 134 patients who did not undergo a CLND and found disease-specific survival to be similar to that of a cohort of patients who underwent a CLND.66 This study, however, has been criticized for a relatively short follow-up period. A recent follow-up study also failed to show a significant difference in recurrence-free and disease-specific survivals in selected patients who did not undergo CLND compared with those who did.67

Research efforts have focused on trying to identify which patients may benefit from CLND. Most of the efforts have focused on characterizing the tumor burden in the SLN to understand if this can
predict the risk of disease in the NSLN (Table 2). Starz et al.\(^6\) determined that invasion deeper than 1 mm below the lymph node capsule of the SLN yielded a survival similar to that of patients undergoing a therapeutic lymph node dissection, and was a powerful predictor of NSLN positivity. These findings were validated in another series of patients.\(^6\) A recent validation study determined that having a metastatic deposit smaller than 0.1 mm and with a maximal depth of invasion less than 0.3 mm yielded a very low probability (0%–5%) of further NSLN metastases.\(^7\) The importance of tumor burden size was also confirmed in a separate study measuring burden as the percentage of surface area.\(^7\),\(^8\) Using several other clinicopathologic features of the SLN and the primary lesion in 409 patients with positive SLN biopsies, a clinical risk score for NSLN involvement was created that further improves on the predictive power of SLN tumor burden alone.\(^9\) These results are promising and further the understanding of the subsequent risk of nodal metastasis. However, the inherent limitations of selection bias in these retrospective series are important to note. Furthermore, the technique of measuring SLN burden has not been standardized and may be subject to variability.

The ongoing MSLT-II trial randomizes patients with a positive SLN biopsy to CLND versus nodal observation with ultrasound. The primary objective of this trial is to determine whether CLND will improve disease-specific survival in patients with a positive SLN biopsy. In Europe, a similar MINTUB study is investigating the role of omitting a CLND in patients with minimal SLN disease burden. Until the results of randomized trials become available, patients found to have a positive SLN should be treated with CLND or enrolled into the MSLT-II trial. Other options will ideally be personalized for each patient and are a subject for debate.

**When Should Adjuvant Radiation Be Used?**

In the adjuvant setting, radiation has the potential to decrease local recurrence, which can be a significant source of morbidity involving high-risk reoperations.

### Table 2 Sentinel Lymph Node Analysis and Complete Lymph Node Dissection Positivity

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Variable</th>
<th>Grouping</th>
<th>Survival (%)</th>
<th>CLND+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reeves et al.,(^8)</td>
<td>98</td>
<td>Score: &gt; 2 mm SLN tumor diameter, ulceration of primary</td>
<td>0</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>NA</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>NA</td>
<td>31</td>
</tr>
<tr>
<td>Starz et al.,(^6)</td>
<td>70</td>
<td>Depth of capsular invasion</td>
<td>≤ 0.3 mm</td>
<td>~80 (5-y)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 0.3 ≤ 1.0 mm</td>
<td>~95 (5-y)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 1.0 mm</td>
<td>~60 (5-y)</td>
<td>NA</td>
</tr>
<tr>
<td>Sabel et al.,(^7)</td>
<td>232</td>
<td>Extracapsular extension, ≥ 3 + SLNs</td>
<td>Extracapsular extension, ≥ 3 + SLNs</td>
<td>NA</td>
<td>3.2 OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td>65.8 OR</td>
</tr>
<tr>
<td>Govindarajan et al.,(^8)</td>
<td>127</td>
<td>SLN tumor diameter</td>
<td>≤ 0.2 mm</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.2–2.0 mm</td>
<td>NA</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 2.0 mm</td>
<td>NA</td>
<td>26.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≤ 0.5 mm</td>
<td>NA</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≤ 0.1 mm(^2)</td>
<td>NA</td>
<td>3.7</td>
</tr>
<tr>
<td>Gershenwald et al.,(^9)</td>
<td>309</td>
<td>SLN tumor diameter, tumor area</td>
<td>≤ 0.1 mm</td>
<td>91 (5-y)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1–1.0 mm</td>
<td>61 (5-y)</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 1.0 mm</td>
<td>51 (5-y)</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Subcapsular</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Parenchymal</td>
<td>NA</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Combined</td>
<td>NA</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multifocal</td>
<td>NA</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extensive</td>
<td>NA</td>
<td>40</td>
</tr>
</tbody>
</table>

Abbreviations: CLND, complete lymph node dissection; NA, not applicable; OR, odds ratio; SLN, sentinel lymph node.
Abundant retrospective data support the use of adjuvant radiation after lymphadenectomy in patients at high risk for local recurrence.\textsuperscript{74,75} High-risk factors include more than 3 involved lymph nodes, lymph node with tumor deposit larger than 3 cm, extracapsular extension in the setting of palpable lymphadenopathy, and recurrent disease. A recent multicenter trial randomized 250 patients after lymph node dissection with macroscopic nodal metastases and high-risk features (multiple or large involved nodes, extranodal extension) to receive 48 Gy in 20 fractions or observation.\textsuperscript{76} Adjuvant radiotherapy in this trial showed improved local control but no significant improvement in overall survival.

Some anatomic considerations warrant mention, because complication rates differ depending on the nodal basin involved.\textsuperscript{77} The addition of radiation therapy after neck dissection can result in excellent regional control, with up to 10% of patients experiencing some degree of hearing loss, wound breakdown, chronic ear pain, and lymphedema in the axilla, which can be as high as 40% after radiation.\textsuperscript{78} Complications for lymphadenectomy with or without surgery are significantly higher for the inguinal nodal basin, with lymphedema occurring in up to 45% of patients.\textsuperscript{79} Radiation serves as a powerful adjunct to surgery for local control. The decision to use radiotherapy ultimately must be individualized, incorporating the estimated biologic aggressiveness of the patient’s disease with the potential morbidity.

**Conclusions**

The regional lymph node basin is the most common first site of cutaneous melanoma metastases. Fortunately, excellent quality level 1 data are available to guide decision-making and accurately quantify risks of intervention; however, numerous questions still remain. The heterogeneity of melanoma will ultimately necessitate long-term follow-up of clinical trials to best determine treatment options. Furthermore, as new and effective therapies become available, the role of staging using the lymph nodes may have renewed importance. Of utmost importance is a discussion between the physician and the patient so that a mutual decision can be made based on individual risk, adverse effects, and patient preference. The past 2 decades have brought sweeping changes in the surgical approach to melanoma, and the hope is that continued research will further narrow the gap between the patients who receive benefit from interventions and those who only experience morbidity.

**References**

53. Plitas and Ariyan


