

# Evidence-Based Clinical Practice Guidelines on the Use of Sentinel Lymph Node Biopsy in Melanoma

Vernon K. Sondak, MD, Sandra L. Wong, MD, Jeffrey E. Gershenwald, MD, and John F. Thompson, MD

## OVERVIEW

Sentinel lymph node biopsy (SLNB) was introduced in 1992 to allow histopathologic evaluation of the “sentinel” node, that is, the first node along the lymphatic drainage pathway from the primary melanoma. This procedure has less risk of complications than a complete lymphadenectomy, and if the sentinel node is uninvolved by tumor the likelihood a complete lymphadenectomy would find metastatic disease in that nodal basin is very low. SLNB is now widely used worldwide in the staging of melanoma as well as breast and Merkel cell carcinomas. SLNB provides safe, reliable staging for patients with clinically node-negative melanomas 1 mm or greater in thickness, with an acceptably low rate of failure in the sentinel node-negative basin. Evidence-based guidelines jointly produced by ASCO and the Society of Surgical Oncology (SSO) recommend SLNB for patients with intermediate-thickness melanomas and also state that SLNB may be recommended for patients with thick melanomas. Major remaining areas of uncertainty include the indications for SLNB in patients with thin melanomas, pediatric patients, and patients with atypical melanocytic neoplasms; the optimal radiotracers and dyes for lymphatic mapping; and the necessity of complete lymphadenectomy in all sentinel node-positive patients.

An estimated 76,690 patients will be diagnosed with invasive melanoma in the United States in 2013, and 9,480 patients will die from the disease.<sup>1</sup> Because of the predilection for melanoma to spread to the regional lymph nodes and the significant effect of nodal metastasis on prognosis,<sup>2</sup> elective regional lymphadenectomy was once routinely performed for most patients with clinically node-negative melanoma. Since most patients with clinically node-negative melanoma do not have and never develop nodal metastases, elective lymphadenectomy exposes many patients to unnecessary risks, including lymphedema, without ever having been shown to improve survival in prospective randomized trials. Sentinel lymph node biopsy was introduced in 1992 as a less invasive alternative that would allow histopathologic evaluation of the “sentinel” node, that is, the first node along the lymphatic drainage pathway from the primary melanoma.<sup>3</sup> This procedure has less risk of complications than a radical lymphadenectomy,<sup>4</sup> and if the sentinel node is uninvolved by tumor, the likelihood a complete lymphadenectomy would find metastatic disease in that nodal basin is less than 5%.<sup>5</sup> SLNB is now widely used worldwide in the staging of melanoma as well as breast and Merkel cell carcinomas. The results of SLNB are incorporated into the American Joint Committee on Cancer (AJCC) pathologic staging system for melanoma patients.<sup>2</sup> By convention, melanoma found in a lymph node removed during SLNB is called “micrometastasis”

(N1a or N2a depending on the number of sentinel nodes involved), whereas melanoma detected by physical examination or imaging is called macrometastasis.

Importantly, the sentinel nodes are evaluated intensively using serial sectioning and a combination of routine histopathology and immunohistochemistry staining for melanoma-associated antigens such as S-100 and MART-1/Melan-A. It is impractical to routinely evaluate the many nodes from a complete lymphadenectomy in this detailed fashion. Even nodes with only one or a few isolated tumor cells detected solely by immunohistochemistry are considered tumor-positive,<sup>2</sup> and in at least some studies these isolated tumor cells in the node have proven prognostically significant.<sup>6</sup> Thus, despite the less invasive nature of a SLNB, the histopathologic staging data obtained can actually be more accurate than from a complete node dissection.

Only patients who have melanoma found within the sentinel node are subjected to the potential complications of a complete lymphadenectomy, whereas those with a negative SLNB are observed without further surgery. There is evidence from a large prospective randomized trial of sentinel node biopsy compared with observation, the Multicenter Selective Lymphadenectomy Trial 1 (MSLT-1),<sup>7</sup> that lymphadenectomies performed after the detection of micrometastatic disease by SLNB are associated with fewer and less severe complications, particularly in terms of lymphedema.<sup>8</sup>

From the Department of Cutaneous Oncology, Moffitt Cancer Center, and Departments of Oncologic Sciences and Surgery, University of South Florida, Tampa, FL; Department of Surgery, University of Michigan Medical Center, Ann Arbor, MI; Departments of Surgical Oncology and Cancer Biology, The University of Texas MD Anderson Cancer Center, Houston, TX; Melanoma Institute Australia and the University of Sydney, Sydney, Australia.

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Corresponding author: Vernon K. Sondak, MD, Moffitt Cancer Center Department of Cutaneous Oncology, 12902 Magnolia Dr., Tampa, FL 33612; email: vernon.sondak@moffitt.org.

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However, despite these apparent advantages, SLNB remains controversial in some circles.<sup>9</sup>

## THE “HIGH LEVEL” EVIDENCE REGARDING SENTINEL NODE BIOPSY IN MELANOMA

Accurate sentinel node identification relies on high-quality preoperative lymphoscintigraphy, careful surgery guided both by vital blue dye and a gamma probe and thorough pathologic examination. The reliability of sentinel node status as an indicator of the presence or absence of metastasis in the entire regional node field was initially reported by Morton and colleagues,<sup>3</sup> and verified by Reintgen and colleagues<sup>10</sup> and Thompson and colleagues.<sup>11</sup> In over 98% of cases, it is possible to identify and remove at least one sentinel node, and there is often more than one.<sup>12</sup> For the SLNB procedure to be accurate, it is of critical importance that all true sentinel nodes are identified and removed for examination.

False-negative rates for SLNB have now been reported in many studies, and range quite widely from 0% to 34%, with a weighted average of 12.5% in a large meta-analysis.<sup>12</sup> It is important to note the way in which a false-negative rate is properly defined: as the number of regional failures in sentinel node-negative basins divided by the total number of node-positive cases (regional failures plus positive sentinel nodes). It should not be confused with the negative predictive value, which relates the number of patients free of recurrence in the regional node field after a negative SLNB to the total number of patients with a negative SLNB (1 minus the negative predictive value represents the percentage of patients with a negative SLNB who fail in the regional basin; this number is virtually always substantially less than the false-negative rate). Reported false-negative rates were substantially higher in early series, consistent with the observation that surgeons require training and experience to undertake SLNB with accuracy.<sup>5</sup>

### KEY POINTS

- SLNB is widely used for the staging of patients with clinically node-negative melanoma.
- ASCO and SSO recently released evidence-based joint clinical practice guidelines for the use of SLNB in melanoma.
- According to the ASCO/SSO joint guidelines, SLNB is recommended for patients with intermediate-thickness melanoma and may be recommended for patients with thick melanoma.
- According to the ASCO/SSO joint guidelines, SLNB is not routinely recommended for patients with thin melanoma, but it may be considered in selected “high-risk” patients.
- According to the ASCO/SSO joint guidelines, completion lymph node dissection is recommended for all patients with a positive SLNB.

To date there have been two large prospective randomized multicenter trials examining SLNB in patients with melanoma. MSLT-1 commenced patient accrual in 1994 and completed accrual in 2002. In this trial, 2001 patients were randomized to wide excision of the primary melanoma and nodal observation compared with wide excision with SLNB and immediate completion lymph node dissection (CLND) if a positive sentinel node was found. Results from the third interim analysis of MSLT-1 were published in 2006, and confirmed the value of SLNB as a reliable staging procedure with very little associated morbidity.<sup>7</sup> The interim results also suggested a substantial survival benefit for patients with intermediate-thickness melanoma who were found to be node-positive and underwent immediate CLND (72.3% 5-year survival) compared with those in the observation group who subsequently developed clinically apparent regional node metastasis and underwent a delayed lymphadenectomy (52.4% 5-year survival [ $p = 0.004$  versus immediate CLND]).<sup>7</sup> The final results of MSLT-1, with long-term follow-up data, have recently been analyzed and publication of the results is expected sometime in 2013.

The second large prospective multicenter study of SLNB in patients with melanoma was the Sunbelt Melanoma Trial, which combined a prospective nonrandomized evaluation of SLNB with investigations of the value of adjuvant high-dose interferon therapy in patients who were found to be sentinel node-positive. Over 3,600 patients with clinically node-negative intermediate or thick melanomas underwent SLNB on this trial, with a sentinel node identified in over 99% of patients<sup>13</sup> and 19.8% of patients having at least one tumor-positive sentinel node.<sup>14</sup> Younger patient age, increasing Breslow thickness, increasing Clark level, and the presence of ulceration were independently associated with the finding of a positive sentinel node on multivariate analysis, with Breslow thickness proving to be the factor of primary importance in a stepwise logistic regression model.<sup>13</sup> Complications of SLNB were infrequent—developing in 4.6% of patients—and generally not severe, and there were no deaths associated with the procedure.<sup>4</sup> False-negative findings occurred in 10.8% of all node-positive cases, which corresponded to a 3% rate of patients with negative SLNB results ultimately developing a regional nodal failure (or a 97% negative predictive value for a negative SLNB).<sup>14</sup> In both the Sunbelt and MSLT-1 trials, there was no significant difference in survival between patients with a positive SLNB and those developing regional recurrence after a negative SLNB.<sup>5,14</sup> The Sunbelt trial also evaluated the potential value of molecular staging of the sentinel node with reverse-transcriptase polymerase chain reaction, but found this to be of no additional value over standard histopathology and immunohistochemistry.<sup>15</sup>

There is far less high-level evidence about the optimum agents for lymphatic mapping, and considerable variation worldwide in practice patterns. In Europe and Australia, Patent Blue dye is approved for use and is used routinely for SLNB, but in the United States isosulfan blue and methylene blue are used. Reports of direct comparisons between dyes

are very limited, but some data suggest methylene blue to be inferior.<sup>16</sup> In the United States, until recently the only radio-colloid approved for sentinel node identification was <sup>99m</sup>Tc-sulfur colloid, which has a very large particle size (up to 3,000 nm) and therefore is often filtered to a particle size of 100 to 200 nm. In Australia, <sup>99m</sup>Tc-antimony trisulfide with a particle size of 10 nm is used, while in Europe, <sup>99m</sup>Tc-nanocolloid is used; proponents feel these agents provide better definition of afferent lymphatic channels than <sup>99m</sup>Tc-sulfur colloid. Recently, a new agent, <sup>99m</sup>Tc-tilmanocept, has been prospectively evaluated in two nonrandomized phase III trials in comparison with vital blue dye. These trials showed <sup>99m</sup>Tc-tilmanocept to have a very high rate of sentinel node identification and allows the detection of more melanoma-containing sentinel nodes than blue dye.<sup>17</sup> On March 13, 2013, the U.S. Food and Drug Administration approved <sup>99m</sup>Tc-tilmanocept (Lymphoseek) for use in lymphatic mapping for patients with melanoma and breast cancer.

It has been suggested that preoperative nodal ultrasonography might be as effective as SLNB; however, there is high-level evidence to refute this contention. In the ongoing Second Multicenter Selective Lymphadenectomy Trial (MSLT-2), routine preoperative ultrasonography has been abandoned because the sensitivity of the technique in detecting a positive node was only 8%.<sup>18</sup> There is, however, good evidence, particularly from European centers, that routine high-resolution ultrasound examination of the regional node field is of value in early detection of nodal recurrence in patients who have not had a sentinel node biopsy procedure, or in those who have been found to be sentinel node-positive and have not had an immediate CLND.<sup>19</sup> Ultrasound follow-up continues to be used in the latter group of patients in MSLT-2, in which patients found to be sentinel node-positive are randomized to immediate CLND or to clinical and ultrasound follow-up of the residual nodes in the relevant node field, with late CLND if evidence of nodal metastasis becomes clinically apparent.

The role of sentinel node biopsy in children and in patients with melanocytic tumors of uncertain malignant potential remains unclear, with only a few small studies reported and no large prospective trials reported to date or currently in progress.<sup>20,21</sup>

## PROGNOSTIC SIGNIFICANCE OF SENTINEL NODE STATUS

Regardless of the state of the evidence for absolute therapeutic benefit from SLNB, the staging information derived from the procedure is unquestionable.<sup>7,22</sup> Clearly, not all melanoma patients can be accurately staged based on primary tumor characteristics (thickness, mitotic rate, and presence of ulceration) alone. SLNB affords surgeons a minimally invasive technique that accurately and reliably identifies the disease status in regional lymph nodes. Without SLNB, patients with clinically occult (e.g., nonpalpable) nodal metastases would go undetected until disease became clinically apparent. Success is dependent on a multidisciplinary team

approach and relies on coordinated efforts between surgeons, nuclear medicine specialists, and pathologists. The information obtained from SLNB informs the nodal category of the tumor, node, metastasis staging system.<sup>2</sup> Once the results of the SLNB are available, accurate staging assignment can be made.

When the status of the sentinel nodes is negative, staging classifications are then based on characteristics of the primary tumor. Because of the known false-negative rate with SLNB, as well as the occasional occurrence of distant metastasis without nodal recurrence, a favorable outcome is not guaranteed by a negative result. However, 5- and 10-year overall survival rates associated with stage I or II melanoma range from approximately 50% to over 90%, with extremely high rates being consistently reported for melanomas less than 1.0 mm in thickness.<sup>2</sup> Over the years, iterative prognostic models have been developed to more precisely predict survival in patients with localized melanoma, and they have variously incorporated clinicopathologic variables in addition to tumor thickness. When sentinel node results are positive, prognosis is clearly worsened, although survival rates for stage III melanoma are quite heterogeneous. Much of the variation is based on the burden of node disease, and 5-year survival ranges from 23% to 87%.<sup>23</sup>

Some studies evaluating SLNB excluded patients with thick melanoma, defined as tumors more than 4.0 mm in thickness. The initial rationale for exclusion of these patients was the poor prognosis attributed to thick tumors due to the high associated risk of distant metastases with or without apparent nodal involvement. However, several studies with SLNB in this subgroup have yielded favorable results, both in terms of feasibility and with the favorable prognosis associated with a negative SLNB. The frequency of sentinel node positivity is increased in this subgroup (estimated at 30% to 40%), but this also means a 60% to 70% possibility of not having regional disease.<sup>24</sup> In fact, a recent study demonstrated that negative sentinel nodes predicted significantly better 5-year disease-free (85.3% vs. 47.8%;  $p < 0.0001$ ) and overall survival rates (80% vs. 47%;  $p < 0.0001$ ) in patients with thick melanomas.<sup>25</sup>

Currently, patients with positive sentinel nodes are advised to undergo CLND. The chance of finding additional disease in the CLND specimen has been reported at 16% in results from MSLT-1<sup>7</sup> and the Sunbelt Melanoma Trial,<sup>13</sup> but it has proved difficult to accurately predict which patients will have positive nonsentinel nodes. The prognostic significance of the number of nodes involved has been incorporated into current staging systems, as has the burden of disease within each node.<sup>2,23</sup> It is clear that detection of disease is correlated to meticulous examination of the specimen by the pathologist. Small clusters of melanoma cells in a node are clearly consistent with metastases, but what is less clear is when the tumor burden is actually too low to be meaningfully reported as true metastatic disease. It is not an uncommon event to find bland melanocytes within a node and the final reading may be equivocal. Taking into account the methods of disease detection (the burden of disease in the CLND specimen tends to be higher because detection methods usually

include routine histopathology as opposed to serial sections accompanied by immunohistochemistry), the true incidence of additional disease in nonsentinel nodes may actually be underestimated. Interim analysis results from MSLT-1 do suggest improved survival for CLND after positive SLNB compared with patients who did not undergo SLNB and later developed clinically detectable recurrence<sup>7</sup>; longer-term analyses are underway and will likely shed additional light on this important question. Extrapolation of results from prior trials of elective versus delayed lymphadenectomy may be instructive. These older data may help elucidate the effect of treating micrometastatic disease (by elective lymphadenectomy) compared to clinically apparent disease. Specifically, a post hoc analysis of a randomized controlled trial showed significantly better 5-year survival (48%) for patients with microscopically positive nodes who underwent elective lymphadenectomy at the time of wide excision compared to those who underwent delayed lymphadenectomy (27%;  $p = 0.04$ ).<sup>26</sup>

Importantly, patients with negative sentinel nodes still require surveillance and CLND in the event of a nodal recurrence. A meta-analysis found the false-negative rate with SLNB (defined as the number of patients with nodal recurrence in the SLNB-negative basin divided by the total number of patients with positive nodes) to be 12.5%.<sup>12</sup>

Some have criticized the ongoing use of SLNB because of the lack of adjuvant treatment options for patients subsequently diagnosed with stage III disease. Indeed, current adjuvant treatments for stage III melanoma are not spectacularly effective and not uniformly used in eligible patients because of associated toxicities and patient preferences. Additionally, the role of locoregional control gain with SLNB and CLND must continue to be taken into account. Furthermore, there have been some encouraging results with systemic agents such as vemurafenib and ipilimumab in patients with advanced (stage IV) disease. As such, expanded indications for treatment of stage III disease could be forthcoming. In order to accurately stratify patients for enrollment in clinical trials, the role of SLNB, likely with CLND to complete staging, will be even more critical.

The availability of sentinel node results for patients with intermediate-thickness melanoma represented a significant paradigm shift from the presentin node era when management revolved around the approaches of elective dissection or nodal observation. However, there remains substantial uncertainty about whether every patient with a positive sentinel node requires CLND, or if some (or even many) could be safely observed instead.<sup>27</sup> The ongoing MSLT-2 trial is a multicenter randomized trial comparing immediate lymphadenectomy to observation (with serial ultrasonography) in patients found to have positive sentinel nodes.

## RECENT PRACTICE GUIDELINES FOR THE USE OF SENTINEL NODE BIOPSY IN MELANOMA

SLNB is currently recommended in the consensus-based management guidelines for clinically node-negative primary cutaneous melanoma of the National Comprehensive Can-

cer Network,<sup>28</sup> and in management guidelines currently used in many other countries around the world.<sup>29,30</sup> In August 2012, ASCO and SSO published evidence-based recommendations for SLNB for melanoma,<sup>31</sup> adding support for the use of SLNB from two of the world's most prestigious and respected oncology treatment organizations. The ASCO/SSO panel's stringently evidence-based approach and broad representation of medical specialties provided a welcome degree of objectivity, while the requirement for high-level evidence limited the data set from which conclusions could be drawn. Four "key recommendations" were issued:<sup>31</sup>

1. Intermediate-thickness melanomas: SLNB is recommended for patients with cutaneous melanomas with Breslow thickness of 1 to 4 mm at any anatomic site. Routine use of SLN biopsy in this population provides accurate staging, with an acceptable false-negative rate.

2. Thick melanomas: SLNB may be recommended for staging purposes and to facilitate regional disease control for patients with melanomas that are T4 or >4 mm in Breslow thickness.

3. Thin melanomas: There is insufficient evidence to support routine SLNB for patients with melanomas that are T1 or <1 mm in Breslow thickness, although it may be considered in selected high-risk patients.

4. Completion lymph node dissection is recommended for all patients with a positive SLNB.

Although each of these recommendations carried with them a degree of controversy, perhaps none was more controversial than the recommendation regarding thin melanomas.<sup>32</sup>

## The Indications for and Value of Sentinel Node Biopsy in Thin Melanoma

Up to 70% of newly diagnosed melanomas are thin (i.e.,  $\leq 1$  mm tumor thickness).<sup>33</sup> Although the vast majority of patients with thin melanoma have an excellent prognosis, some develop clinically evident regional lymph node metastasis, classically occurring years after initial diagnosis and treatment. According to the AJCC melanoma staging system, thin primary melanomas are classified as T1.<sup>2</sup> If a thin melanoma is not ulcerated and the mitotic rate is less than  $1/\text{mm}^2$ , which in fact means no dermal mitoses are seen by the pathologist, it is classified as T1a. If either ulceration is present or the mitotic rate is  $1/\text{mm}^2$  or greater (i.e., at least one dermal mitosis seen regardless of the tumor's size), it is classified as T1b. According to the AJCC analysis, 10-year survival for patients with T1 melanomas was 92%.<sup>2</sup> Despite the low risk of death from thin melanoma, given its high incidence, it represents an important health issue based on the absolute number of potential individuals affected.<sup>33</sup>

Although SLNB has emerged as a standard of care for patients with intermediate-thickness melanoma, and is recommended in the ASCO/SSO<sup>27</sup> and other contemporary guidelines<sup>28,29,30</sup> for nearly all patients with melanomas 1 mm or larger, the use of SLNB in patients with thin melanoma remains controversial. Some contend that this procedure is not indicated in patients with thin melanoma because of the low incidence of nodal metastasis, the uncertain prognostic

value of a positive sentinel node, and the risks and costs associated with the procedure; however, several (mostly single-institution) studies have demonstrated that a subset of patients have a sufficiently high incidence of positive sentinel nodes (whether defined as  $\geq 5\%$  or  $\geq 10\%$ ) to justify the procedure.<sup>34,35,36</sup> Currently, no consensus exists regarding which prognostic factors best predict the risk of nodal metastasis or the threshold risk for which SLNB should be considered. Nonetheless, some patterns are emerging that help shed light on this important clinical scenario.

The overall probability of finding a positive sentinel node among patients with thin melanoma who were offered and had an SLNB is approximately 5%. Across several studies, in the subset of these patients whose primary tumor is less than 0.76 mm, the reported probability of a positive node is quite low ( $<2\%$  to  $4\%$ ), regardless of whether these very thin tumors are T1a or T1b.<sup>33,32</sup> Hence, recommendations regarding SLNB for thin melanoma should largely be restricted to the subset of patients with tumors between 0.76 and 1.0 mm. In patients whose T1 primary tumor is in this range, the probability of a positive sentinel is between 6% and 11%. Patients with T1b melanomas in this group are at greatest risk of a positive SLN. Available data do not provide convincing evidence that Clark level, regression, growth phase, gender, or primary tumor site as sole criteria significantly inform this decision-making process. Although in several predictive models younger patients are more likely to have a positive sentinel node, available data do not adequately define what age serves as an appropriate clinical cutoff.<sup>32</sup>

What have we learned regarding the prognostic significance of SLN status in patients with a thin melanoma? Relatively few studies assessing the role of SLNB in patients with thin melanoma have sufficient follow-up to report long-term (e.g., 10-year) survival, and many have not reported follow-up at all. This issue remains particularly vexing since only long-term follow-up can adequately address melanoma-specific survival in this population. For example, two recent single-institution studies with median follow-up durations under 3 years demonstrated no significant survival

difference between patients with positive and negative sentinel nodes.<sup>35,36</sup> In contrast, in a large series with a median follow-up of 57 months, sentinel node status was an independent predictor of both disease-free and melanoma-specific survival.<sup>34</sup> The prognostic significance of sentinel node status in thin melanoma remains an area of intense investigation; long-term follow-up studies of this large fraction of melanoma patients are clearly warranted.

The incidence of nonsentinel node metastasis found at CLND in patients with thin sentinel node-positive melanoma is low.<sup>37,38</sup> Nonetheless, the current recommendation of the joint ASCO/SSO guidelines is to perform completion lymphadenectomy in all such patients. Although an argument can be made to forego CLND in patients with sentinel node-positive thin melanoma, there are insufficient data to support or refute this proposition. The role of postoperative adjuvant systemic therapy in these patients is also uncertain.

Although no consensus has yet been reached as to which patients with thin melanoma should be offered SLNB, one rational result of integrating available data is a recommendation for SLNB in many patients with melanomas at least 0.76 mm in thickness, but only rarely if ever for patients with melanomas less than 0.76 mm.<sup>32,36</sup> Future studies will be needed to shed additional light on this important clinical problem.

## CONCLUSIONS

SLNB provides safe, reliable staging for patients with clinically node-negative melanomas 1 mm or greater in thickness with an acceptably low rate of failure in the sentinel node-negative basin. National consensus-based guidelines have advocated its routine use for many years, and now an evidence-based guideline jointly produced by ASCO and SSO has come to the same conclusion. Major remaining areas of uncertainty include the indications for SLNB in patients with thin melanomas, pediatric patients, and patients with atypical melanocytic neoplasms; the optimal radiotracers and dyes for lymphatic mapping; and the necessity of lymphadenectomy in all sentinel node-positive patients.

## Disclosures of Potential Conflicts of Interest

*Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Relationships marked "U" are uncompensated.*

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Sentinel lymph node biopsy (SLNB) was introduced in 1992 to allow histopathologic evaluation of the "sentinel" node, that is, the first node along the lymphatic drainage pathway from the primary melanoma. SLNB is now widely used worldwide in the staging of melanoma as well as breast and Merkel cell carcinomas. SLNB provides safe, reliable staging for patients with clinically node-negative melanomas 1 mm or greater in thickness, with an acceptably low rate of failure in the sentinel node-negative basin. Evidence-based guidelines jointly produced by ASCO and the Society of Surgical Oncology (SSO) recommend SLNB for patients with intermediate-thickness melanomas and also state that SLNB may be recommended for patients with thick melanomas.