The Laryngoscope

Contemporary Review

Is Sentinel Lymph Node Biopsy the Standard of Care for Cutaneous Head and Neck Melanoma?

Cecelia E. Schmalbach, MD; Carol R. Bradford, MD

Objectives/Hypothesis: Sentinel lymph node biopsy (SLNB) is considered one of the most important melanoma advancements to date. Since its inception in 1992, a plethora of data and associated controversies has emerged leading to the question: Is SLNB considered the standard of care for head and neck (HN) cutaneous melanoma?

Study Design: English literature (1990–2014) review.

Methods: The PubMed database search was conducted using key terms "melanoma" and "sentinel node." This review included both dedicated HN SLNB studies and larger prospective SLNB studies, in which HN patients were included among the cohort. Bibliography cross-referencing was conducted to ensure a comprehensive search.

Results: SLNB is safe and accurate in the HN region. Review of large prospective SLNB trials identified the pathologic status of the SLN as the most important prognostic factor for recurrence and survival. Early lymphadenectomy following a positive SLNB imparts a survival benefit.

Conclusions: Our review of the current literature suggests that SLNB is the standard of care for selected cases of HN cutaneous melanoma. It is now incorporated into the American Joint Committee on Cancer staging system, the National Comprehensive Cancer Network practice guidelines, and numerous national and international consensus statements.

Key Words: Cutaneous melanoma; sentinel node.

***Laryngoscope*, 125:153–160, 2015**

INTRODUCTION

The incidence of cutaneous melanoma continues to rise at epidemic proportions in the United States,[1,2] with 137,990 new cases of melanoma estimated in 2014. This rate has steadily increased by 2.8% per year since 1981. The lifetime risk of developing melanoma will reach 1 in 50 Americans in 2015.[3] One in four new cases present before the age of 40; given this relatively young age, melanoma is second only to adult leukemia in lost potential life years. Melanoma mortality has also risen by 3% each year since 2004. As many as 9,710 Americans will die from melanoma this year, approximately one patient per hour.[2] In 2010, the total direct cost of treating melanoma in the United States exceeded $2.3 billion.[4]

Regional metastasis remains the most important prognostic factor for melanoma recurrence and survival.[5] Up to 20% of patients presenting with a clinically and radiographically N0 neck are harboring occult stage III disease. In an effort to accurately stage patients and identify individuals who may benefit from adjuvant therapy, Donald Morton introduced sentinel lymph node biopsy (SLNB) in 1992.[6] This minimally invasive technique is regarded as one of the most important melanoma advancements to date.[7] Over the past two decades, a plethora of data and associated controversies have emerged. This contemporary review investigates the question: Is SLNB now the standard of care for head and neck (HN) cutaneous melanoma?

RATIONALE BEHIND SLNB

Historically, patients with intermediate thickness melanoma (1.0–3.9 mm) stage I and II disease underwent elective neck dissection (END). Although initial retrospective studies demonstrated a survival benefit,[8] all four prospective, randomized trials failed to replicate the overall survival benefit of END in the absence of regional metastasis.[9–12] Statistical power remains one challenge in determining the survival benefits of early detection of nodal disease.[13] Only 20% of melanoma patients presenting with localized stage I and II disease actually harbor occult nodal metastasis and would benefit from early removal; END is not expected to impart a

From the Division of Otolaryngology–Head and Neck Surgery (C.E.S.), The University of Alabama at Birmingham, Birmingham, Alabama; and the Department of Otolaryngology–Head and Neck Surgery (C.R.B.), University of Michigan Health System, Ann Arbor, Michigan, U.S.A.

Editor's Note: This Manuscript was accepted for publication June 6, 2014.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Cecelia E. Schmalbach, MD, FACS, Associate Professor of Surgery, Division of Otolaryngology-HNS, The University of Alabama at Birmingham, BDB 563, 1720 2nd Avenue S, Birmingham, AL 35209-0012. E-mail: cschmalbach@uabmc.edu

DOI: 10.1002/lary.24807

TABLE I.
Sentinel Node Biopsy Indications for Stage I/II Cutaneous Melanoma.

Breslow depth >1 mm
Breslow depth 0.76–1.0 mm in setting of adverse factors
Ulceration
Extensive regression to 1.0 mm
Young age
Mitotic rate $\geq$1/ mm^2
Angiolymphatic invasion
Deep positive margin

survival benefit on the remaining 80% of stage I/II patients with localized disease only. Detecting this small difference requires extremely large clinical trials, with enrollment numbering in the thousands. McMasters et al. point out that the Intergroup Melanoma Surgical Trial (IMST), World Health Organization (WHO), and Mayo Clinic trials lacked adequate statistical power to detect this small survival benefit.[14]

An additional challenge in identifying occult nodal metastasis is the minute tumor burden harbored within the node. In an END, entire at-risk nodal basins are given to the pathologist for lymph node identification, which is preformed manually via palpation. The nodes are bivalved and stained with hematoxylin and eosin (H&E). This technique can easily miss occult disease, which can measure as small as 0.1 mm.[3,15] In addition, only 21% to 23% of positive sentinel lymph node (+SLN) patients are diagnosed using traditional H&E staining.[16,17] Current National Comprehensive Cancer Network (NCCN) guidelines require only melanoma-specific immunohistochemical staining (IHCS) alone within individual cells to diagnose metastatic disease.[18] Rigorous pathology evaluation of all lymph nodes harvested in an END specimen (to include serial microsectioning and IHCS) is not feasible from a time or cost perspective.

SLNB TECHNIQUE

Because multiple prospective, randomized trials failed to demonstrate an overall survival benefit for patients undergoing END,[8,10,11,19] the NCCN no longer advocates routine END for melanoma.[18] The procedure has been replaced by SLNB, which represents a minimally invasive, cost-effective, and efficient means of staging and screening patients for regional metastasis.[20] SLNB indications are summarized in Table I.

In brief, patients undergo preoperative injection of a radioactive colloid. Lymphoscintigraphy is performed to determine the number, location, and laterality of at-risk draining nodal basins (Fig. 1). Fused single-photon emission computed tomography/computed tomography (SPECT/CT) is emerging as a superior imaging modality because of the increased anatomical three-dimensional detail and improved resolution (Fig. 2). The largest prospective study comparing SPECT/CT to planar lymphoscintigraphy included 403 melanoma patients.[21] SPECT/CT was found to be superior, altering the surgical plan in

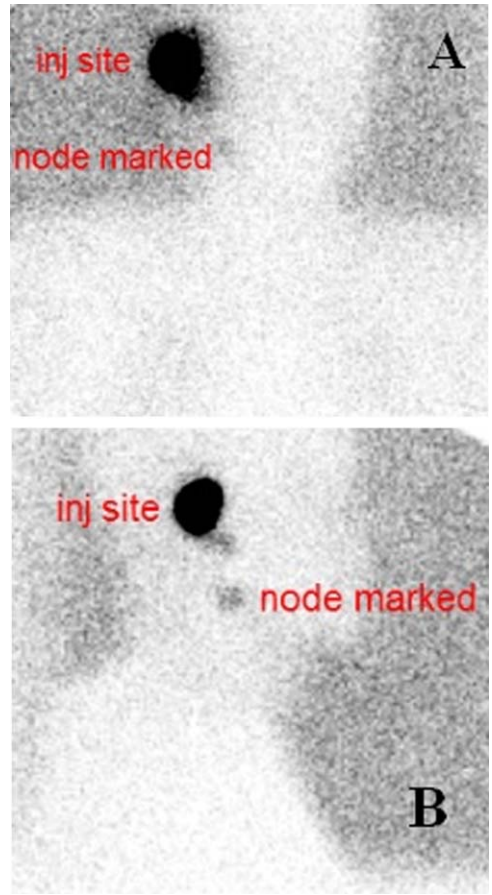

Fig. 1. Lymphoscintigraphy planar imaging of a right auricular melanoma draining to the right cervical chain. (A) Axial view. (B) Right lateral view. Inj = Injection [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

22% of cases. It yielded a higher number of +SLNs per patient (2.4 vs. 1.87; $P < .001$) as well as a higher metastatic rate (0.34 vs. 0.21; $P = .04$). At a mean follow-up of 28.8 months, patients undergoing SLNB utilizing SPECT/CT had a higher disease-free survival (DFS) compared to the lymphoscintigraphy group (94% vs. 79%; $P = .02$). Multivariate analysis identified use of SPECT/CT as a factor associated with DFS (hazard ratio [HR] = 4.11; $P = .02$).

Once under anesthesia, patients undergo intraoperative lymphatic mapping with vital blue dye.[6] Approximately 1 mL of dye is injected intradermally into the four quadrants surrounding the primary melanoma lesion. Studies consistently demonstrate increased SLNB sensitivity when visual cues from blue dye are combined with auditory cues from a radionucleotide.[22,23]

Unlike trunk and extremity melanomas, wide local excision (WLE) of the HN primary is performed first, because the close proximity of the tumor and draining lymphatics creates radioactive "shine-through," which renders the gamma probe useless. Following WLE, at risk nodal basins are evaluated for increased radioactivity using a handheld gamma probe (Fig. 3). By definition, a lymph node demonstrating 10% or greater counters per minute compared to the hottest node ex vivo is considered "sentinel."[24] A 1- to 3-cm incision is

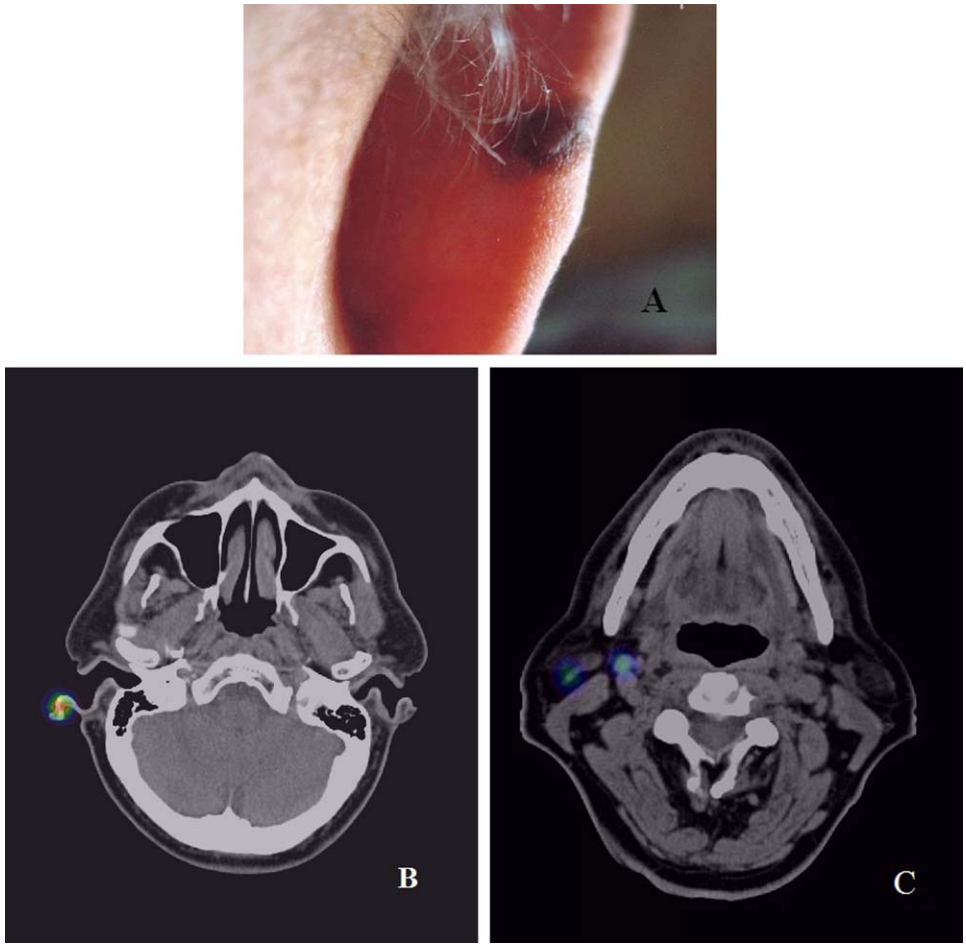

Fig. 2. (A) Single-photon emission computed tomography/computed tomography (SPECT/CT) of right auricular melanoma. (B) SPECT/CT of the radioactive colloid injection site surrounding auricular melanoma. (C) SPECT/CT demonstrating lymphatic draining to a right level II sentinel node superficial to the internal jugular vein. Note the increased anatomic detail compared to lymphoscintigraphy in Figure 1. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

made overlying the areas of increased radioactivity. A preauricular incision and facial nerve monitoring are recommended in the parotid region (Fig. 3).

Using a combination of the gamma probe and visual cues from the blue dye, individual SLNs are identified and sent separately for permanent histologic evaluation, because a melanoma frozen sections carries a false negative rate of between 5% and 10%.[25] The evaluation includes serial microsectioning and H&E staining. Melanoma specific IHCS for S-100, melan-A (MART-1), and HMB-45 are performed for all SLNs negative on H&E staining. The mean number of SLNs per patient is 2.4,[17] which allows for a more practical, thorough, and complete histologic evaluation compared to an entire lymphadenectomy specimen.[26] Patients with a +SLN return to the operating room within 2 weeks of diagnosis for definitive therapeutic lymph node dissection (TLND); patients with a negative biopsy are followed clinically.

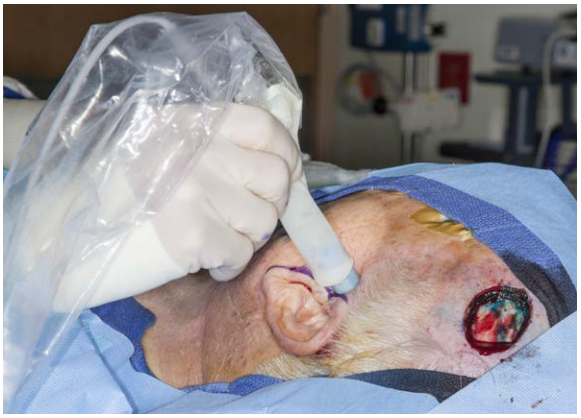

Fig. 3. Handheld gamma probe used to identify increased area of radioactivity associated with sentinel node. Note the use of a preauricular incision for sentinel lymph node biopsy in the parotid nodal basin. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

The success of SLNB hinges upon communication and a collaborative effort. An experienced nuclear medicine team is imperative because inappropriate administration of the radioactive tracer causes shine through. As noted above, the pathologist plays an extremely critical role given the tedious task of identifying micrometastatic disease. The referring dermatology team is vital in working up and identifying appropriate SLNB candidates. Last, the surgeon requires experience in the SLNB technique. Morton et al. prospectively identified a 55-case learning curve to achieve at least 95% accuracy with SLNB.[25]

SUPPORTING EVIDENCE FOR SLNB

SLNB is considered standard of care in 2014 for eight reasons.

TABLE II.
Multivariate Analysis of Prognostic Factors Impacting Melanoma Survival.[27]

	Disease-Free Survival			Melanoma-Specific Survival		
Prognostic factor	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Tumor thickness	1.21	1.11-1.31	<.00001	1.23	1.10-1.38	.0004
Ulceration	1.73	1.13-2.65	.01	1.62	0.85-3.08	.14
SLN status	3.41	2.25-5.17	<.00001	6.53	3.39-12.58	<.00001

CI = confidence interval; HR = hazard ratio; SLN = sentinel lymph node.

First, the pathologic status of the SLN is the most important prognostic factor for melanoma recurrence and survival. In 1999, Gershenwald et al. conducted a multivariate analysis on 580 stage I/II melanoma patients (8.1% HN subsite) and found the SLN status (positive or negative for micrometastasis) to be the most significant prognostic factor for both DFS (HR = 3.41; $P < .00001$) and melanoma specific survival (MSS) (HR = 6.53; $P < .0001$).[27] Table II lists other recognized prognostic variables for comparison. The largest single-institution SLNB study dedicated to HN melanoma prospectively followed 353 patients and reported similar results.[17] Best multivariate model analyses revealed +SLN status as the strongest factor associated with decreased DFS and MSS (Table III). At 10 years follow-up, the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1) trial confirmed sentinel node status as the strongest predictor for disease recurrence and death.[28]

Second, lymph node tumor burden (microscopic vs. macroscopic disease) is the second most important prognostic factor following number of nodal metastasis for stage III melanoma. A prospective analysis of 1,429 melanoma patients (trunk, extremity, and HN subsites) with lymph node metastasis identified an improved 5-year survival rate for patients presenting with clinically negative but pathologically positive nodal disease, compared to patients with both clinically and pathologically palpable nodal disease ($P < .0001$).[29] These data were so compelling that the American Joint Committee on Cancer (AJCC) incorporated SLN status into the revised 2002 sixth edition cancer staging system.[30] This utilization of SLNB for staging was validated in the follow-up multi-institutional prospective trial of 3,307 stage III melanoma patients.[5] Cox multivariate analysis identified the number of metastatic lymph nodes, tumor burden (microscopic vs. macroscopic) at the time of staging, tumor ulceration, and depth of invasion as the most important independent predictors of survival (all *P* values < .001).

Third, SLNB remains the most specific and sensitive means for regional staging. It is important to recognize that, even in 2014, the SLN technique remains a staging tool no different than magnetic resonance imaging, computed tomography, and positron emission tomography. Cross-sectional imaging using traditional radiographic modalities only identifies 0.5% to 3.7% of occult stage III melanoma cases.[31–34] Given the minute tumor volume in a +SLN, it is unsurprising that serial sectioning with melanoma IHCS carries greater sensitivity.

Fourth, SLNB is now incorporated into the current NCCN guidelines.[18] Given the above-noted prognostic significance of a +SLN, as well as the inability to reliably identify occult nodal disease with radiographic imaging alone, the NCCN panel has incorporated SLNB into the treatment algorithm. Patients meeting criteria listed in Table I warrant a discussion on the utility of SLNB.

Fifth, staging with SLNB imparts a survival benefit. The MSLT-1 trial[28] commenced in 1994 to determine if immediate completion lymphadenectomy yields a survival benefit compared to observation. This study included trunk, extremity, and HN cutaneous melanoma patients. A total of 2,001 stage I/II melanoma patients were randomized to WLE with observation and delayed lymphadenectomy for nodal recurrence versus WLE + SLNB with immediate lymphadenectomy for micrometastatic disease (Fig. 4). A 10-year follow-up demonstrated that SLNB correctly determined the pathologic nodal stage in 96% of cases. Patients with intermediate (1.20–3.5 mm) and thick (>3.5 mm) melanomas in the WLE + SLN group demonstrated an improved 10-year DFS compared to their observation counterparts. Although a significant treatment-related difference in MSS was not identified among the entire cohort, this finding was expected given that only 20% of study patients harbored regional disease and would benefit from intervention. Subgroup analysis of patients with nodal disease confirmed an improved MSS in the

TABLE III.
Best Multivariate Model for Melanoma Survival.[17]

Prognostic Factor	HR	95% CI	*P* Value
Disease-free survival			
Breslow depth	1.15	1.04-1.27	.0049
Age	1.03	1.02-1.04	<.0001
+SLN	4.23	2.73-6.54	<.0001
Melanoma-specific survival			
Ulceration	2.05	1.22-3.45	.0069
Age	1.03	1.03-1.05	<.0001
+SLN	3.33	1.99-5.58	<.0001

CI = confidence interval; HR = hazard ratio; +SLN = positive sentinel lymph node.

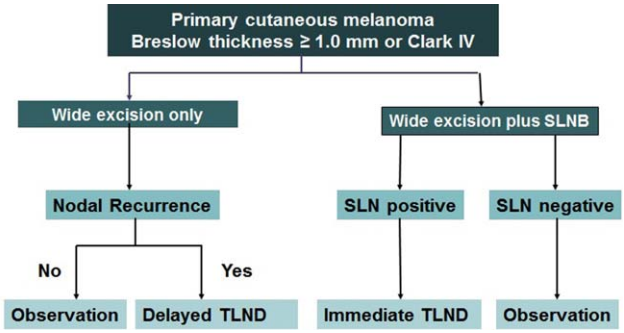

Fig. 4. Randomization schema for multicenter selective lymphadenectomy trial. SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; TLND = therapeutic lymph node dissection. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

WLE + SLN group compared to observation (62% vs. 41.5%; $P = .006$). This treatment-related difference was unique to patients with intermediate-thickness melanomas but not thick melanomas. These long awaited MSLT-1 results demonstrate that early lymphadenectomy following a positive SLNB decreases nodal recurrence, distant metastasis, and death from melanoma for intermediate- thickness melanoma patients with occult regional disease.

Sixth, the American Society of Clinical Oncology and the Society of Surgical Oncology recently published updated clinical practice guidelines recommending the use of SLNB for melanoma.[35] SLNB is recommended for all patients meeting the criteria listed in Table I, regardless of the primary lesion. Their recommendation followed an evidence-based systematic review of the literature yielding 73 studies.

Seventh, The WHO issued a statement that SLNB is the standard of care for melanoma.[36] This position statement was issued in 1999, and SLNB was recognized as "the starting point for future policies on surgery and adjuvant treatment strategies."

Eighth, SLNB allows for accurate staging and identification of a homogeneous population of patients to enroll in clinical trials.[14] Stage III melanoma is a heterogeneous category with broad 5-year survival rates, ranging from 78% for patients with one positive micrometastatic node (stage IIIA) to a dismal 40% for patients with three or more positive nodes (stage IIIC).[5] SLNB remains the most accurate means of regional staging, which is imperative to identify a homogeneous population of patients with like outcomes. Without accurate pathologic staging, stratification is impossible, and the result of clinical trials would be difficult to interpret.

SLNB "CONTROVERSIES"

Feasibility in the HN Region

A 34% discordance between clinical prediction of HN lymphatic drainage and lymphoscintigraphy findings in 97 melanoma cases raised concern about the reliability of SLNB in the watershed lymphatics of the HN region.[37] Concerns for damage to surrounding vital structures, such as the great vessels, facial nerve, and spinal accessory nerve, also limited popularity.[38] Throughout the past two decades, studies have consistently demonstrated that SLNB can be accurately performed in cervical nodal basins without significant risk to the cranial nerves and great vessels.[39–42] The largest HN SLNB prospective study identified in 352 of 353 cases (99.7%) no reported permanent facial nerve, cranial nerve, or vascular damage. Sixty-nine of 353 patients (19.6%) had a +SLN biopsy.[17] This 19.6% positivity rate mirrors the results achieved in other anatomic sites such as the trunk and extremities.[10,43] At a mean follow-up of 48 months, 12 of 283 negative SLN patients where locally free of disease but developed regional recurrence within a previously mapped nodal basin, yielding a false-negative rate of 14.8% (12 false negatives/12 false negatives + 69 true positives). The negative predictive value of 95.8% and false rate of omission of 4.2% mirrors that of trunk and extremity melanoma, thus demonstrating feasibility of SLNB in the HN region.

SLNB Safety in the Parotid Basin

Overall, 25% to 30% of HN cutaneous melanomas drain to the parotid nodal basin,[37,39] where injury to the facial nerve has led some surgeons to advocate for superficial parotidectomy over SLNB.[38] Numerous studies have demonstrated that SLNB can be reliably and safely performed within the parotid nodal basin, especially when utilizing continuous facial nerve monitoring.[39,44,45] Inflammation and fibrosis from SLNB was thought to place the facial nerve at increased risk when a therapeutic superficial parotidectomy was required after a +SLNB.[38] Erman et al. reported preservation of facial nerve function in all patients undergoing therapeutic superficial parotidectomy following a positive SLNB.[17]

In-transit Metastasis

Authors have suggested that SLNB increases the risk of in-transit metastasis (ITM), which is defined as intralymphatic tumor dissemination within cutaneous or subcutaneous tissue located between the primary lesion and draining nodal basin.[46–48] ITM presents a therapeutic challenge and carries a poor prognosis.[30] Original reports citing increased ITM following SLNB often entailed pooled data from small cohorts, and failed to control for important prognostic factors such as tumor thickness and ulceration.[46,49] A follow-up prospective review comparing 4,412 patients undergoing WLE, WLE with SLNB, and elective lymph node dissection (ELND) identified a correlation between ITM and increasing Breslow depth, Clark level, and T stage.[50] A statistically significant difference between ITM and tumor recurrence was not found among the treatment groups, once adjustment was made for T-stage, age, sex, tumor thickness, and site. Additional studies have concluded that it is the tumor biology, as opposed to the surgical procedure (SLNB, ELND), that dictates melanoma metastatic behavior.[46,51] Finally, a correlation between ITM and

SLNB was not reported with MSLT-1, thus negating this concern.[25]

FUTURE SLNB ENDEAVORS

Future SLNB research endeavors hold exciting promise. In an effort to investigate the therapeutic potential of SLNB, recent research efforts focus on identifying markers of both the primary lesion and SLN, which are predictive of tumor remaining in non-SLNs.[52–54] Such markers may allow identification of a subset of +SLN patients who do not require formal TLND. Unfortunately, current studies have failed to identify a consistent and 100% accurate marker. For this reason, the ongoing MSLT-II trial is designed to investigate the indications for TLND following a +SLNB.[25] It will determine whether immediate TLND provides a survival benefit over postoperative, diligent, ultrasonographic monitoring of the draining nodal basins. The European Organization for Research and Treatment (EORTC) Melanoma Group MINITUB trial is also designed to determine if patients with minimal +SLN tumor burden require TLND. Until the results of these trials are available, TLND following +SLNB remains the standard of care.[7,18,35]

Molecular staging of melanoma has also gained increased interest. Reverse transcriptase polymerase chain reaction (RT-PCR) analysis of SLNs for melanoma-associated genes such as *MART-1*, tyrosinase, and tyrosinase-related protein 2 (TRP-2) have proven helpful in identifying a subset of patients harboring occult nodal disease at a submicroscopic level that cannot be detected with traditional IHCS.[55–57] In one study, 30% (49 of 162) of patients with at least one melanoma marker identified with RT-PCR experienced an increased rate of recurrence despite a negative SLNB.[58] Currently, RT-PCR carries a high false-positive rate attributed to the inability to differentiate melanoma cells from occult benign nevus cells. Through future research efforts, molecular staging may prove helpful in the identification of a subset of high-risk melanoma patients who develop nodal or distant metastases despite presentation with a thin primary tumor.[59]

Near-infrared (NIR) fluorescence utilizing indocyanine green (ICG) provides the surgeon real-time transcutaneous visualization of superficial draining lymphatic channels.[60] The fluorescence signal potentially aids the pathologist in preparing and analyzing SLNs.[61,62] Optical imaging with ICG as a lymphatic tracer has been successfully applied in various cancers.[63] Four dedicated cutaneous carcinoma studies have been published.[64–67] The investigations are limited to case reports and small series for a total of 42 patients. Although NIR fluorescence has outperformed traditional blue dye in several SLN clinical trials,[62,68,69] tissue depth and large body mass index remains the rate-limiting factor. A hybrid tracer combining ICG with ^{99m}Tc-radioactive colloid has been introduced to increase depth of detection and lengthen retention time of the tracer.[69] The application of SLN optical imaging remains investigational at present but is promising.

Application in Thin Melanomas

The majority of SLNB studies focus upon intermediate thickness melanomas, which carry approximately a 20% rate of occult nodal metastasis. The utility of this technique in thin melanomas remains to be determined. Morton et al. could not draw meaningful conclusions from the 340 MSLT-1 patients with thin melanomas measuring $<$1.20 mm invasion.[28] A meta-analysis of SLN positivity in thin melanomas $\leq$1 mm identifies a pooled occult nodal disease rate of 5.6%.[70] Consistent clinical and histopathologic criteria to reliability identify this small at-risk thin melanoma populaiton is lacking. Future studies are required and will need to balance benefit with cost and associated morbidity.

CONCLUSION

Regional metastasis remains the most important prognostic factor in melanoma. Decreased melanoma mortality ultimately hinges upon accurate staging, especially because the majority of stage III melanoma patients are now diagnosed with micrometastatic as opposed to macrometastatic disease.[71] SLNB represents a minimally invasive, cost-effective, and efficient means of staging and screening patients for regional metastasis.[20] It is now considered the standard of care for intermediate thickness melanomas as supported by its incorporation into the AJCC staging system,[5] NCCN guidelines,[18] and numerous oncology consensus statements.[35,72–74]

BIBLIOGRAPHY

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9–29.
2. Society AC. Cancer facts and figures 2013. Available at: http://www.cancer.org/research/cancerfactsfigures/cancerfactsfigures/cancer-facts-figures-2013. Accessed June 25, 2014.
3. Rigel DS, Russak J, Friedman R. The evolution of melanoma diagnosis: 25 years beyond the ABCDs. *CA Cancer J Clin* 2010;60:301–316.
4. Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol* 2006;55:490–500.
5. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 2009;27:6199–6206.
6. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992;127:392–399.
7. Ross MI, Gershenwald JE. Sentinel lymph node biopsy for melanoma: a critical update for dermatologists after two decades of experience. *Clin Dermatol* 2013;31:298–310.
8. Balch CM. The role of elective lymph node dissection in melanoma: rationale, results, and controversies. *J Clin Oncol* 1988;6:163–172.
9. Sim FH, Taylor WF, Ivins JC, Pritchard DJ, Soule EH. A prospective randomized study of the efficacy of routine elective lymphadenectomy in management of malignant melanoma. *Preliminary results. Cancer* 1978;41:948–956.
10. Cascinelli N, Morabito A, Santinami M, MacKie RM, Belli F. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. *WHO Melanoma Programme. Lancet* 1998;351:793–796.
11. Veronesi U, Adamus J, Bandiera DC, et al. Inefficacy of immediate node dissection in stage 1 melanoma of the limbs. *N Engl J Med* 1977;297:627–630.
12. Balch CM, Soong SJ, Bartolucci AA, et al. Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. *Ann Surg* 1996;224:255–263; discussion 263–256.
13. McMasters KM, Sondak VK, Lotze MT, Ross MI. Recent advances in melanoma staging and therapy. *Ann Surg Oncol* 1999;6:467–475.
14. McMasters KM, Reintgen DS, Ross MI, et al. Sentinel lymph node biopsy for melanoma: controversy despite widespread agreement. *J Clin Oncol* 2001;19:2851–2855.

15. Wagner JD, Davidson D, Coleman JJ III, et al. Lymph node tumor volumes in patients undergoing sentinel lymph node biopsy for cutaneous melanoma. *Ann Surg Oncol* 1999;6:398–404.
16. Joseph E, Brobeil A, Glass F, et al. Results of complete lymph node dissection in 83 melanoma patients with positive sentinel nodes. *Ann Surg Oncol* 1998;5:119–125.
17. Erman AB, Collar RM, Griffith KA, et al. Sentinel lymph node biopsy is accurate and prognostic in head and neck melanoma. *Cancer* 2012;118: 1040–1047.
18. Network NCC. NCCN clinical practice guidelines in oncology: melanoma. Available at: www.nccn.org. Accessed April 14, 2014.
19. Urist MM, Balch CM, Soong SJ, et al. Head and neck melanoma in 534 clinical stage I patients. *A prognostic factors analysis and results of surgical treatment. Ann Surg* 1984;200:769–775.
20. Morton DL, Thompson JF, Essner R, et al. Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. Multicenter Selective Lymphadenectomy Trial Group. *Ann Surg* 1999;230:453–463; discussion 463–455.
21. Stoffels I, Boy C, Poppel T, et al. Association between sentinel lymph node excision with or without preoperative SPECT/CT and metastatic node detection and disease-free survival in melanoma. *JAMA* 2012;308:1007–1014.
22. Uren RF, Howman-Giles RB, Shaw HM, Thompson JF, McCarthy WH. Lymphoscintigraphy in high-risk melanoma of the trunk: predicting draining node groups, defining lymphatic channels and locating the sentinel node. *J Nucl Med* 1993;34:1435–1440.
23. Bostick P, Essner R, Sarantou T, et al. Intraoperative lymphatic mapping for early-stage melanoma of the head and neck. *Am J Surg* 1997;174: 536–539.
24. Kroon HM, Lowe L, Wong S, et al. What is a sentinel node? Re-evaluating the 10% rule for sentinel lymph node biopsy in melanoma. *J Surg Oncol* 2007;95:623–628.
25. Morton DL, Cochran AJ, Thompson JF, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg* 2005;242:302–311; discussion 311–303.
26. Cascinelli N, Belli F, Santinami M, et al. Sentinel lymph node biopsy in cutaneous melanoma: the WHO Melanoma Program experience. *Ann Surg Oncol* 2000;7:469–474.
27. Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol* 1999;17:976–983.
28. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med* 2014; 370:599–609.
29. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol* 2001;19:3622–3634.
30. Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol* 2001;19:3635–3648.
31. Aloia TA, Gershenwald JE, Andtbacka RH, et al. Utility of computed tomography and magnetic resonance imaging staging before completion lymphadenectomy in patients with sentinel lymph node-positive melanoma. *J Clin Oncol* 2006;24:2858–2865.
32. Gold JS, Jaques DP, Busam KJ, Brady MS, Coit DG. Yield and predictors of radiologic studies for identifying distant metastases in melanoma patients with a positive sentinel lymph node biopsy. *Ann Surg Oncol* 2007;14:2133–2140.
33. Miranda EP, Gertner M, Wall J, et al. Routine imaging of asymptomatic melanoma patients with metastasis to sentinel lymph nodes rarely identifies systemic disease. *Arch Surg* 2004;139:831–836; discussion 836–837.
34. Pandalai PK, Dominguez FJ, Michaelson J, Tanabe KK. Clinical value of radiographic staging in patients diagnosed with AJCC stage III melanoma. *Ann Surg Oncol* 2011;18:506–513.
35. Wong SL, Balch CM, Hurley P, et al. Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guideline. *Ann Surg Oncol* 2012;19: 3313–3324.
36. Cascinelli N. WHO declares lymphatic mapping to be standard of care for melanoma. Available at: http://www.cancernetwork.com/articles/who-declares-lymphatic-mapping-be-standard-care-melanoma. Accessed June 24, 2014.
37. O'Brien CJ, Uren RF, Thompson JF, et al. Prediction of potential metastatic sites in cutaneous head and neck melanoma using lymphoscintigraphy. *Am J Surg* 1995;170:461–466.
38. Eicher SA, Clayman GL, Myers JN, Gillenwater AM. A prospective study of intraoperative lymphatic mapping for head and neck cutaneous melanoma. *Arch Otolaryngol Head Neck Surg* 2002;128:241–246.
39. Schmalbach CE, Nussenbaum B, Rees RS, Schwartz J, Johnson TM, Bradford CR. Reliability of sentinel lymph node mapping with biopsy for head and neck cutaneous melanoma. *Arch Otolaryngol Head Neck Surg* 2003;129:61–65.
40. de Rosa N, Lyman GH, Silbermins D, et al. Sentinel node biopsy for head and neck melanoma: a systematic review. *Arch Otolaryngol Head Neck Surg* 2011;145:375–382.
41. Alex JC, Krag DN, Harlow SP, et al. Localization of regional lymph nodes in melanomas of the head and neck. *Arch Otolaryngol Head Neck Surg* 1998;124:135–140.
42. Patel SG, Coit DG, Shaha AR, et al. Sentinel lymph node biopsy for cutaneous head and neck melanomas. *Arch Otolaryngol Head Neck Surg* 2002;128:285–291.
43. Gershenwald JE, Colome MI, Lee JE, et al. Patterns of recurrence following a negative sentinel lymph node biopsy in 243 patients with stage I or II melanoma. *J Clin Oncol* 1998;16:2253–2260.
44. Wells KE, Stadelmann WK, Rapaport DP, Hamlin R, Cruse CW, Reintgen D. Parotid selective lymphadenectomy in malignant melanoma. *Ann Plast Surg* 1999;43:1–6.
45. Ollila DW, Foshag LJ, Essner R, Stern SL, Morton DL. Parotid region lymphatic mapping and sentinel lymphadenectomy for cutaneous melanoma. *Ann Surg Oncol* 1999;6:150–154.
46. Pawlik TM, Ross MI, Thompson JF, Eggermont AM, Gershenwald JE. The risk of in-transit melanoma metastasis depends on tumor biology and not the surgical approach to regional lymph nodes. *J Clin Oncol* 2005; 23:4588–4590.
47. Thomas JM, Clark MA. Sentinel lymph node biopsy: not yet standard of care for melanoma. *BMJ* 2004;329:170; author reply 170–171.
48. Estourgie SH, Nieweg OE, Kroon BB. High incidence of in-transit metastases after sentinel node biopsy in patients with melanoma. *Br J Surg* 2004;91:1370–1371.
49. Thomas JM, Clark MA. Are there guidance issues relating to sentinel node biopsy for melanoma in the UK? *Br J Plast Surg* 2004;57:689–690; author reply 690–681.
50. Kang JC, Wanek LA, Essner R, Faries MB, Foshag LJ, Morton DL. Sentinel lymphadenectomy does not increase the incidence of in-transit metastases in primary melanoma. *J Clin Oncol* 2005;23:4764–4770.
51. van Poll D, Thompson JF, Colman MH, et al. A sentinel node biopsy does not increase the incidence of in-transit metastasis in patients with primary cutaneous melanoma. *Ann Surg Oncol* 2005;12:597–608.
52. Cochran AJ, Wen DR, Huang RR, Wang HJ, Elashoff R, Morton DL. Prediction of metastatic melanoma in nonsentinel nodes and clinical outcome based on the primary melanoma and the sentinel node. *Mod Pathol* 2004;17:747–755.
53. Lee JH, Essner R, Torisu-Itakura H, Wanek L, Wang H, Morton DL. Factors predictive of tumor-positive nonsentinel lymph nodes after tumor-positive sentinel lymph node dissection for melanoma. *J Clin Oncol* 2004;22:3677–3684.
54. Sabel MS, Griffith K, Sondak VK, et al. Predictors of nonsentinel lymph node positivity in patients with a positive sentinel node for melanoma. *J Am Coll Surg* 2005;201:37–47.
55. Bostick PJ, Morton DL, Turner RR, et al. Prognostic significance of occult metastases detected by sentinel lymphadenectomy and reverse transcriptase-polymerase chain reaction in early-stage melanoma patients. *J Clin Oncol* 1999;17:3238–3244.
56. Ribuffo D, Gradilone A, Vonella M, et al. Prognostic significance of reverse transcriptase-polymerase chain reaction-negative sentinel nodes in malignant melanoma. *Ann Surg Oncol* 2003;10:396–402.
57. Shivers SC, Wang X, Li W, et al. Molecular staging of malignant melanoma: correlation with clinical outcome. *JAMA* 1998;280:1410–1415.
58. McMasters KM. Molecular staging of melanoma: sensitivity, specificity, and the search for clinical significance. *Ann Surg Oncol* 2003;10:336–337.
59. Whited JD, Grichnik JM. The rational clinical examination. *Does this patient have a mole or a melanoma? JAMA* 1998;279:696–701.
60. Hirche C, Murawa D, Mohr Z, Kneif S, Hunerbein M. ICG fluorescence-guided sentinel node biopsy for axillary nodal staging in breast cancer. *Breast Cancer Res Treat* 2010;121:373–378.
61. Kitai T, Inomoto T, Miwa M, Shikayama T. Fluorescence navigation with indocyanine green for detecting sentinel lymph nodes in breast cancer. *Breast Cancer* 2005;12:211–215.
62. Tagaya N, Yamazaki R, Nakagawa A, et al. Intraoperative identification of sentinel lymph nodes by near-infrared fluorescence imaging in patients with breast cancer. *Am J Surg* 2008;195:850–853.
63. Schaafsma BE, Mieog JS, Hutteman M, et al. The clinical use of indocyanine green as a near-infrared fluorescent contrast agent for image-guided oncologic surgery. *J Surg Oncol* 2011;104:323–332.
64. Fujiwara M, Mizukami T, Suzuki A, Fukamizu H. Sentinel lymph node detection in skin cancer patients using real-time fluorescence navigation with indocyanine green: preliminary experience. *J Plast Reconstr Aesthet Surg* 2009;62:e373–e378.
65. Mizukami T, Fujiwara M, Suzuki A, Nagata T, Fukamizu H. Sentinel lymph node detection by indocyanine green fluorescence imaging in skin cancer patients: technical refinement. *Open Surg Oncol J* 2010;2:57–61.
66. Tanaka R, Nakashima K, Fujimoto W. Sentinel lymph node detection in skin cancer using fluorescence navigation with indocyanine green. *J Dermatol* 2009;36:468–470.
67. Tsujino Y, Mizumoto K, Matsuzaka Y, Niihara H, Morita E. Fluorescence navigation with indocyanine green for detecting sentinel nodes in extramammary Paget's disease and squamous cell carcinoma. *J Dermatol* 2009;36:90–94.
68. Ogasawara Y, Ikeda H, Takahashi M, Kawasaki K, Doihara H. Evaluation of breast lymphatic pathways with indocyanine green fluorescence imaging in patients with breast cancer. *World J Surg* 2008;32:1924–1929.

69. Schaafsma BE, Verbeek FP, Rietbergen DD, et al. Clinical trial of combined radio- and fluorescence-guided sentinel lymph node biopsy in breast cancer. *Br J Surg* 2013;100:1037–1044.
70. Warycha MA, Zakrzewski J, Ni Q, et al. Meta-analysis of sentinel lymph node positivity in thin melanoma ($\leq$1 mm). *Cancer* 2009;115:869–879.
71. Balch CM, Gershenwald JE, Soong SJ, et al. Multivariate analysis of prognostic factors among 2,313 patients with stage III melanoma: comparison of nodal micrometastases versus macrometastases. *J Clin Oncol* 2010;28:2452–2459.
72. Bichakjian CK, Halpern AC, Johnson TM, et al. Guidelines of care for the management of primary cutaneous melanoma. *American Academy of Dermatology. J Am Acad Dermatol* 2011;65:1032–1047.
73. Ross MI. Sentinel node biopsy for melanoma: an update after two decades of experience. *Semin Cutan Med Surg* 2010;29:238–248.
74. Balch CM, Morton DL, Gershenwald JE, et al. Sentinel node biopsy and standard of care for melanoma. *J Am Acad Dermatol* 2009;60:872–875.