Sentinel Node Biopsy for Head and Neck Cutaneous Melanoma

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KEYWORDS

• Melanoma • Sentinel node biopsy • MSLT • Head and neck • Lymphadenectomy

KEY POINTS

- Sentinel node biopsy provides the most precise staging information for patients with any thickness melanoma allowing for accurate prognostication and guidance toward adjuvant care.
- Completion nodal dissection for sentinel node–positive patients with low disease burden demonstrates no additional survival benefit as long as the patient undergoes close and frequent clinical observation, including serial ultrasound, for at least 2 years.
- Sentinel node biopsy is safe and accurate for head and neck melanoma. Despite lack of data indicating survival benefit, completion neck dissection reduces regional recurrence. Surgeons must walk patients through this lengthy risk/benefit discussion to ensure shared decision making.
- Low enrollment of patients with head and neck melanoma in large clinical trials renders the conclusions less generalizable to this patient population.

INTRODUCTION

The most important prognostic factors as reflected in the current staging of melanoma include:

- Primary tumor depth of invasion.
- Ulceration at the primary site.
- Regional lymph node involvement.

This article explores the birth and evolution of sentinel node biopsy for melanoma and the controversies surrounding its application in the head and neck (HN). The story provides fascinating study into how new technology is often fraught with opposition

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and what it takes to foster the collaborations necessary to provide evidence of its benefits. The progression of data from Multicenter Selective Lymphadenectomy Trial I (MSLT-I) to the designing and resulting of Multicenter Selective Lymphadenectomy Trial II (MSLT-II) affirms that evidence-based medicine is the key component in advancing practice change.

SENTINEL LYMPH NODE BIOPSY: A BRIEF HISTORY

Gould and coworkers[1] published the first case series of sentinel lymph node biopsy (SLNB) in 1960. During a parotidectomy, his team astutely observed "a normal-appearing node at the junction of the anterior and posterior facial vein" and sent this for frozen section. The node was reported as "metastatic tumor" and the surgeons proceeded with radical neck dissection. Twenty-eight additional cases were similarly performed and results are seen in **Box 1**.[1] It was from this work that the term "sentinel node" was coined.

Sixteen years later, Cabanas[2] presented his series of penile cancer cases using lymphangiograms to locate sentinel lymph nodes. His study of 100 patients concluded that (1) lymphangiograms identify the sentinel node; (2) the sentinel node is the first site of metastasis; and (3) positive SLNB should be followed by lymphadenectomy, whereas negative SLNB can be observed.[2]

In the 1980s, Morton[3] and his team began to use these concepts and mapping techniques toward the management of melanoma. Early adopters were spurred by concerns regarding significant lymphedema associated with routine elective lymphadenectomy for melanoma, particularly because only 20% patients who underwent elective lymph node dissection demonstrated positive nodes[3]; knowing which patients would truly benefit from comprehensive lymphadenectomy would spare those with N0 disease the morbidity of a full lymph node dissection.[3] As such, SLNB is considered one of the first forms of targeted therapy.

EARLY TECHNIQUE

SLNB aims to identify the primary echelon of nodal drainage from a specific anatomic region. Initial work in melanoma used vital blue dye alone to identify cutaneous drainage.[4] Morton's early work was performed in cats where blue dye injection reliably identified the lymphatic watershed. Subsequent clinical study examined 223 consecutive patients and successfully identified 194 sentinel nodes in 237 lymphatic basins.[4] This "open and see approach"[5] posed a challenge because early surgeries were burdensome given the requirement to lift large areas of skin flaps and thoroughly trace lymphatic drainage pathways down to nodes of interest.

Box 1

The follow-up, 6–8 years, on the group of patients with neck dissection and parotidectomy shows all patients living and well except one who died of encephalomalacia 8 years after surgery. The four patients who had malignant parotid tumors but negative lymph nodes, and who therefore did not have a radical neck dissection, have been observed for 2–8 years, and none shows evidence of either recurrence or metastasis.

From Gould ED, Winship T, Philbin PH, Kerr HH. Observations on a "sentinel node" in cancer of the parotid. *Cancer.* 1960 Jan-Feb; 13:77-8, with permission.

Lymphoscintigraphy for cutaneous lesions was first described in 1953 when the authors found this technique could reliably predict lymphatic flow.[6] Because of the complex lymphatic patterns in HN, it is no surprise that an otolaryngologist was part of the first team[7] to apply this technique intraoperatively for malignant melanoma, building on Morton's work. Because blue dye alone is not visible on the skin surface, lymphoscintigraphy with gamma probe use in the operating room allowed for localizing radiocolloid tracer in the preoperative and intraoperative setting (**Box 2**). Lymphoscintigraphy planar images helped to better localize lymphatic drainage patterns and paved the way for more innovative "see and open approaches."[5] Despite this advancement, planar images were not precise for deep nodes, could not distinguish nodes near the injection site, had less sensitivity with doublet nodes, and were challenging to use with complex lymphatic drainage.[5] Single-photon emission computed tomography (SPECT) uses three-dimensional functional imaging fused with anatomic computed tomography (CT) correlates to improve localization of sentinel nodes. SPECT/CT can distinguish a sentinel node from a lymphangioma, lymphatic lake, or skin contamination.[5] Using blue dye in addition to SPECT/CT technology, the surgeon can "see, open, hear and see" to improve chances of accurately identifying sentinel nodes and minimizing false negatives.

SLNB needs to be gracefully orchestrated among the surgeon, nuclear medicine team, and pathologist. There is a learning curve for each specialty involved. The surgeon requires comfort with minimally invasive approaches and reliance on sight and sound to identify nodes. The nuclear medicine team must learn the timing in which to capture and map lymphatic drainage. The pathology workflow includes the need for additional processing and evaluation of nodal tissue to identify micrometastasis. With so many moving parts, validation of this new technique required a multicenter clinical trial.

MULTICENTER SELECTIVE LYMPHADENECTOMY TRIAL

MSLT-I was initiated to study whether SLNB can identify patients with clinically occult nodal metastases.[8] Its goal was to confirm the accuracy of nodal staging based on SLNB and determine whether immediate completion lymphadenopathy (CLND) in patients with tumor-positive sentinel nodes can improve outcome. **Fig. 1** describes the schema of the trial.[8]

Box 2
Gamma-probe localization has several advantages

- Aids in the precise location of the position of an underlying lymph node on the surface of the skin.
- Provides intraoperative guidance for the surgeon to the lymph node during dissection.
- Verifies that the correct node has been biopsied.
- Helps the surgeon determine the possible presence of residual lymph nodes.
- Allows for lymph nodes to be harvested through a small incision as opposed to raising a skin flap.
- Can be rapidly and easily performed.

Adapted from Alex JC, Weaver DL, Fairbank JT, Rankin BS, Krag DN. Gamma-probe-guided lymph node localization in malignant melanoma. *Surg Oncol*. 1993 Oct; 2(5):303-8, with permission.

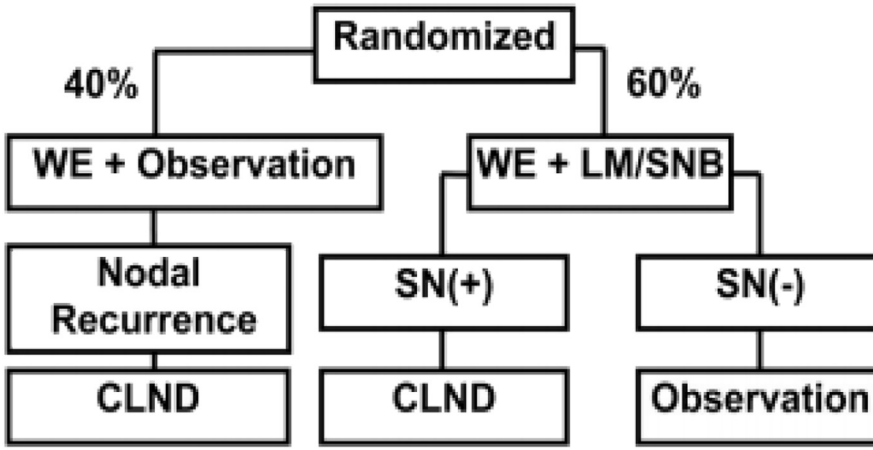

Fig. 1. Biopsy-proven melanoma. MSLT-I study design. Patients with primary cutaneous melanoma ≥1 mm or Clark level IV are assigned in a 60:40 distribution to wide excision plus lymphatic mapping and sentinel node biopsy, with immediate CLND for occult nodal metastases; or to wide excision plus observation, with delayed CLND or other treatment of palpable nodal metastases. All patients are followed up for disease-free and melanoma-specific survival. LM, lymphatic mapping; SNB, sentinel node biopsy; WE, wide excision. (*Data from* Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Elashoff R, Essner R, Nieweg OE, Roses DF, Hoekstra HJ, Karakousis CP, Reintgen DS, Coventry BJ, Glass EC, Wang HJ; MSLT Group. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med*. 2006 Sep 28; 355(13):1307-17.)

The primary end point of this study was melanoma-specific survival (MSS; survival until death from melanoma). The secondary end points included disease-free survival (DFS), survival with tumor-positive or tumor-negative sentinel nodes, and the incidence of sentinel node metastases, as compared with the incidence of clinically detected nodal metastases. Detailed results from the final trial report are listed in **Box 3**.[9]

Overall, patients with intermediate-thickness melanoma seemed to benefit the most with significant improvement in DFS in the biopsy group (**Box 4**). For patients with intermediate-thickness melanoma and subsequent nodal metastasis, MSS and DFS was improved for patients who underwent SLNB.

Several findings were published in a series of papers from the MSLT-1 group. Twelve years after accrual of the last patients, the final analysis was reported in 2014 and generated a lively and unfortunately, acerbic debate over the next few years.[13–17] Opponents took issue with the lack of difference seen in MSS indicating the procedure cannot be used as a therapeutic intervention.[13,15] MSLT-1 authors also performed several subgroup analyses to conclude that SLNB results in improved DFS. Critics argue that there is a clear lead time bias effect when patients who have already undergone nodal dissection are compared with those who have not when disease free is defined as the development of new nodal disease.[14] Some detractors even argue against the use of SLNB as standard of care for prognostication.[16]

The trial investigators responded in kind.[18–22] In the final report, they describe a clear and significant reduction in disease recurrence in the SLNB arm.[9] Furthermore, Faries and colleagues[12] demonstrated that those who underwent delayed nodal

Box 3
MSLT-I: final trial report results[9]

Survival data
- 10-year MSS: no difference for intermediate or thick melanomas when comparing SLNB with observation group.
- 10-year DFS: significantly higher in the SLNB versus observation group for intermediate (71.3% vs 64.7%) and thick (50.7% vs 40.5%) melanomas.

Prognostic significance of SLNB
- 10-year MSS for intermediate-thickness melanoma and SLNB-positive (62.1%) versus SLNB-negative (85.1%) (hazard ratio [HR] for death from melanoma, 3.09; 95% confidence interval [CI], 2.12–4.49; *P*<.001).
- 10-year MSS for thick melanoma and SLNB-positive (48.0%) versus SLNB-negative (64.6%) (HR for death from melanoma, 1.75; 95% CI, 1.07–2.87; *P* = .03).
- In multivariate analysis, sentinel node status was the strongest predictor of disease recurrence or death from melanoma.

Nodal metastasis (estimated cumulative incidence at 10 years) was the same between SLNB and observation group
- 20.0% for patients with intermediate-thickness melanoma.
- 41.4% for patients with thick melanoma.

In groups with nodal metastasis, survival advantages were seen in the intermediate-thickness group
- 10-year MSS was 62.1% (SLNB group) versus 41.5% (observation group) (HR for death from melanoma, 0.56; 95% CI, 0.37–0.84; *P* = .006).
- Distant DFS improved for patients with intermediate thickness (HR, 0.62; 95% CI, 0.42–0.91; *P* = .02).
- There were no differences seen in the patients with thick melanoma.

Post hoc latent-subgroup analysis performed to address lead time bias
- This subgroup specifically reviewed patients with intermediate-thickness melanoma that underwent immediate node dissection when SLNB-positive compared with those with delayed nodal development under observation.
- The estimated treatment effect on DFS (1.17; *P*<.001), distant DFS (0.73; *P* = .04), and MSS (0.68; *P* = .05). This translates to increases in survival times by factors of 3.2, 2.1, and 2.0, respectively.

Adapted from Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, Hoekstra HJ, Karakousis CP, Puleo CA, Coventry BJ, Kashani-Sabet M, Smithers BM, Paul E, Kraybill WG, McKinnon JG, Wang HJ, Elashoff R, Faries MB; MSLT Group. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med*. 2014 Feb 13; 370(7):599-609, with permission.

dissection suffered from greater disease burden and increased morbidity. Data from other international groups also support these findings. Moncrieff and Garioch[20] showed a significantly increased risk of extracapsular spread (22.7% vs 42.7%; *P*<005; odds ratio, 253; 95% confidence interval, 126–514) in macroscopic compared with microscopic nodal metastases. Furthermore, data presented in the UK guidelines for management of cutaneous melanoma indicate that patients with macroscopic disease are likely to be offered more extensive resections and adjuvant radiotherapy as a result.[23]

In addressing the question of survival benefit, the authors admit that the trial was underpowered because of unexpected favorable outcomes among all patients enrolled. Their findings conclude that 80% of the patients with intermediate-thickness melanoma had no nodal metastasis and therefore early nodal excision would not improve survival in such a group, thus skewing survival results. Therefore,

Box 4
Suite of papers generated from MSLT-I data

1999: Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early stage melanoma: a multicenter trial. This first report aimed to evaluate the accuracy of lymphatic mapping and SLNB and transferability of this technique worldwide. They compared rates of node identification in the MSLT-I group versus incidence of SN metastasis in a retrospective cohort at the organizing center (John Wayne Cancer Institute). Identification reached 97% in the MSLT cohort and incidence of metastasis approached that seen at John Wayne Cancer Institute. The paper concluded that lymphatic mapping and SLNB can be learned and applied in a standardized fashion.[10]

2005: Sentinel node biopsy for early stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. This article presented the learning phase each participating center had to complete before patient enrollment. All centers were required to present 30 consecutive cases where blue dye and radiocolloid injection were performed followed by lymphoscintigraphy. SLNB plus immediate CLND resulted in SN identification rate of 85%; each individual surgeon had to report at least 15 cases to show proficiency. Patients were then enrolled as noted in **Fig. 1**. This article demonstrated that lymphatic mapping and SLNB are safe and low-morbidity procedures for identifying nodes in the lymphatic basin.[11]

2006: Sentinel node biopsy or nodal observation in melanoma. This was the third interim analysis but first article from the MSLT-I working group to report detailed demographics, clinical results, and survival data for this multicenter trial. Pretrial statistical modeling indicated immediate versus delayed CLND could affect survival in intermediate-thickness melanoma (1.2–3.5 mm). This article evaluated 1269 patients with intermediate-thickness primary melanoma and demonstrated significantly higher DFS in the SLNB versus the observation group but no difference in MSS. When comparing SN-positive with SN-negative, survival curves widened significantly for DFS and MSS demonstrating the prognostic value of SLNB for intermediate-thickness melanoma.[8]

2010: The impact on morbidity and length of stay of early versus delayed complete lymphadenectomy in melanoma: results of the Multicenter Selective Lymphadenectomy Trial (I). This article demonstrated significantly worse lymphedema after delayed CLND compared with early CLND (for axillary and inguinal dissection). They also noted increased length of stay by 1.5–2 days in delayed CLND. No differences were seen with regards to other chronic toxicities, such as nerve dysfunction, motor weakness, or dysesthesias.[12]

2014: Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *New England Journal of Medicine*. This was the fifth and final paper reporting 10-year findings (see **Box 3**).[9]

they performed cumulative rates of nodal metastasis after 10 years and noted that no differences were found in SLNB versus observation group countering the argument of "false-positive sentinel nodes." In addition, latent subgroup analysis was performed to exclude possible ascertainment bias in patients with SLNB-positive versus patients with delayed nodal development under observation. This statistical method estimated the treatment effect of performing immediate node dissection in the SLNB-positive group. For intermediate-thickness melanomas, DFS, distant DFS, and MSS all demonstrated significant increase in survival (see **Box 3**).[9]

Finally, the investigators correctly argue that accurate staging via SLNB is critical to timely referral for adjuvant therapies and enrollment in clinical trial. At the time of final report publication, available adjuvant treatments included completion node dissection and interferon gamma. These treatments were fraught with concerns regarding associated toxicity/morbidity and limited benefit. With the current success of immunotherapy for melanoma, the information garnered from SLNB is essential for establishing appropriate care for patients with advanced disease.[18,24,25]

HEAD AND NECK MELANOMA: A UNIQUE SUBSITE

Extensive lymphatics within HN have prompted questions and debate as to the accuracy and prognostic value of SLNB. The classic multi-institutional trials include few HN patients (eg, only 18% of MSLT-1 enrollees had HN melanoma)[9] and are thus underpowered with respect to definitive conclusions for this anatomic subsite. Some have argued that the conclusions drawn in these studies cannot be applied to HN patients without some qualifications.

Accuracy of SLNB for HN cases has been questioned. Interim analysis of MSLT-I in 2005 showed an SLNB success rate of 85% in HN cases compared with 98% for melanoma in other sites.[11] Since that time, several series have invalidated this concern. Erman and colleagues[26] studied 353 SLNB for HN melanoma performed in an academic otolaryngology setting. Accuracy was reported at 99.7%. Sentinel node involvement in this study was 19.6%.[26] These numbers match other large series, such as the Sunbelt Trial for melanoma at non-HN sites.[27] Multivariate analysis showed SLN status was the single most prognostic clinicopathologic factor taking into account Breslow depth and ulceration.[26]

There have been reports of increased false omission rates in HN cases compared with other sites.[28] This has been attributed to variable lymphatic drainage but also, drainage to several nodal basins, closeness to primary site, proximity to cranial nerves, and small sentinel nodes.[24,28] Roy and colleagues[24] analyzed 37 studies assessing accuracy of SLNB in HN melanoma. They report overall failure rates after melanoma surgery to be 3.3% to 6.9%, and false-negative rates from 10.4% to 24.5%. For HN melanoma, they noted a mean failure rate of 4.9% (0%–25%) and a false-negative rate of 20.6% (0%–50%). The wide incidence range reflects results from various institutions, many of which report low numbers of HN cases.[24]

Furthermore, the safety of SLNB in HN has been questioned because of complex cranial nerve anatomy and proximity to great vessels. Several large trials have disproven this and in fact have shown less morbidity overall for SLNB of HN. Wrightson and colleagues[29] reviewed complication after SLNB and demonstrated higher rates in the groin (8.1%) and axilla (4.4%) than HN (2.4%). The Sunbelt Melanoma Trial included greater than 300 HN patients and had no cases of permanent facial nerve paresis.[26]

Finally, similar to melanoma at other sites, SLN status remains the most important prognostic indicator in cN0 HN melanoma.[30] Hanks and colleagues[31] reviewed a 356-patient cohort of HN cutaneous melanoma cases over 10 years. They demonstrate 10-year overall survival (OS) and MSS (61%, 81%) for SLNB-negative patients dropped considerably in SLNB-positive patients (31%, 60.3%). In fact, 10-year OS, recurrence-free survival (RFS), regional RFS, distant DFS, PFS, and MSS all significantly diminished in patients with positive sentinel node status.[31] SLNB in HN melanoma is safe and accurate. It is now incorporated into the American Joint Committee on Cancer staging system, the National Comprehensive Cancer Network (NCCN) practice guidelines, and numerous national and international consensus statements.[30]

CURRENT INDICATIONS FOR SENTINEL LYMPH NODE BIOPSY

In 2018, the joint American Society of Clinical Oncology/Society of Surgical Oncology (ASCO-SSO) guidelines offered a systematic review of the literature regarding SLNB. This review included nine observational studies, two systematic reviews, and an updated randomized controlled trial of SLNB. Their recommendations are seen in **Box 5**. The rate of sentinel node metastasis in T1a and T1b lesions is 5.2% and 8%, respectively.[32] Despite this marginal difference, there does seem to be improved

Box 5
2018 ASCO-SSO practice guidelines[32]

Recommendation 1.1. Thin melanomas. Routine SLNB is not recommended for patients with melanomas that are T1a (nonulcerated lesions <0.8 mm in Breslow thickness). SLNB may be considered for T1b patients (0.8–1.0 mm Breslow thickness or <0.8 mm Breslow thickness with ulceration) after a thorough discussion with the patient of the potential benefits and risk of harms associated with the procedure.

Recommendation 1.2. Intermediate-thickness melanomas. SLN biopsy is recommended for patients with melanomas that are T2 or T3 (Breslow thickness of >1.0–4.0 mm).

Recommendation 1.3. Thick melanomas. SLNB may be recommended for patients with melanomas that are T4 (>4.0 mm in Breslow thickness), after a thorough discussion with the patient of the potential benefits and risks of harm associated with the procedure.

Data from Practice guidelines from Wong SL, Faries MB, Kennedy EB, Agarwala SS, Akhurst TJ, Ariyan C, Balch CM, Berman BS, Cochran A, Delman KA, Gorman M, Kirkwood JM, Moncrieff MD, Zager JS, Lyman GH. Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. J Clin Oncol 2018;36(4):399-413.

prognosis for patients with T1b disease who have negative SLNB compared with those who do not undergo SLNB.

SLNB for intermediate-thickness melanoma generates the least controversy. Several studies reviewed demonstrate that SLNB imparts improved regional disease control and guides selection of adjuvant treatment. Prognostic significance of SLN status and the low rate of complications reveals that the benefits of performing SLNB outweigh the risks of observation (16%–20% expected metastatic rate).[32]

For thick melanomas, the lack of perceived benefit from SLNB because of assumed high rates of occult distant disease has led to fewer studies in this area. Most papers evaluating SLNB in thick melanomas have been published in the last few years and are retrospective.[33] A SEER database study found no difference in 5-year DSS with SLNB versus observation groups.[34] MSLT-I also described a cohort of thick melanomas with improved 10-year DFS but no difference in 10-year MSS between SLNB and observations groups (see **Box 3**).[9] Nonetheless, these studies have demonstrated that SLNB provides important prognostic information, in particular for SLNB-negative patients.[35] Results from SLNB can provide critical information to help guide treatment plans including intensity of surveillance and suitability for adjuvant treatments (**Box 6**).

MANAGEMENT OF THE NECK AFTER A POSITIVE SENTINEL NODE: THE NEW DEBATE

Although MSLT-I confirmed that SLNB is a reliable technique and that the pathologic status of the sentinel node is the most important predictor of survival outcome in patients with melanoma, important recent studies addressing the merits of CLND have further changed surgical practice. Although not without controversy, these studies also validate the importance of SLNB as a diagnostic tool and therapeutic intervention for many patients with melanoma.

THE GERMAN DERMATOLOGIC COOPERATIVE ONCOLOGY GROUP SELECTIVE LYMPHADENECTOMY TRIAL

DeCOG-SLT, a multicenter prospective randomized phase 3 trial published in June of 2016, compared CLND with observation in patients with sentinel node–positive

Box 6
SLNB contemporary technique: pearls

- Under optimal circumstances, WLE and SLNB should occur on the same day. This recommendation from NCCN attempts to minimize false-negative rates that might be elevated because of disrupted lymphatics from previous biopsy.
- The melanoma is injected with 2–4 aliquots of radiocolloid, usually in a four-quadrant fashion around the lesion.
- Acquisition of lymphoscintigraphy images may begin 3 minutes postinjection.
- Anatomic landmarks delineated by SPECT/CT are critical to the minimally invasive approach favored for HN.
- 1–3 mL of blue dye is injected through needles 25G or smaller. The bevel of the needle should be facing up and inserted nearly parallel to the skin. After injection, dermal lymphatics are seen arborizing around the lesion.
- Consideration must be given to where incisions for SLNB are placed and how that would affect future skin incisions should the patient need to return for completion lymphadenectomy.
- The radiotracer read of the node, usually a 10-second ex vivo count, should be documented. The bed from which the sentinel node was removed should have a radiotracer read of 10% or less of the ex vivo node.
- Sentinel nodes are labeled specifically as sentinel nodes when sent to pathology. This alerts the pathology team toward special handling. NCCN guidelines recommend submission of the entire node. Large nodes should be sliced at 2-mm intervals, whereas smaller nodes (<5 mm) should be submitted whole.
- If initial biopsy results indicate positive margins (MIS or invasive melanoma), staged reconstruction is recommended to allow for additional resection should this be necessary after return of the final pathology.

melanoma. It should be stated at the outset that this trial purposely excluded patients with HN melanoma because of the controversies discussed previously. That said, the trial's hypothesis that CLND would confer a survival benefit for positive SLNB patients was refuted. Distant metastasis-free survival (DMFS; the primary study end point), OS, and RFS were all comparable between the treatment groups. On multivariable analysis, sentinel node tumor burden ($\leq$1 mm including single cells vs >1 mm deposits) and primary melanoma tumor thickness ($\leq$2 mm vs >2 mm) were significant predictors of DMFS, OS, and RFS, whereas CLND, primary melanoma ulceration, number of positive sentinel nodes, and adjuvant interferon therapy were not. Further analysis of DMFS in the subgroups of positive sentinel node patients by nodal tumor burden was conducted, with no difference between the two treatment groups noted. The authors did note a small increase in regional disease control for patients treated with CLND, 8% versus 15% in the observation group. This was attended by a 24% "adverse event" rate in the CLND group, with lymphedema cited as the most common complication of further surgery.[36]

Based on these results, the DeCOG-SLT authors concluded that CLND may be avoided in patients whose sentinel node tumor burden is 1 mm or less. They remained open to the possibility that CLND is useful in patients with higher nodal burden, acknowledging that the 66% to 34% skew of low versus high nodal burden patients in their study impacts this recommendation.[36] The high rate of surgical complications in the study population likely influenced these recommendations. Having closed DeCOG-SLT early because of accrual challenges and power analyses impacted by

better-than-expected survival of the study population, the authors looked to additional data from prospective trials being conducted elsewhere in the world. Even so, the final report by Leiter and colleagues[37] of the DeCOG-SLT, with updated analysis through 6 years of follow-up, did not shift their recommendations.

THE SECOND MULTICENTER SELECTIVE LYMPHADENECTOMY TRIAL

MSLT-II was designed to examine the benefit of immediate CLND versus serial clinical observation with ultrasonography in patients with melanoma with positive sentinel nodes. The randomized phase 3 trial was significantly larger than the DeCOG-SLT and was adequately powered to detect a difference between the treatment groups of 5% for the primary end point of MSS. The patients randomized to the observation arm of the trial were followed with clinical examination and regional nodal basin ultrasound every 4 months for the first 2 years, followed by every 6 months for years 3 and 4, and then annually thereafter. MSLT-II noted no significant differences in MSS, even after adjusting for other prognostic factors, between SLNB-positive patients undergoing immediate CLND and those observed by ultrasound. This was also true with respect to DMFS, but there was a small difference in DFS in favor of the CLND group ($68 \pm 1.7\%$ vs $63 \pm 1.7\%$ in the observation group; $P = .05$). This was likely caused by improved regional control in a previously dissected nodal basin ($92 \pm 1.0\%$ in dissection group vs $77 \pm 1.5\%$ in the observation group; $P<.001$). Nonsentinel node metastases were discovered on pathologic assessment of 11.5% of CLND patients; this increased over time to an actuarial rate of 17.9% (3 year) and 19.9% (5 year). In the observation arm, nonsentinel node metastases were located by ultrasound or physical examination in 22.9% (3 year) and 26.1% (5 year), a statistically significant difference between the two groups at both time points. Finally, the CLND group, much like that in the DeCOG-SLT trial, was more likely to experience an adverse event, with lymphedema noted in approximately 24% of patients postdissection.[38]

MSLT-II provides strong evidence that "no significant survival benefit" is provided by CLND to melanoma patients with positive sentinel nodes. The authors do, however, note that nodal dissection allows for complete staging and the opportunity to control regional metastasis; indeed, completion nodal dissection reduced the rate of regional nodal recurrence by almost 70%. Much like the DeCOG-SLT, most of the patients had a low nodal burden of metastatic melanoma; median diameter of largest tumor deposit was 0.61 mm in the dissection group and 0.67 mm in the observation group, and some nodes were deemed positive only through real-time polymerase chain reaction. As such, the authors caution against making conclusions about CLND in patients with higher nodal metastatic burden. They also note that it is unclear if avoiding CLND is safe in the absence of the rigorous follow-up schedule or in centers without specialized ultrasound services. MSLT-II confirmed the findings of MSLT-I that the pathologic status of the sentinel node is of critical prognostic value in melanoma, and additionally revealed that CLND, although offering additional prognostic information and improved regional control, does not impact MSS or DFS.[38]

TO DISSECT OR OBSERVE THE NECK?

With the new data provided by MSLT-II and DeCOG-SLT, CLND after positive SLNB is no longer the default decision for patients and surgeons. Both studies, including an updated final analysis of the DeCOG-SLT, demonstrate that survival is not impacted by additional surgery to remove remaining at-risk regional lymph nodes. Indeed, these studies provide additional evidence to MSLT-I that the survival benefit of surgery comes from SLNB itself. This point should be made abundantly clear to patients

with positive sentinel nodes as they contemplate next steps in their treatment. Patients with surgically removed microscopic nodal disease should be offered close clinical observation, including ultrasound of the regional nodal basins, as one of their options, and be considered for available clinical trials and/or adjuvant therapy as part of a multidisciplinary approach to their ongoing melanoma care.

That completion nodal dissection reduces the regional recurrence rate should also be disclosed to the patient. Although this is not the same as providing a survival benefit, nodal dissection may be warranted in several circumstances. These include patients who are not able or interested in ongoing surveillance with serial ultrasounds at 4-month intervals for the first 2 years of surveillance. In their review of CLND after SLNB, Delman and Wong[39] argue that another subset of patients who might benefit from further surgery are those with significant projected life expectancy to avoid the development of clinically significant regional disease. Given the low but real risk of surgical morbidity from CLND, balancing this risk with the timing of surgery (immediate vs when nodal recurrence become evident) is important in a population where there is no survival benefit. This is particularly true in the era of tremendous developments in adjuvant therapy efficacy.[39]

There remain unanswered questions, however, for many HN surgical oncologists and their patients. Only 13.7% of the patients in the MSLT-II had melanomas of HN, and no HN melanoma patients were enrolled in the DeCOG-SLT. The surgical morbidity of axillary and groin nodal dissections is different from that of neck dissection, particularly with respect to lymphedema, which tends to be less common and less impactful than in the extremities. Risk to cranial nerves and major vasculature prompts concern for the sequelae of losing early opportunities to control regional disease for patients with HN melanoma, irrespective of their OS.[40] That positive nonsentinel nodes portend a poor prognosis leaves some surgeons reticent to adopt a watchful waiting approach; moreover, having this information early may lead to improved decisions around adjuvant therapies for patients at higher risk for poor survival outcomes. Finally, given that both prospective randomized trials noted a preponderance of low metastatic nodal burden in their study population, it remains uncertain whether observation protocols can be safely applied to patients with larger nodal metastatic deposits. The Minimal Sentinel Node Tumor Burden (MINITUB) trial of the European Organization for Research and Treatment of Cancer is examining small metastases and patterns of nodal burden (ie, subcapsular vs parenchymal location) in hopes of further defining the patients least likely to benefit from CLND; results are expected in 2023.

NCCN and the ASCO-SSO guidelines have been modified as a result of MSLT-II and DeCOG-SLT.[39,41] How HN surgeons adopt these guidelines remains to be seen. The University of Michigan recently looked at surgical activity during the year before, year after, and 2 years after MSLT-II; of the 235 consecutive SLNB-positive patients included over those 3 years, 67% underwent immediate CLND the year before, 33%, and 26%, respectively, after MSLT-II was published. Patients with HN melanoma were more likely to undergo completion nodal dissection compared with other primary sites (59% vs 33% [$P = .003$]; odds ratio, 5.22 [$P = .002$]), likely reflecting many of the aforementioned concerns. Patients with higher sentinel node tumor burden were also more likely to undergo further surgery (43% vs 10% for tumor burden $\geq$0.1 mm [$P<.001$]; odds ratio, 8.64 [$P = .002$]).[42]

This single institution's experience is a snapshot of the impact of MSLT-II overall: steady, progressive adoption of regional observation in appropriate SLNB-positive patients, coupled with reticence in applying the new recommendations to the group that was least represented in the MSLT-II cohort.[42] Low enrollment of HN patients

in large melanoma trials is a common challenging issue and one that must be addressed in future trials. In the meantime, as the data evolve and surgeons gain experience with surveillance protocols, we must continue to make decisions with our patients based on the best available evidence.

SUMMARY

Over the last 60 years, SLNB has advanced from an interesting observation to the most precise and accurate staging technique performed for malignant melanoma. This is a result of international collaborations and technical innovations across subspecialties and systematic and methodical study of real-time clinical problems. Although there remain unanswered questions in this field, these extraordinary collective efforts continue to push toward less invasive, more informative and effective approaches to managing this deadly disease for patients.

DISCLOSURE

Nothing to disclose.

REFERENCES

1. Gould ED, Winship T, Philbin PH, et al. Observations on a "sentinel node" in cancer of the parotid. Cancer 1960;13:77–8.
2. Cabanas RM. An approach for the treatment of penile carcinoma. Cancer 1977; 39(2):456–66.
3. Morton DL. Overview and update of the phase III Multicenter Selective Lymphadenectomy Trials (MSLT-I and MSLT-II) in melanoma. Clin Exp Metastasis 2012; 29(7):699–706.
4. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 1992;127(4):392–9.
5. Perissinotti A, Vidal-Sicart S, Nieweg O, et al. Melanoma and nuclear medicine. Melanoma Manag 2014;1(1):57–74.
6. Sherman AI. Ter-Pogossian M. Lymph-node concentration of radioactive colloidal gold following interstitial injection. Cancer 1953;6(6):1238–40.
7. Alex JC, Weaver DL, Fairbank JT, et al. Gamma-probe-guided lymph node localization in malignant melanoma. Surg Oncol 1993;2(5):303–8.
8. Morton DL, Thompson JF, Cochran AJ, et al, MSLT Group. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med 2006;355(13):1307–17.
9. Morton DL, Thompson JF, Cochran AJ, et al, MSLT Group. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med 2014;370(7):599–609.
10. 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(4):453–63 [discussion 463–5].
11. Morton DL, Cochran AJ, Thompson JF, et al. Multicenter selective lymphadenectomy trial group. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. Ann Surg 2005;242(3): 302–11 [discussion 311–3].
12. Faries MB, Thompson JF, Cochran A, et al. MSLT Cooperative Group. The impact on morbidity and length of stay of early versus delayed complete

lymphadenectomy in melanoma: results of the multicenter selective lymphadenectomy trial (I). Ann Surg Oncol 2010;17(12):3324–9.
13. van Akkooi AC, Eggermont AM. Melanoma: MSLT-1–SNB is a biomarker, not a therapeutic intervention. Nat Rev Clin Oncol 2014;11(5):248–9.
14. van Akkooi AC. Sentinel node followed by completion lymph node dissection versus nodal observation: staging or therapeutic? Controversy continues despite final results of MSLT-1. Melanoma Res 2014;24(4):291–4.
15. Sladden M, Zagarella S, Popescu C, et al. No survival benefit for patients with melanoma undergoing sentinel lymph node biopsy: critical appraisal of the multicenter selective lymphadenectomy trial-I final report. Br J Dermatol 2015;172(3):566–71.
16. Yang JC, Sherry RM, Rosenberg SA. Melanoma: why is sentinel lymph node biopsy 'standard of care' for melanoma? Nat Rev Clin Oncol 2014;11(5):245–6.
17. Yang JC, Sherry RM. MSLT-I-response of clinical trial investigators. Nat Rev Clin Oncol 2014;11(11). https://doi.org/10.1038/nrclinonc.2014.65-c2.
18. Faries MB, Cochran AJ, Thompson JF. MSLT-I-response of clinical trial investigators. Nat Rev Clin Oncol 2014;11(11). https://doi.org/10.1038/nrclinonc.2014.65-c1.
19. Faries MB, Cochran AJ, Elashoff RM, et al. Multicenter selective lymphadenectomy trial-I confirms the central role of sentinel node biopsy in contemporary melanoma management: response to 'No survival benefit for patients with melanoma undergoing sentinel lymph node biopsy: critical appraisal of the Multicenter Selective Lymphadenectomy Trial-I final report. Br J Dermatol 2015;172(3):571–3.
20. Moncrieff M, Garioch J. MSLT-I: it's all about the lymph nodes. Br J Dermatol 2015;173(2):626–7.
21. McGregor JM, Sasieni P. MSLT-I: it's all about the lymph nodes…: reply from the authors. Br J Dermatol 2015;173(2):627–8.
22. Ross MI, Gershenwald JE. How should we view the results of the multicenter selective lymphadenectomy trial-1 (MSLT-1)? Ann Surg Oncol 2008;15(3):670–3.
23. Marsden JR, Newton-Bishop JA, Burrows L, et al. Revised UK guidelines for the management of cutaneous melanoma 2010. British Association of Dermatologists (BAD) Clinical Standards Unit. J Plast Reconstr Aesthet Surg 2010;63(9):1401–19.
24. Roy JM, Whitfield RJ, Gill PG. Review of the tole of sentinel node biopsy in cutaneous head and neck melanoma. ANZ J Surg 2016;86(5):348–55.
25. Wright FC, Souter LH, Kellett S, et al, Melanoma Disease Site Group. Primary excision margins, sentinel lymph node biopsy, and completion lymph node dissection in cutaneous melanoma: a clinical practice guideline. Curr Oncol 2019;26(4):e541–50.
26. Erman AB, Collar RM, Griffith KA, et al. Sentinel lymph node biopsy is accurate and prognostic in head and neck melanoma. Cancer 2012;118(4):1040–7.
27. McMasters KM, Egger ME, Edwards MJ, et al. Final results of the sunbelt melanoma trial: a multi-institutional prospective randomized phase III study evaluating the role of adjuvant high-dose interferon Alfa-2b and completion lymph node dissection for patients staged by sentinel lymph node biopsy. J Clin Oncol 2016;34(10):1079–86.
28. de Rosa N, Lyman GH, Silbermins D, et al. Sentinel node biopsy for head and neck melanoma: a systematic review. Otolaryngol Head Neck Surg 2011;145(3):375–82.
29. Wrightson WR, Wong SL, Edwards MJ, et al. Complications associated with sentinel lymph node biopsy for melanoma. Ann Surg Oncol 2003;10:676–80.

30. Schmalbach CE, Bradford CR. Is sentinel lymph node biopsy the standard of care for cutaneous head and neck melanoma? Laryngoscope 2015;125(1):153–60.
31. Hanks JE, Kovatch KJ, Ali SA, et al. Sentinel lymph node biopsy in head and neck melanoma: long-term outcomes, prognostic value, accuracy, and safety. Otolaryngol Head Neck Surg 2020;162(4):520–9.
32. Wong SL, Faries MB, Kennedy EB, et al. Sentinel lymph node biopsy and management of regional lymph nodes in melanoma: American Society of Clinical Oncology and Society of Surgical Oncology clinical practice guideline update. J Clin Oncol 2018;36(4):399–413.
33. Kachare SD, Singla P, Vohra NA, et al. Sentinel lymph node biopsy is prognostic but not therapeutic for thick melanoma. Surgery 2015;158:662–8.
34. Ribero S, Osella-Abate S, Sanlorenzo M, et al. Sentinel lymph node biopsy in thick-melanoma patients (N=350): what is its prognostic role? Ann Surg Oncol 2015;22:1967–73.
35. Monroe MM, Pattisapu P, Myers JN, et al. Sentinel lymph node biopsy provides prognostic value in thick head and neck melanoma. Otolaryngol Head Neck Surg 2015;153(3):372–8.
36. Leiter U, Stadler R, Mauch C, et al. German Dermatologic Cooperative Oncology Group (DeCOG). Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol 2016;17(6):757–67.
37. Leiter U, Stadler R, Mauch C, et al. German Dermatologic Cooperative Oncology Group. Final analysis of DeCOG-SLT trial: no survival benefit for complete lymph node dissection in patients with melanoma with positive sentinel node. J Clin Oncol 2019;37(32):3000–8.
38. Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med 2017;376(23):2211–22.
39. Delman KA, Wong SL. Completion node dissection after sentinel node biopsy in melanoma. JAMA Surg 2018;153(11):1045–6.
40. Schmalbach CE, Bradford CR. Completion lymphadenectomy for sentinel node positive cutaneous head & neck melanoma. Laryngoscope Investig Otolaryngol 2018;3(1):43.
41. Coit DG, Thompson JA, Albertini MR, et al. Cutaneous melanoma, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019;17(4):367–402.
42. Bredbeck BC, Mubarak E, Zubieta DG, et al. Management of the positive sentinel lymph node in the post-MSLT-II era. J Surg Oncol 2020. https://doi.org/10.1002/jso.26200.