Laryngoscope Investigative Otolaryngology
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published by Wiley Periodicals, Inc. on behalf of The Triological Society

Completion Lymphadenectomy for Sentinel Node Positive Cutaneous Head & Neck Melanoma

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Abstract: The application and utility of melanoma sentinel lymph node biopsy (SLNB) has evolved significantly since its inception over two decades ago. The current focus has shifted from a staging modality to potentially a therapeutic intervention. Recent research to include large multi-institutional randomized trials have attempted to answer the question: is a completion lymph node dissection (CLND) required following a positive SLNB? This review provides an evidence-based, contemporary review of the utility of CLND for SLNB positive head and neck cutaneous melanoma patients.

Key Words: Melanoma, sentinel node biopsy, completion lymphadenectomy.
Level of Evidence: NA

INTRODUCTION

The incidence of melanoma continues to climb at staggering rates with 87,110 new invasive cases projected in the United States for 2017 and an additional 9,730 melanoma deaths this same year.[1] Regional metastasis remains the most important prognostic factor for melanoma recurrence and survival which underscores the importance of accurate staging.[2] Up to 20% of melanoma patients presenting with localized stage I and II disease will actually harbor occult regional metastasis despite a clinically and radiographically N-0 neck. For this reason, Dr. Donald Morton introduced the sentinel lymph node biopsy (SLNB) technique in 1992 as a means to identify these patients with aggressive melanoma who may benefit from additional therapy to include completion lymphadenopathy (CLND) and adjuvant therapy.[3]

Since its inception, SLNB has replaced elective neck (END) as standard of care for staging of localized melanoma because four prospective randomized trials failed to demonstrate a survival benefit with END.[4–7] Ultimately head and neck (HN) SLNB emerged as a reliable staging modality, more so than END and alternative imaging techniques. In the ensuring two decades, SLNB was formally incorporated into American Joint Committee on Cancer staging system[2] as well as evidenced-based national[8–10] and international guidelines.[11,12] Currently, the World Health Organization recommends use of the technique for accurate staging of patients enrolled into clinical trials. Ultimately dedicated HN studies definitively demonstrated that SLNB is safe and reliable in the HN region,[13–15] carrying the same false rate of emission of 4.2% as trunk and extremity SLNB.[16] The pathologic status of the sentinel node is recognized as the most important prognostic feature for disease recurrence and overall survival.[16]

Current evidence based guidelines to include the National Comprehensive Cancer Network recommend CLND for all patients with a positive SLNB.[8] The rationale for CLND is that uncontrolled regional disease will ultimately lead to systemic metastasis with decreased survival. However, this practice is variable and recent studies challenge the need and associated benefit afforded by CLND because patients with negative SLNB are at risk for subsequent distant disease.[17–19] This state of the art review provides an evidence-based, contemporary review of the utility of CLND for sentinel node positive HN cutaneous melanoma patients.

Current practice of CLND

Current National Comprehensive Cancer Network (NCCN) guidelines advocate the use of SLNB for patients with localized Stage I and II melanoma, as well as patients with resectable satellite and *in transit* disease.[8] Specifically, patients with Stage IB (0.76–1.0 mm thickness with $\geq$1 mitotic feature/mm^2 or Stage II $>$1.0 mm thickness) should also be offered SLNB. Stage IA patients (0.76–1.0 mm thickness in the absence of ulceration and/or increased mitotic rate) should have the opportunity to discuss and consider SLNB staging.

Per NCCN guidelines, patients with SLNB-positive stage III nodal disease should be offered a CLND.[8] Panel members acknowledge the increased cost and morbidity associated with immediate CLND. At the same time, they highlight benefits of CLND to include: the increased known probability of additional positive non-SLNs, improved regional control, lower morbidity when compares to TLND, and potential to improve long-term disease specific survival (DSS) in these aggressive tumors.[8]

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Editor's Note: This Manuscript was accepted for publication 24 December 2017.

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DOI: 10.1002/lio2.136

While CLND following a positive SLNB is standard of care, review of the National Cancer Data Base (2004–2005) revealed only 50% of patients with a positive SLNB undergoing CLND.[20] Patients were more likely to undergo CLND if care was rendered in an NCCN or NCI-designated center; patients were more likely to be observed if they were >75 years of age or had an extremity melanoma.

Mosquiera et al. utilized the Surveillance Epidemiology and End Results (SEER) registry to conduct a population based analysis of intermediate thickness (1–4 mm depth of invasion) melanoma patients undergoing CLND.[21] Thirteen percent of the 2172 study patients were primary HN. Ninety-one patients with HN melanoma underwent SLNB + observation; 190 HN patients underwent SLNB + CLND for regional disease. Overall, 68% of HN patients received CLND which mirrored that of trunk melanoma (70%) but was significantly higher than extremity melanoma (65%; $p = 0.05$). CLND correlated with male gender (OR: 1.27), geographic location (Michigan OR = 2.31; Iowa OR = 1.69), and younger age. While male gender, primary site, ulceration, depth of invasion, Clark level of invasion and number of positive lymph nodes were associated with survival ($p < 0.05$), CLND did not reach statistical significance ($p = 0.83$). The study demonstrated <2% five-year DSS advantage following CLND which was not significantly different from observation alone (70.4 vs. 72.3; $p = 0.83$).

Prognostic Heterogeneity of SLN-Positive Patients

Patients with a positive SLNB represent a heterogeneous cohort with survival rates ranging from a promising 90% to a dismal 30%.[22] *SLN tumor burden* is a recognized prognostic factor with high tumor volume patients portending a worse prognosis.[22–24] Tumor burden is defined as the maximum diameter of the largest metastatic deposit without lymphocytic interruption. Consensus has not been reached as to the specific cut-point between high versus low tumor burden. Several studies demonstrate a similar disease-free survival (DFS) and melanoma specific survival (MSS) rate between SLN-negative and SLN-positive patients with tumor burden measuring <0.1 mm.[25–27] Scheri et al. demonstrated a significant change in MSS when the minimal tumor burden cut point was increased from <0.1mm (90% MSS) to 0.2 mm (80% MSS).[28] It is important to note that SLN pathology sectioning protocols significantly impact patients classified. Patients initially deemed low SLN tumor burden (<0.1 mm) will actually be harboring high tumor burden identified only after additional SLN cuts are made for pathologic evaluation.[29] A current standardized pathology protocol for assessing SLN tumor burden does not exist.[30]

Tumor penetrative depth (TPD) of the micrometastatic disease within the SLN also impacts prognosis. The Dewar Criteria classifies patients based on subcapsular anatomic site.[31] Subcapsular metastasis is defined as melanoma cells confined to the subcapsular sinus or the paratrabecular region without associated irregularity.[31] This location is found in approximately 20–30% of patients and portends a better prognosis compared to metastatic melanoma beyond the subcapsular region.[29,31] Alternatively, the S-classification divides TPD into three categories: S1 (≤0.3 mm), S2 (>0.3 to ≤1.0 mm) and S3 (>1.0 mm).[24] Approximately 30% of SLN positive patients fall into the S1 category and have an improved survival over S2 and S3 metastatic deposits. The Rotterdam criteria is a similar classification with even integer TPD cut-points (<0.1mm, 0.1–1.0 mm, >1.0 mm).[32] Approximately 10–15% of SLN positive patients harbor TPD <0.1 mm and portend a better overall prognosis compared to deeper TPD.

Van der Ploeg et al. combined the prognostic information from both tumor burden utilizing the Dewar criteria and TPD utilizing the Rotterdam criteria.[28] Patients harboring <0.1 mm tumor burden confined to the subcapsular region demonstrated an excellent overall melanoma specific survival (MSS) with 95% five-year and 10-year rates. Unfortunately, only 6% of SLN positive patients fall into this specific category.

Therapeutic Value of CLND: Non-Randomized Trials

Numerous single institution and non-randomized trials investigated the survival benefit of CLND following a positive SLNB. Bamboat et al. conducted a non-randomized study of their Memorial Sloan-Kettering Cancer Center (MSKCC) experience.[33] Of their 4310 melanoma, 495 (11%) had a positive SLNB. 167 (34%) underwent observation while the remaining 328 (66%) underwent immediate CLND. There was no difference between the two treatment arms with respect to tumor depth of invasion, Clark's level of invasion, or ulceration. The observation arm was significantly older (66 years vs. 56 years; $p < 0.001$) and was more likely to have a lower extremity melanoma. Patients had a minimum of 23 months follow-up in the observation arm and 80 months in the CLND arm. There was no difference in local or *in transit* metastasis between the two groups. Patients in the observation arm were more likely to have a regional recurrence (15% vs. 6%; $p = 0.002$) while patients in the CLND arm were more likely to develop systemic recurrence (27% vs. 8%; $p < 0.001$). Sixteen percent of the SLN-positive patients who went on to CLND had additional positive non-SLNs. Recurrence free survival (RSS) rates were higher in the CLND arm (34.5 vs. 20.9 months; $p = 0.02$) but MSS did not differ ($p = 0.09$).

Wong et al. conducted a multi-institutional study among 16 melanoma centers to determine the impact of observation following a positive SLNB compared to historic controls.[34] The median age for the study cohort was 59 years. The median depth of invasion was 2.6 mm. Seventy-seven percent of all tumors were classified as Clark level 4/5 and 33% of the tumors were ulcerated. Only 12% of study patients had a primary melanoma involving the HN region. 134 patients were observed for a median period of 20 months which was shorter than the 36-month follow-up for the 164 CLND.

Overall, 20 patients (15%) in the observation arm went on to develop nodal recurrence at a median time of 11 months. The nodal RFS did not differ between the observation and CLND cohorts ($p = 0.07$), and the DSS did not differ between the groups ($p = 0.65$).

Kingham et al. conducted a prospective database study (1992–2008).[35] Of the 2269 patients undergoing SLNB, 313 had at least one positive node. 271 (87%) of patients received CLND, with the remaining 42 (13%) were observed with serial ultrasound for the first two years. Only 28 of the 313 patients (9%) were HN primaries. Patients in the observation cohort were older (70 years vs. 56; $p < 0.01$) and were more likely to have an extremity melanoma (40% vs. 13%; $p < 0.01$). Patient refusal was the most common reason for observation (45%). The observation cohort had a median follow-up of 32 months and the CLND cohort 43 months. No difference was identified between the two groups with respect to location of first recurrence, RFS or DSS. Similarly, a retrospective EORTC trial included 1174 positive SLNB patients to compare CLND (n = 1113) to observation (n = 61).[36] CLND did not impact DSS on univariate and multivariate analysis.

Therapeutic Value of CLND: Randomized Trials

DeCOG-SLT is a multicenter, phase III trial randomizing SLN-positive patients to immediate CLND (n = 241) versus observation with serial nodal ultrasound (n = 242).[37] The primary endpoint was distant metastasis-free survival. At a median follow-up of 35 months, the authors reported no difference in three-year distant metastatic rates between the CLND arm (75%) and the observation arm (77%). Similarly, CLND did not impact RFS or overall survival (OS) beyond that of observation. A slight improvement in regional control was noted with CLND (92% vs. 85%). However multivariate analysis failed to identify CLND as an independent variable impacting distant metastatic-free survival, OS or RFS. Overall, 34 (14%) of patients in the CLND arm experienced complications to include: lymphedema (n = 20; 58%), lymph fistula (n = 3; 8.8%), seroma (n = 3; 8.8%), infection (n = 3; 8.8%), and wound healing complications (n = 5;14.7%).

There are several limitations of the trial. 331 patients (66%) had low tumor burden SLNs measuring $\leq$1mm. The authors also acknowledge difficulties in accrual, disclosing that the study was under powered. The original study was planned for nine years, with an accrual period of six years to enroll 550 patients and detect a 10% difference in distant metastasis-free rate in the setting of a CLND. After eight years of accrual, only 473 patient met inclusion criteria. Therefore, the principle investigators elected to close the trial early, acknowledging that the study did not achieve the required number of events.

DeCOG-SLT must be interpreted with caution for HN cutaneous melanoma patients. Most importantly, this study excluded the HN subsite because the authors felt that the technique was "controversial" in the HN, citing a review article from 2011.[38] Since that publication, the largest single institution, dedicated HN melanoma SLNB study prospectively followed 353 patients for a mean of 48 months.[16] Of patients with a negative SLNB, 4.24% developed isolated regional recurrence. The negative predictive value for a negative HN SLNB was reported as 95.8%, which mirrored that of trunk and extremity melanoma where the technique is considered standard of care.

Results of the long awaited Second Multicenter Selective Lymphadenectomy Trial (MSLT-II) are published.[39] This international, multi-institutional randomized prospective trial was designed to determine the value of CLND for patients with a positive SLN. From 2004–2014, 1934 were enrolled in the trial. Of these, 824 patients underwent SLNB + CLND and 931 underwent SLNB + observation. At a median follow-up of 43 months, the three-year MSS rate was similar between the CLND and observations arms (68% vs. 86%; $p = 0.42$). The CLND arm did experience an improved DFS (68% vs. 64%; $p = 0.05$). Regional control was also improved in the setting of CLND (92% vs. 77%; $p < 0.001$). Of patients undergoing CLND, 11.5% had additional positive non-SLNs identified on final pathology, and a positive non-SLN was an independent prognostic factor for recurrence (Hazard ration: 1.78; $p = 0.005$). Overall, the MSLT-II research team conclude that immediate CLND increased the rate of regional control and provided prognostic information but did not impact MSS among melanoma patients with a positive SLNB.

The clinical implications of this trial for HN cutaneous melanoma warrants several considerations. The representation of the HN subsite was small. In the MSLT-II trial, 241 patients had HN cutaneous melanoma (13.7%); 113 underwent CLND and 128 underwent observation. Subgroup analysis of the three-year hazards ratio for MSS was not found to differ based on CLND (0.81; 0.44–1.48) versus observation following a positive SLNB (1.60; 0.96–2.66; $p = 0.07$). In addition, the authors stress the high rate of lymphedema following CLND, a complication rarely seen in the HN region (see below).

The European Organization for Research and Treatment of Cancer (EORTC) Melanoma Group is currently conducting the Minimal Sentinel Node Tumor Burden (MINITUB) trial to investigate the ability for CLND to portent a therapeutic benefit and to identify patients who may potentially be spared the procedure without oncologic compromise.[40] The estimated enrollment is 260 SLN positive patients randomized to observation versus CLND. Inclusion criteria are metastasis limited to the SLN with either 1) subcapsular tumor burden $\leq$0.4 mm and without parenchymal infiltration or 2) submicrometastatic disease $\leq$0.1 mm regardless of node subsite. The primary outcome measure is distant metastasis-free interval. Secondary outcomes include: regional control, relapse-free interval, MSS, OS, and morbidity to include wound infection, lymphedema, and neurological damage. Results from the trial are anticipated in 2023.

CHALLENGES OF INTERPRETING THE CURRENT CLND DATA

Paucity of Head and Neck–Specific Data

A paucity of data exists specific to HN cutaneous melanoma CLND. As outlined above, large prospective multi-institutional studies often lump the HN subset of patients (who are known to carry a worse prognosis) with trunk and extremity melanoma or exclude the site altogether. Given small representation of HN patients in CLND cutaneous melanoma studies, Lentsch et al. utilized the SEER database to investigate the ability for CLND to improve survival in the HN population.[41] Three hundred fifty SLN positive patients were identified: 201 (60%) underwent SLNB + CLND while 140 (40%) received SLNB alone + observation. Overall, a five-year DSS was not imparted following CLND. However, a subset of younger patients (<60 years) with non-ulcerated tumors measuring a depth of invasion ≤2 mm benefited from immediate CLND ($p = 0.03$). Interestingly, it is this same patient demographics that benefited from END in the prior Intergroup Melanoma Surgical Trial (IMST) back in 2000.[42] This finding leaves in question the ability to rely on prognostic features to forgo CLND in the younger patient population; the authors warn that younger patients traditionally deemed low risk for metastatic recurrence may actually miss their window for curative intervention if CLND is not performed.

While the strength of this investigation is the specific focus on the HN subsite, the retrospective nature inherent to database reviews remains a bias. In addition, the SEER database only represents 28% of the patient population. Lastly, the authors acknowledge that information is unavailable with respect to surgical margin status, adjuvant therapy, and the differentiation between positive SLNs versus non-SLNs in the registry.

Lack of standardized pathology protocols for evaluation of non-SLNs

Non-sentinel lymph node (non-SLN) status is another recognized prognostic feature for the cutaneous HN melanoma patient population; however, the data is conflicting.[43] Numerous studies attempted to identify SLN positive patients who are at risk for additional positive non-SLNs (identified following CLND). While primary tumor depth of invasion and SLN characteristics (see above) have emerged as prognostic markers in some investigations, the outcomes are not consistently replicated. [44–46]

In theory, patients with metastatic regional disease limited to SLNs alone should receive the lowest benefit from a CLND. The SEER database was utilized to test this hypothesis specifically among HN melanoma patients.[47] The primary study objectives were 1) to identify prognostic features associated with a low risk for harboring non-SLNs and 2) to analyze the five-year DSS between patients stratified on risk for non-SLN positivity. Two hundred ten patients in the national database received SLNB + CLND while 140 patients received SLNB alone. Minimal tumor thickness (depth of invasion) and non-ulceration were both associated with a low risk of harboring non-SLN in the CLND specimen ($p < 0.25$). Patient age, anatomic site, and sex were not prognostic. Patients <60 years of age who underwent CLND had a markedly improved DSS compared to SLNB alone (>90% vs. <25%; $p < 0.0025$) but a DSS survival advantage with CLND over observation was not found in the subgroup deemed at higher risk for non-SLN metastasis ($p > 0.25$). The authors conclude that selecting patients for CLND based on non-SLN risk of metastasis may be unreliable.

MSLT-II found that patients with positive non-SLNs portend a worse prognosis but at the current time a reliable way to identify this high-risk subgroup is lacking.[39] A recognized challenge in identifying prognostic models for non-SLN positivity is the lack of standardized protocols for thorough evaluation of CLND nodes. Wrightson et al. retrospectively reviewed 117 non-SLNs harvested from 13 patients who underwent CLND following a positive SLN biopsy.[48] Initially all 117 nodes harvested during CLND were deemed negative for metastasis on traditional hematoxylin and eosin staining. However, 18 (15%) of the nodes were reclassified as positive following examination with reverse transcription polymerase chain reaction. This change led to a staggering 7 of the 13 patients (54%) being reclassified as having positive non-SLNs.

Completion Lymphadenectomy Complications

The overall complication rates associated with CLND are extremely variable, ranging from 20% to 60%.[8] Proponents for observation over CLND cite the higher complications rates and associated morbidity as part of their rationale. Complications associated with CLND include: wound infection/dehiscence, hematoma, seroma, neuropathy, lymphocele, and lymphedema. Lymphedema can impact as many as 50% of patients and carries an association with obesity, age, and groin dissection.[8]

Moody et al. conducted a systematic review of the literature to investigate the associated postoperative morbidity associated with a CLND following SLNB compared to a TLND following regional recurrence in patients observed following a positive SLNB.[49] Eighteen articles met inclusion criteria. A surgical complication rate of 39.3% was reported in the 1627 undergoing TLND which mirrored the 37.2% reported among 1929 patients receiving CLND.

The applicability of the above cite complications within the HN patient population remains in question. The most recent MSLT-II trial reported a statistically higher rate of lymphedema in the setting of CLND (24.1%) compared to 6.3% in the observation arm ($p < 0.001$).[39] However, lymphedema is a known complication of groin and extremity CLND, but does not carry the same challenges for the neck.

CONCLUSIONS AND FUTURE ENDEAVORS

The data surrounding the need for CLND following a positive SLNB remains controversial. HN cutaneous

melanoma patients are a unique subset, carrying a worse prognosis compared to their trunk and extremity counterparts. In addition, they do not traditionally suffer from the lymphedema often seen at other sites. The importance of achieving regional control in the head and neck given proximity to critical structures (carotid artery, trachea, esophagus) bears thoughtful consideration. Regional failure in the head and neck can have significant implications on both quality and quantity of life.

In order to truly determine the therapeutic utility of SLNB, large, prospective, randomized trials specific to the HN cutaneous melanoma population are required. Prior to conducting such trials, a standardized, evidence-based pathology protocol to evaluate of non-SLNs in a meticulous fashion with incorporation of molecular analysis are also required. In the interim, surgeons should have a candid conversation with their HN melanoma patients about CLND. Ultimately the decision will be made based on surgeon experience and patient preference.

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