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# International Center-Level Variation in Utilization of Completion Lymph Node Dissection and Adjuvant Systemic Therapy for Sentinel Lymph Node-Positive Melanoma at Major Referral Centers

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**Objective:** The aim of this study was to determine overall trends and center-level variation in utilization of completion lymph node dissection (CLND) and adjuvant systemic therapy for sentinel lymph node (SLN)-positive melanoma.

**Summary Background Data:** Based on recent clinical trials, management options for SLN-positive melanoma now include effective adjuvant systemic therapy and nodal observation instead of CLND. It is unknown how these findings have shaped practice or how these contemporaneous developments have influenced their respective utilization.

**Methods:** We performed an international cohort study at 21 melanoma referral centers in Australia, Europe, and the United States that treated adults with SLN-positive melanoma and negative distant staging from July 2017 to June 2019. We used generalized linear and multinomial logistic regression models with random intercepts for each center to assess center-level variation in CLND and adjuvant systemic treatment, adjusting for patient and disease-specific characteristics.

**Results:** Among 1109 patients, performance of CLND decreased from 28% to 8% and adjuvant systemic therapy use increased from 29 to 60%. For both CLND and adjuvant systemic treatment, the most influential factors were nodal tumor size, stage, and location of treating center. There was notable variation among treating centers in management of stage IIIA patients and use of CLND with adjuvant systemic therapy versus nodal observation alone for similar risk patients.

**Conclusions:** There has been an overall decline in CLND and simultaneous adoption of adjuvant systemic therapy for patients with SLN-positive melanoma though wide variation in practice remains. Accounting for differences in patient mix, location of care contributed significantly to the observed variation.

**Keywords:** active surveillance, adjuvant therapy, completion lymph node dissection, de-implementation, implementation science, melanoma, sentinel lymph node

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Advances in melanoma management have introduced new treatment paradigms for patients with sentinel lymph node (SLN) metastases. Two randomized surgical trials, the German Cooperative Dermatologic Oncology Group study (DeCOG-SLT) published in 2016 and the Second Multicenter Selective Lymphadenectomy Trial (MSLT-II) published in 2017, demonstrated the survival equivalence of nodal observation to routine completion lymph node dissection (CLND), prompting surgeons to reconsider the necessity of regional surgery for SLN-positive disease.[1–3] Simultaneous publication of positive adjuvant systemic therapy trials showed that anti-CTLA4, anti-PD1, and BRAF/MEK inhibitors are more effective and less toxic than historic alternatives, providing additional treatment options for surgically-resected melanoma patients at high risk of recurrence and death.[4–7] Based on these findings, the Food and Drug Administration approved ipilimumab in 2015, nivolumab in 2017, dabrafenib/trametinib in 2018, and pembrolizumab in 2019 for adjuvant treatment of resected stage III melanoma, with subsequent approvals by the corresponding regulatory bodies in Europe, the United Kingdom, and Australia (Fig. 1).[8]

These landmark trials provide evidence to omit (de-implement) regional surgery for SLN-positive patients while simultaneously administering (implementing) new medical therapies to high-risk patients in the adjuvant setting.[9] Although there is some evidence to suggest a long average time to implementation for most practices, less is known about how quickly practices are de-implemented or reasons for variation in de-implementation practices.[10,11] Furthermore, it is unknown how implementation of systemic therapies might influence de-implementation of local or regional treatments such as CLND. Although nodal observation and adjuvant systemic therapy trials were performed in parallel, neither were studied in combination, leaving patients and physicians with 4 potential treatment strategies—nodal observation alone, nodal observation with adjuvant systemic therapy, CLND alone, or CLND with adjuvant systemic therapy—with widely ranging treatment intensity, morbidity, and cost. There are presently no comparative data to discern which option is optimal for each individual patient.

This unique scenario provides an opportunity to understand how new results are incorporated into practice for a single disease site and to study the dynamics of concurrent de-implementation of surgical treatment and implementation of adjuvant systemic therapy. As results from large oncologic databases are not yet mature, we used the database from the International High-Risk Melanoma Consortium consisting of 21 major melanoma referral centers throughout the world.[12] Our objectives were to evaluate overall trends and centerlevel variation in de-implementation of CLND and implementation of adjuvant systemic therapy for SLN-positive melanoma.

## METHODS

The International High-Risk Melanoma Consortium was established in 2017 and includes a geographically diverse network of 21 melanoma referral centers from Australia, Europe (including the United Kingdom), and the United States.[12] In this retrospective cohort study, each participating center provided data on adult patients with SLN-positive cutaneous melanoma who were treated from July 1, 2017 to June 30, 2019. Requirements for center participation included having a nodal surveillance protocol in place before study initiation, attainment of institutional ethics/review board approval, negotiation of a data use agreement with the coordinating center, Moffitt Cancer

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Center, and provision of de-identified patient data by established deadlines. There was no designated funding source for this study. Reporting is in accordance with EQUATOR guidelines (Supplemental File, http://links.lww.com/SLA/D628).

Data were collected during routine care of patients with clinically node negative melanoma who had metastatic melanoma in at least 1 SLN. Included patients were required to have margin-negative resection of the primary tumor and no evidence of distant metastases on staging studies performed either before or after positive SLN biopsy but before further treatment planning. Completion lymph node dissection was defined as anatomic dissection performed after positive sentinel lymph node biopsy in the absence of clinical nodal disease. Patients who were identified to have clinical nodal disease on staging studies performed after positive sentinel lymph node biopsy were not included given the presence of clinical nodal disease. Performance of nodal observation versus CLND and use of adjuvant systemic therapy (ie, anti-PD1 or anti-CTLA4 immunotherapy, BRAF/MEK inhibitor) were determined by treating physicians and patients. Unlike previous adjuvant systemic therapy studies, patients were not required to undergo CLND before receiving adjuvant systemic treatment.

We determined center-level rates of de-implementation of CLND and implementation of adjuvant systemic therapy for each 3-month period (quarter) over the 2 years of study to describe change over time. We also described variation in comprehensive management for SLN-positive patients treated at each center including the four possible treatment strategies—nodal observation alone, nodal observation with adjuvant systemic therapy, CLND alone, or CLND with adjuvant systemic therapy. To adjust for patient-, disease-specific, and treating center characteristics associated with treatment selection, we used 2 types of multilevel modeling. Using generalized linear mixed models with random intercepts for each center, we assessed variation in likelihood of de-implementation of CLND (Model 1) and implementation of adjuvant systemic treatment (Model 2). Adjuvant treatment and CLND, respectively, were included in the CLND and adjuvant models to assess their relative influence. Then we created a multinomial logistic regression model (Model 3) to obtain reliability-adjusted estimates of the likelihood of receiving each of the 4 combined treatment strategies (nodal observation alone, nodal observation with adjuvant systemic therapy, CLND alone, or CLND with adjuvant systemic therapy). All models were adjusted forthe following patient and disease factors: primary site (head/neck, trunk, extremity), tumor ulceration, presence of microsatellitosis, American Joint Committee on Cancer 8th edition stage, size of largest nodal metastasis ( < 1mmor > 1 mm), and extranodal tumor extension. Included treating center characteristics were geographic region (Australia or Europe vs United States), whether the center previously participated in the MLST-II trial (no DeCOG-SLT sites were included in this study), designation as a cancer center by the National Cancer Institute, the European Society of Medical Oncology, or self-designated for Australian centers, and number of SLN-positive patients treated (volume reported by tertile). Values are reported as odds ratios with 95% confidence intervals (CI). To demonstrate center-level variation not explained by disease-specific factors, the models were used to determine the adjusted probability of each treatment strategy by



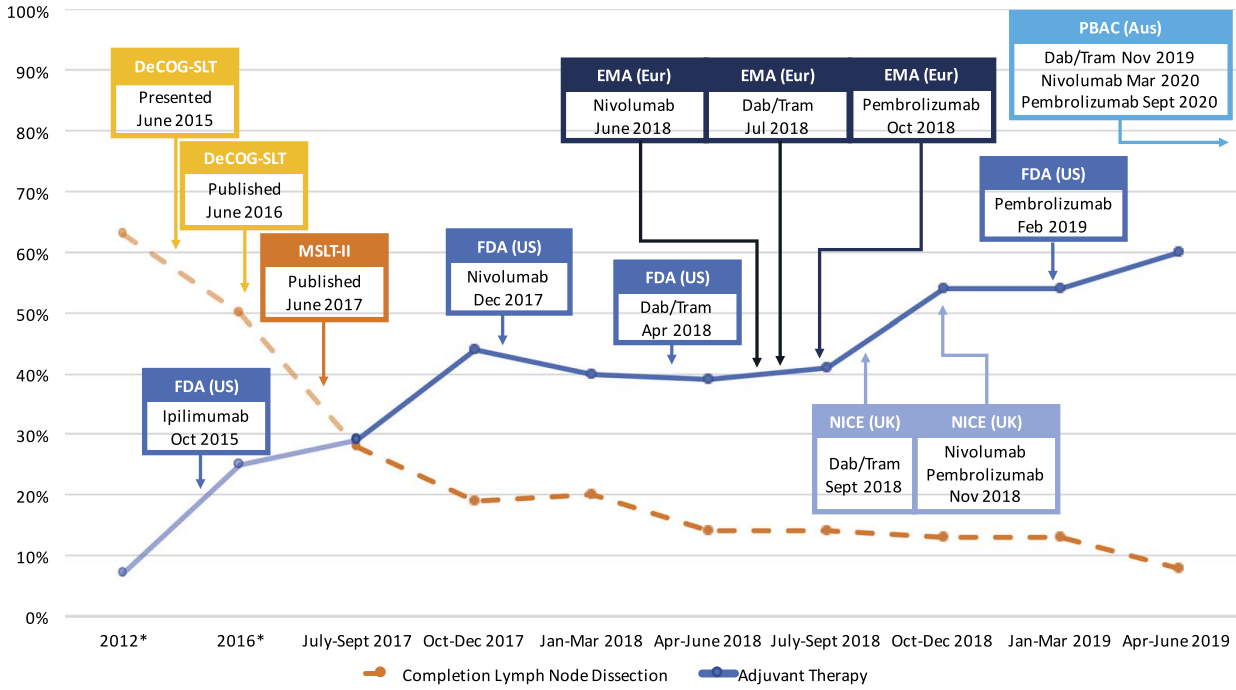


**FIGURE 1.** Proportion of patients who underwent completion lymph node dissection and received adjuvant systemic therapy before and after DeCOG-SLT and MSLT-2 publication and region-specific regulatory approvals of adjuvant immunotherapies and BRAF/MEK inhibitor therapy. *Historical rates of CLND for years 2012 and 2016 and of adjuvant systemic therapy for 2016 for resected stage III melanoma were obtained from the National Cancer Database; historical rate of adjuvant systemic therapy from 2012 derived from MSLT-II and DeCOG-SLT publications. Dab/tram, dabrafenib/trametinib; DeCOG-SLT, German Dermatologic Oncology Group Trial; EMA, European Medicines Agency (Europe); FDA, United States Food and Drug Administration; NICE, National Institute for Healthcare Excellence (United Kingdom); PBAC, Pharmaceutical Benefits Advisory Committee (Australia).

treating center. We then evaluated the relative importance of each covariate in treatment selection by computing the Nagelkerke pseudo $r^2$ for each covariate alone and for all covariates except the covariate of focus. This enabled us to evaluate the independent contribution of the covariate and its incremental effect.[13] Finally using the multinomial model (Model 3) we compared the adjusted probability of specific treatment combinations by treating center including CLND with adjuvant systemic therapy versus adjuvant therapy alone and CLND with adjuvant systemic therapy versus nodal observation alone.

We also performed clinically relevant sensitivity analyses based on eligibility criteria for adjuvant therapy trials and pertinent treatment guidelines. As some guidelines do not recommend adjuvant systemic therapy for stage IIIA patients, we separately evaluated center-level variation in use of adjuvant systemic therapy for this group.[14] Likewise, we examined differences in provision of adjuvant systemic therapy for patients with nodal tumor deposits < 1mm because eligibility criteria for clinical trials of adjuvant systemic therapy required a minimum nodal tumor deposit of 1 mm.[4–7] Lastly, models were repeated using size of largest nodal metastasis as a continuous rather than categorical variable to better understand how this clinical factor is being used in treatment decision making. We compared Akaike and Bayesian Information Criteria (AIC/BIC) for the models with size of largest nodal tumor included as a categorical versus continuous variable to determine which model had a better fit.

## RESULTS

### Temporal Trends in De-Implementation of CLND and Implementation of Adjuvant Systemic Therapy

Participating centers collectively treated 1109 SLN-positive patients (Table 1). In the earliest quarter of study, which was concurrent with MSLT-II publication, 28% of patients underwent CLND. This was lower than previously published rates and decreased to 8% by the last quarter of the 2-year study period. At the same time adjuvant systemic therapy use increased from 29% to 60% over the 2-year period (Fig. 1). Combining nodal management and adjuvant systemic treatment strategies, patients were managed with nodal observation alone (n = 519, 47%), nodal observation with adjuvant systemic therapy (n = 411, 37%), CLND alone (n = 102, 9%), or CLND with adjuvant systemic therapy (n = 77, 7%) (Fig. 2, Supplemental File 1, http://links.lww.com/SLA/D628).

US centers treated more patients with adjuvant therapy than European centers during the period of study, whether doing nodal observation ($P = 0.01$) or CLND ($P = 0.04$), whereas adjuvant systemic therapy use at Australian centers was not significantly different from US or European centers (Table 2). At the center level there were no significant associations between performance of CLND or use of adjuvant systemic therapy and melanoma patient volume, region, cancer center designation, or previous participation in MSLT-II (Table 2).

### Adjusted Estimates of CLND and Adjuvant Systemic Therapy

In the multilevel models, higher odds of CLND were associated with head and neck primary site (relative to extremity) and nodal tumor deposit of ≥ 1 mm (Table 3). Accounting for disease-specific and treating center factors, the adjusted probability of CLND based on treating center ranged from 1% to 83% (median 10%) (Model 1) (Table 2, Fig. 3). Odds of adjuvant systemic therapy increased for nodal tumor deposit of ≥ 1 mm and decreased for patients with stage IIIA disease relative to IIIC or IIID (Table 3). Adjusted probabilities of adjuvant systemic

**TABLE 1.** Characteristics of Treating Centers and SLN-Positive Melanoma Patients

| Treating Centers | | Patients | |
|---|---|---|---|
| No. of centers | 21 | No. of patients | 1109 |
| Region | | Male sex, N (%) | 672 (61%) |
| Australia | 3 (14%) | Age, y, median (25th-75th %ile) | 61 (49–71) |
| Europe | 5 (24%) | Tumor location, N (%) | |
| United States | 13 (62%) | Head and Neck | 144 (13%) |
| Volume tertile (#SLN+ pts/y) | Trunk | 428 (39%) | |
| Low (6–15) | 8 (38%) | Extremity | 537 (48%) |
| Middle (16–27) | 6 (29%) | Breslow depth, mm, median (25th-75th %ile) | 2.5 (1.5–4.2) |
| High (28–90) | 7 (33%) | Tumor ulceration, N (%) | 453 (41%) |
| Cancer center* | | Microsatellites, N (%) | 95 (9%) |
| No | 5 (24%) | No. of positive SLN, N (%) | |
| Yes | 16 (76%) | 1 | 842 (76%) |
| MSLT-2 trial participant | 2–3 | 247 (22%) | |
| No | 14 (67%) | 4 or more | 20 (2%) |
| Yes | 7 (33%) | Size of largest nodal tumor deposit, N (%) | |
| | | <1 mm | 508 (46%) |
| | | ≥1 mm | 475 (43%) |
| | | Unknown | 126 (11%) |
| | | Extranodal extension N (%) | 71 (6%) |
| | | AJCC 8th edition stage, N (%) | |
| | | IIIA | 333 (30%) |
| | | IIIB | 242 (22%) |
| | | IIIC | 490 (44%) |
| | | IIID | 21 (2%) |
| | | III, not specified | 23 (2%) |

AJCC indicates American Joint Committee on Cancer; pts, patients.

*National Cancer Institute-designated, European Society of Medical Oncology-designated, or self-designated cancer centers for those outside NCI or ESMO jurisdiction.

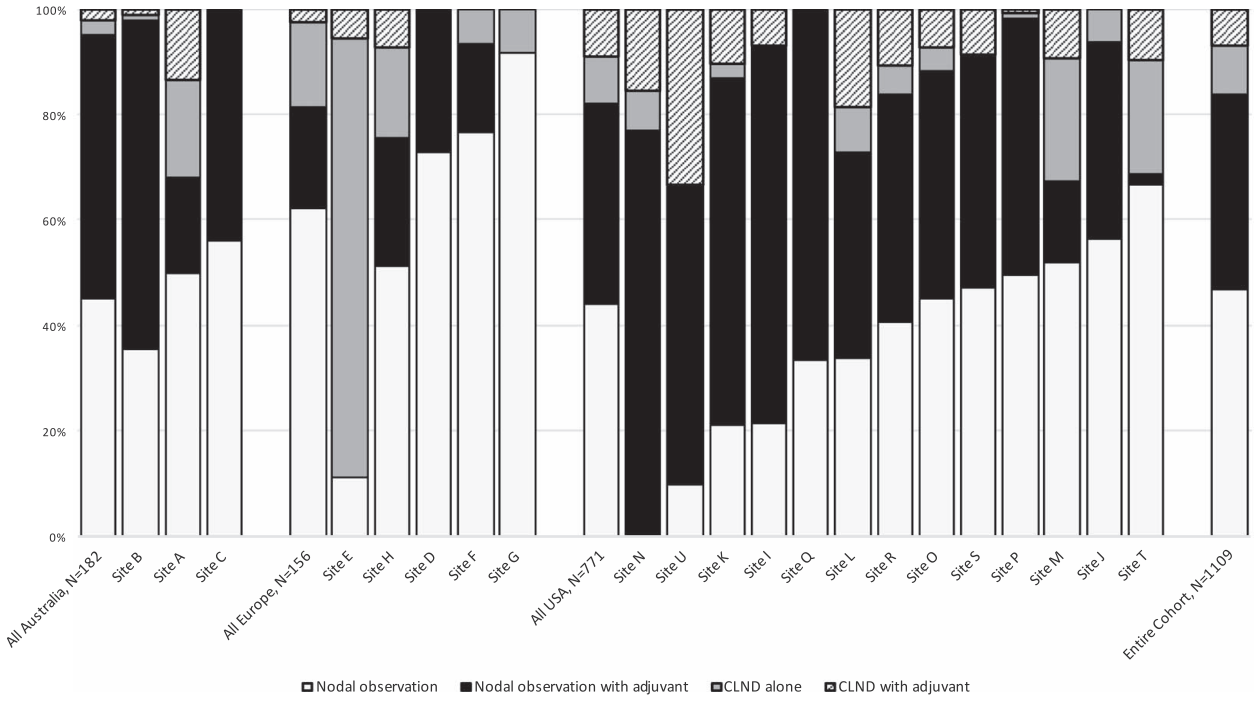


**FIGURE 2.** Nodal management with observation versus CLND and adjuvant systemic therapy use for patients with melanoma treated at 21 participating institutions in Australia, Europe, and the United States.



therapy ranged from 9% to 87% by treating center (median 46%) (Model 2) (Table 2, Fig. 3). For both CLND and adjuvant systemic therapy, the most influential factors in explaining observed variation were treating center, nodal tumor size, and stage (Supplemental File 1, http://links.lww.com/SLA/D628). Use of adjuvant systemic treatment did not impact the likelihood of CLND. Likewise, performance of CLND was not associated with likelihood of adjuvant systemic treatment.

**TABLE 2.** Reliability-Adjusted Likelihood of Completion Lymph Node Dissection (Model 1) and Adjuvant Systemic Therapy (Model 2) Based on Patient, Disease, Treating Center, and Treatment factors*

| | Model 1: Completion Lymph Node Dissection | | Model 2: Adjuvant Systemic Therapy | |
|---|---|---|---|---|
| | **Odds Ratio (95% Confidence Interval)** | ***P*** | **Odds Ratio (95% Confidence Interval)** | ***P*** |
| Primary site | | 0.017 | | 0.953 |
| Head and neck | **2.22 (1.27–3.86)** | | 1.04 (0.66–1.62) | |
| Trunk | 1.10 (0.73–1.67) | | 1.05 (0.76–1.45) | |
| Extremity | Reference | | Reference | |
| Tumor ulceration | 0.87 (0.53–1.42) | 0.571 | 1.19 (0.81–1.74) | 0.371 |
| Microsatellites | 0.84 (0.45–1.55) | 0.575 | 0.89 (0.52–1.51) | 0.659 |
| AJCC 8th edition stage | | 0.173 | | **< 0.001** |
| IIIA | 0.71 (0.39–1.29) | | **0.37 (0.23–0.59)** | |
| IIIB | 0.57 (0.32–1.03) | | 0.72 (0.48–1.09) | |
| IIIC/D | Reference | | Reference | |
| Nodal tumor ≥ 1mm | **3.59 (2.30–5.58)** | **< 0.001** | **1.66 (1.20–2.30)** | **0.002** |
| Extranodal tumor extension | 1.69 (0.89–3.23) | 0.111 | 1.48 (0.81–2.68) | 0.200 |
| US center† | 1.85 (0.30–11.49) | 0.509 | **6.61 (2.08–21.00)** | **0.001** |
| MSLT II center | 0.43 (0.08–2.37) | 0.335 | **3.40 (1.21–9.55)** | **0.020** |
| Cancer center | 0.46 (0.07–5.69) | 0.692 | 0.95 (0.23–3.97) | 0.943 |
| Center volume | | 0.613 | | 0.283 |
| Low | 2.77 (0.32–23.64) | | 1.74 (0.45–6.75) | |
| Middle | 2.22 (0.32–15.37) | | 0.66 (0.20–2.19) | |
| High | Reference | | Reference | |
| Adjuvant systemic therapy‡ | 1.14 (0.73, 1.77) | 0.563 | N/A | |
| CLND§ | N/A | | 1.12 (0.73, 1.73) | 0.593 |

*Models contained random intercept for treating center to account for clustering of patients within centers.
†Reference Europe or Australia; CLND, completion lymph node dissection.
‡CLND model adjusted for adjuvant treatment.
§Adjuvant model adjusted for CLND.

**TABLE 3.** Reliability-Adjusted Likelihood of Each Overall Management Strategy for Sentinel Node Positive Melanoma (Ref = Nodal observation alone)* (Model 3)

| Covariate | Adjuvant Only | CLND Only | CLND With Adjuvant | P† |
|---|---|---|---|---|
| Primary site (ref = head/neck) | | | | **0.042** |
| Trunk | 0.85 (0.51–1.43) | **0.31 (0.15–0.64)** | **0.79 (0.35–1.81)** | |
| Extremity | 0.88 (0.53–1.44) | **0.35 (0.18–0.69)** | **0.56 (0.24–1.28)** | |
| Ulcerated‡ | 1.45 (0.96–2.19) | 1.47 (0.76–2.84) | 0.64 (0.33–1.25) | **0.047** |
| Stage§ (Ref = IIIA) | | | | **0.001** |
| IIIB | **1.92 (1.21–3.05)** | 0.86 (0.41 –1.81) | 1.13 (0.42–3.02) | |
| IIIC or IIID | **2.41 (1.45–3.99)** | 1.09 (0.51 –2.36) | 4.27 (1.78–10.21) | |
| Size of largest nodal tumor ≥ 1mm | **1.64 (1.16–2.32)** | **3.33 (1.94–5.72)** | **6.45 (3.25–12.80)** | **< 0.001** |
| Microsatellitosis | 0.88 (0.49–1.59) | 0.75 (0.32–1.79) | 0.78 (0.34, 1.78) | 0.888 |
| Extranodal extension | **0.89 (0.45–1.76)** | 0.42 (0.12–1.46) | **2.74 (1.23–6.14)** | **0.007** |
| US center‖ | **4.20 (1.35–13.06)** | 0.82 (0.11–5.99) | **24.11 (5.93–98.07)** | **< 0.001** |
| MSLT II center¶ | 3.28 (1.25–8.59) | 0.53 (0.08–3.53) | 1.11 (0.40–3.07) | 0.091 |
| Cancer center | 1.62 (0.40–6.65) | 2.14 (0.20–23.43) | 0.17 (0.03–0.87) | 0.107 |
| Center volume (ref = low)# | | | | 0.416 |
| Middle | 0.30 (0.10–0.95) | 0.62 (0.07–5.31) | 0.48 (0.13–1.73) | |
| High | 0.39 (0.10–1.47) | 0.24 (0.02–2.55) | 0.45 (0.11–1.85) | |

*Multinomial logistic regression model reported as odds ratios (95% confidence intervals), reference category =nodal observation alone (no CLND or adjuvant systemic therapy), treating center was included in model as random clustering effect, although called a random intercept.
†Pvalue from test for adding this variable, given that all others are in the model.
‡Ulcerated (CLND with Adjuvant) is significantly different from Adjuvant only and CLND only.
§AJCC 8th Edition.
‖Treating center located in the United States (US) versus Europe or Australia.
¶Treating center participated in MSLT II trial.
#Volume categorized in tertiles.



## Factors Associated With Overall Management

In the multinomial model (Model 3) adjusted for patient, disease, and treating center characteristics (Table 3), factors associated with overall management (nodal observation alone, nodal observation with adjuvant systemic therapy, CLND alone, or CLND with adjuvant systemic therapy) included primary tumor location, tumor ulceration, stage, size of largest nodal tumor, extranodal extension, and whether the treating center was located in the United States versus Europe or Australia. Patients with trunk and extremity tumors were less likely to undergo CLND with or without adjuvant systemic therapy relative to patients with head or neck primaries. Increasing stage was associated with increasing likelihood of adjuvant systemic therapy, with or without CLND. Relative to nodal observation alone, nodal tumor size of 1 mm or greater was associated with incrementally greater odds of adjuvant systemic therapy alone, CLND, and CLND with adjuvant systemic therapy, respectively. Patients with extranodal extension were more likely to receive CLND with adjuvant systemic therapy. Patients treated in the United States, relative to Europe or Australia, were more likely to receive adjuvant systemic therapy, with or without CLND. Based on the model, we compared adjusted odds of the most aggressive treatment strategy, CLND with adjuvant systemic therapy. Patients treated in the United States, relative to Europe or Australia, were more likely to receive adjuvant systemic therapy, with or without CLND. Based on the model, we compared adjusted odds of the most aggressive treatment strategy, CLND with adjuvant systemic therapy, to nodal

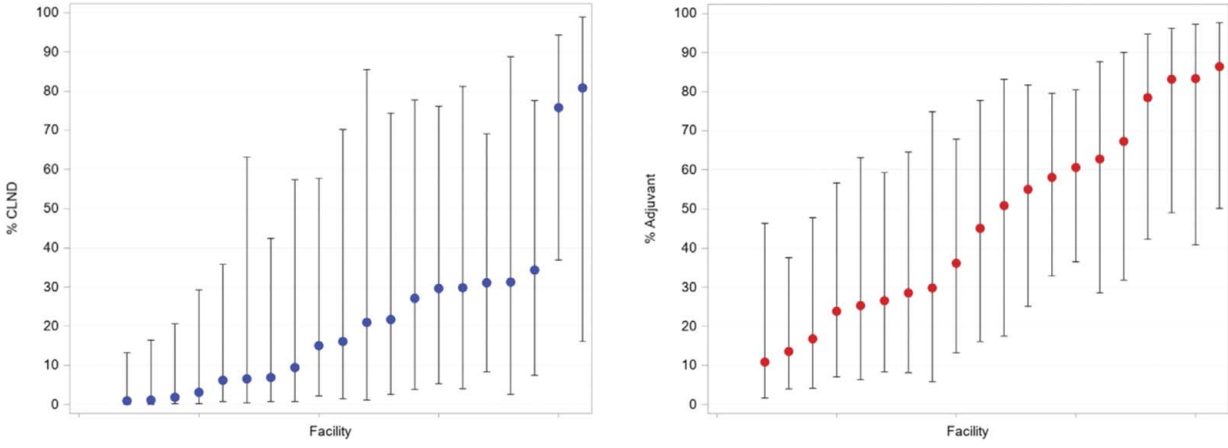


**FIGURE 3.** Probability of CLND and adjuvant systemic treatment by treating center*. *Adjusted for primary tumor site, ulceration, AJCC 8th edition stage, size of largest nodal tumor deposit, microsatellitosis, extranodal tumor extension, treating center region, MSLT II participant, cancer center designation, and center volume;models contained random intercept to account for clustering of patients within facility.

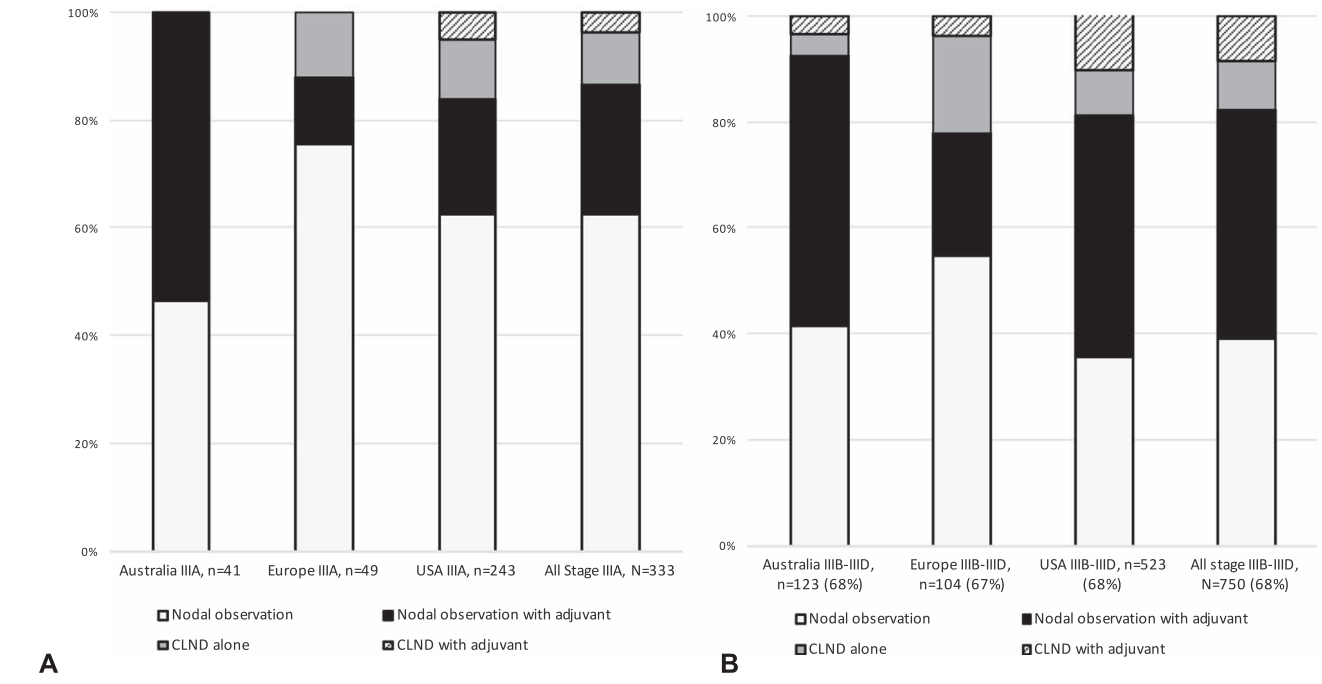


**FIGURE 4.** Nodal management and adjuvant systemic therapy for AJCC 8th Edition Stage IIIA (A) versus Stage IIIB-D (B) melanoma patients based on region of treating center. AJCC indicates American Joint Committee on Cancer.

observation alone. At most treating centers, patients had lower adjusted odds of the most aggressive treatment than the least, although at a minority of centers the odds were equal (Supplemental File 1, http://links.lww.com/SLA/D628). Comparing adjusted odds of the most aggressive treatment (CLND with adjuvant systemic therapy) to adjuvant systemic therapy alone, at all but one facility there were lower odds of the most aggressive treatment relative to adjuvant systemic therapy alone (Supplemental File 1, http://link-s.lww.com/SLA/D628).

### Sensitivity Analyses

By stage, the proportion of patients receiving adjuvant systemic therapy was IIIA 28%, IIIB 44%, IIIC/D 55%. There were differences in adjuvant treatment for Stage IIIA versus Stage IIIB-D disease at the regional and center levels (Fig. 4). By center, the proportion of stage IIIA patients who received adjuvant systemic therapy ranged from 0% to 88% with 5 centers not treating any stage IIIA patient with adjuvant systemic therapy and ten centers using adjuvant therapy in more than one-quarter of patients with stage IIIA disease. The inclusion of size of largest nodal tumor as a continuous variable did not significantly impact model performance and resulted in poorer fit (lower AIC and BIC), likely due to the skewed nature of the variable, suggesting that a threshold of 1 mm is relevant in clinical practice. Center-level variation was similarly observed when patients were stratified by size of largest nodal tumor deposit. Median rates of adjuvant systemic therapy use for patients with nodal tumor deposits < 1 mm ranged by center from 0 to 100% with 10 of 21 centers using adjuvant systemic therapy for more than one-quarter of their patients with nodal tumor deposits < 1 mm.

## DISCUSSION

This study has three main findings. First, at major melanoma centers world-wide there has been rapid but varied incorporation of surgical trial findings into routine care for SLN-positive patients. Second, there has been a simultaneous increase in use of adjuvant therapy in SLN-positive patients. Third, although performance of CLND and administration of adjuvant systemic treatment were associated with disease-specific factors including primary tumor features and burden of SLN-positive disease, there was also significant variation in CLND and adjuvant systemic treatment patterns based on the center where patients received care.

The pace of CLND de-implementation was swift in the two years after MSLT II publication, demonstrating a much shorter time to practice change than the average 17 years often cited in implementation research.[15–17] Rates of CLND at this study initiation and in prior studies demonstrate that CLND was already being performed selectively, perhaps due to a preexisting acknowledgement of the limitations of CLND, its associated risk of potentially life-altering lymphedema, or surgeons' lack of comfort with performing the procedure.[18,19] Before MSLT-II publication, several large retrospective cohort studies already suggested limited benefit of CLND, with most patients having no additional positive (non-sentinel) nodes in CLND specimens.[20–22] Furthermore, available risk prediction tools for nonsentinel node positivity could support a decision not to perform CLND.[20,23-26] Finally, MLST-II trial results were well-disseminated, with a recent survey of the Society of Surgical Oncology membership finding that 98% of respondents were aware of its findings.[27] Research findings that are particularly impactful to a highly specialized provider group may disseminate more quickly due to existing relationships among specialists outside their immediate practice environments.

Similar to trends in de-implementation of CLND, the implementation of adjuvant systemic therapy for SLN-positive melanoma began before the start of this study but rapidly escalated in a comparable timeframe. In our 21 melanoma referral centers, adjuvant systemic treatment increased from 29% in July 2017 to 60% in June 2019. Centers with high adoption used adjuvant systemic therapy in up to 92% of SLN-positive patients, including large proportions of patients with stage IIIA disease and nodal tumor deposits < 1 mm. Other reports from single institution cohorts of SLN-positive patients not undergoing CLND have reported use of adjuvant systemic therapy in 69% to 75%.[16,28] There are several potential reasons for the accelerated implementation of adjuvant systemic therapy in SLN-positive melanoma. Historically, regionally metastatic melanoma carried a poor prognosis, with only 28% to 44% of patients having recurrence-free survival at 5 years. Effective, well-tolerated adjuvant treatments represented a significant therapeutic advance.[29] These agents had previously been tested in the setting of stage IV and unresectable stage III disease, demonstrating often dramatic response rates and significant improvements in progression-free survival.[30-32] Finally, concurrent trials of immunotherapy in other solid tumors increased widespread knowledge within and outside the medical community, with drug companies broadly disseminating information about the medications, including direct to consumer advertising in the United States.[33]

Finally, it is notable that the curves for de-implementation of CLND and implementation of adjuvant systemic therapy had an inverse relationship. Although there is no available evidence to suggest that adjuvant systemic treatment is an effective replacement for CLND or that it confers additional regional control, patients and physicians may have been more comfortable forgoing additional surgery when alternative treatments were available to mitigate recurrence.[9] We did not observe a direct association between adjuvant treatment and performance of CLND. This warrants additional study. Randomized trials of nodal observation and adjuvant systemic therapy have been informative, but uncertainty remains for specific patient populations and clinical situations. Adjuvant trials, for instance, mandated CLND before systemic treatment, whereas < 10% of nodal observation trial participants received adjuvant therapy. As a result, high-level evidence is lacking on outcomes of nodal observation in adjuvant systemic therapy recipients.[1,2,5,6,34,35] Also, certain populations of SLN-positive patients were underrepresented in these trials. Although adjuvant systemic therapy trials required a minimal nodal tumor deposit dimension of 1 mm, patients with low nodal tumor burden constituted the majority of participants in the randomized surgical trials of nodal observation.[1,2,5,6,34,35] Despite these significant differences in the study populations, our data demonstrate that many treatment teams have readily integrated the two contemporary strategies, offering patients nodal observation with adjuvant systemic treatment despite a lack of randomized evidence and only limited survival data from observational cohorts, even in patients whose tumor and nodal burdens were not represented in the randomized trials.[16,28,36,37]

Despite overall adoption of these evidence-based practices, there remained variation both in de-implementation of CLND and implementation of adjuvant systemic treatment based on where patients were treated. Observed regional variation, particularly when comparing US centers to those in Europe and Australia, may be explained by policy including regulatory approvals and health care payment models. Although Food and Drug Administration approval occurred during the study period for several of the contemporary adjuvant systemic therapies, regulatory approvals were later in Europe and Australia. Although the payer mix in US centers is heterogenous, all participating centers in Europe and Australia have some form of universal, government-run health care, which initially might delay or limit access to new, expensive adjuvant systemic treatments. Still, even within the studied US centers there was profound variation in both nodal observation and adjuvant systemic treatment rates for SLN-positive patients that could not be explained by differences in the burden of disease in their patient populations. Unmeasured patient factors such as travel time to the treating center may have influenced patients' preferences for both nodal observation and receiving a year of adjuvant systemic treatment. For example, a center with a persistent high rate of CLND reported that long travel distance to the treating center was influential. However, it is likely that physicians' knowledge, interpretation, and application of available evidence also contributed. A recent survey demonstrated that most SLN-positive melanoma patients prefer to follow their physicians' recommendations regarding CLND, highlighting the importance of the local context in which patients receive care and the constitution of patients' treatment teams.[9,38]

In certain cases and centers, interpretations of available evidence may have resulted in overuse of adjuvant systemic therapy or non-evidence-based de-implementation of CLND in patients who were not represented in the nodal management trials.[12] For example, a sizeable proportion of stage IIIA patients with nodal tumor deposits of < 1 mm received adjuvant systemic therapy despite the absence of efficacy data for patients with low nodal tumor burdens.[14] For such patients, the risk of adjuvant systemic treatment-related adverse events may exceed potential benefits. Even in the same treating center, there was wide variation in management of patients with similar risk. Although in most centers, the risk adjusted odds of nodal observation alone or adjuvant systemic therapy alone were greater than the most aggressive treatment strategy (CLND with adjuvant systemic therapy), in some centers the risk-adjusted odds of receiving nodal observation alone were the same as that of receiving CLND with adjuvant systemic therapy.

The observed variation in treatment intensity for SLN-positive melanoma, from nodal observation alone to CLND with adjuvant treatment, is associated significant differences in patient morbidity, travel burden, anxiety, and cost. Although we are limited in our ability to measure these less overt influences on physician recommendations, future work in this area is critical. Qualitative studies with individual providers and treatment teams at different centers in different countries may elucidate a more nuanced understanding of how they incorporate available evidence into clinical care and how specific contextual or organizational factors may influence their treatment recommendations. Furthermore, additional patient-oriented outcomes are needed to better advise patients when making decisions about CLND and adjuvant systemic therapy. Specifically, patients should understand how surgery, adjuvant treatment, and nodal observation may impact outcomes that were not measured in this study including frequency of travel for surveillance visits, ability to work, and out-of-pocket costs.

Until national datasets mature, the experience of this multi-institutional international collaborative represents the best available data on de-implementation of CLND and implementation of adjuvant systemic therapy for SLN-positive melanoma. One limitation of the study is reliance on data from melanoma referral centers which may not reflect management in other patient populations. As location of care and specifically treatment at a cancer center has been found to significantly

impact implementation of evidence-based care, trends in implementation of nodal observation and adjuvant systemic treatment at non-referral centers may differ.[39–44] In addition, although our international collaborative represents countries with some of the highest worldwide incidences of melanoma, it was limited to higher income countries with populations of predominantly European ancestry, limiting generalizability to other populations.[45] With this retrospective study using clinical data, we were not positioned to study the specific reasons for CLND or adjuvant systemic therapy use at each center, nor could we evaluate potentially time-variant changes in barriers to or facilitators of implementation such as availability of adjuvant systemic treatments or high-quality ultrasound to perform nodal basin surveillance.



## CONCLUSIONS

In an evolving treatment landscape for SLN-positive melanoma, fewer patients are undergoing CLND and more are receiving adjuvant systemic therapy. These changes in practice began before the publication of landmark trials of nodal observation and adjuvant immunotherapy and targeted therapy but accelerated dramatically at the included melanoma referral centers over a 2-year time period post-publication. Location of care contributed significantly to the observed variation in de-implementation of CLND and implementation of adjuvant systemic treatment and was not explained by differences in patient mix. As there are significant differences in potential morbidity and cost of available treatment strategies, future work should explore how the context of care delivery, interprofessional interactions, and patient-oriented outcomes impact the incorporation of these evidence-based findings into clinical care.

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