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CONTINUING EDUCATION– MELANOMA

The Role of Completion Lymph Node Dissection for Sentinel Lymph Node-Positive Melanoma

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ABSTRACT

Purpose and Methods. Completion lymph node dissection (CLND) for sentinel lymph node (SLN)-positive melanoma patients has been guideline-concordant standard of care since adoption of lymphatic mapping and SLN biopsy for the management of clinically node-negative melanoma patients more than 20 years ago. However, a trend for omission of CLND has been observed over the past decade, and we now have randomized, controlled clinical trial data to help guide treatment recommendations. Publication of these data prompted an American Society of Clinical Oncology—Society of Surgical Oncology 2018 clinical practice guideline update for these patients.

Results and Conclusions. Systematic review of current evidence supports a selective, individualized approach to CLND for SLN-positive melanoma. For low-risk, low-volume micrometastatic disease, SLN biopsy may be both diagnostic and therapeutic, and close clinical follow-up with imaging or CLND are reasonable options for appropriately selected patients. For higher-risk patients, omission of CLND requires careful consideration of risks versus benefits, relevant histopathology, and individualized patient discussion. This should address patient comorbidities and life expectancy, the predicted likelihood of additional positive nodes, availability of imaging surveillance, likelihood of adherence to imaging and clinical follow-up, consequences of regional recurrence, and the prognostic value of complete nodal staging and its impact on adjuvant therapy recommendations or clinical trial participation. Data on long-term outcomes, cost, and patient-reported quality of life measures are not yet available.

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Completion lymph node dissection (CLND) for sentinel lymph node (SLN)-positive melanoma has been standard of care since the adoption of lymphatic mapping and sentinel lymph node biopsy (SLNB) for the management of clinically node-negative melanoma patients in the early 1990s.[1] CLND also has been considered a quality measure, endorsed by international guidelines and a consideration for clinical trial enrollment.[2–4] Heralded benefits of CLND included more accurate disease staging, improved regional disease control, a possible survival benefit, and selection of appropriate patients for adjuvant therapies and clinical trial enrollment. Despite post hoc clinical trial and retrospective data showing a benefit to CLND for SLN-positive patients, there has been a growing trend for omission of CLND for melanoma patients with a positive SLN.[3,5–7] The CLND rate for SLN-positive melanoma in Surveillance, Epidemiology, and End Results anlayses shows a decline from 76% in 1998 to 66% by 2001.[8] Similar investigations using the National Cancer Data Base (NCDB) found that just over half of SLN-positive melanoma patients underwent a CLND from 2004 to 2012.[9,10] The impetus to avoid CLND is based on potential morbidity and the observation that no more than 18–30% of patients have a positive nonsentinel lymph node (NSLN).[7,11,12]

Results of two recently published, randomized, controlled clinical trials now provide data to help guide treatment recommendations for SLN-positive melanoma patients.[13,14] Publication of these data led to an American Society of Clinical Oncology—Society of Surgical Oncology 2018 clinical practice guideline update recognizing surveillance as an option for selected patients.[15] Concurrently, the rapidly changing landscape of adjuvant treatment options present a logical rationale for

reevaluating the precise role of surgery in the management of these patients. This review of the potential benefits and harms of CLND for SLN-positive melanoma may better define the role of CLND in this setting and help guide individualized patient care, with due consideration of evolving data.

METHODS

A librarian-assisted PubMed search was performed on December 9, 2015 to inform content for the American College of Surgeons Operative Standards for Cancer Surgery Volume II.[16] Key word combinations were included in medical subject heading (MeSH) terms (mh), title/abstract words (tiab), and subject headings (sh):

(*melanoma* [mh] or *melanoma* [tiab] and *sentinel lymph node biopsy* [mh] or *sentinel lymph node biopsy* [tiab] or *sentinel lymph node biopsies* [tiab] or *sentinel lymph node* [tiab] or *sentinel lymph nodes* [tiab] or *sentinel biopsy* [tiab] or *sentinel biopsies* [tiab] or *sentinel node biopsy* [tiab] or *sentinel node biopsies* [tiab] or *sentinel lymphadenectomy* [tiab] or *sentinel lymphadenectomies* [tiab] or *slnb* [tiab]) and (*surgical procedures, operative* [mh] or *surgery* [sh] or *surgery* [tiab] or *surgeries* [tiab] or *surgical* [tiab] or *surgically* [tiab] or *surgeon* [tiab] or *surgeons* [tiab] or *operation* [tiab] or *operations* [tiab]).

The initial search yielded 2818 publications. Based on defined methodology for the operative standards text, the search was further refined by the following filters: human species, English language, and type (clinical trial, guideline, meta-analysis or validation study).[16] Abstracts from 243 relevant publications were reviewed in detail, and 205 were excluded for failure to address the clinical question of interest around completion lymph node dissection compared to observation (no additional surgery) for SLN-positive melanoma. The full texts of the remaining 38 publications were reviewed, and an additional 29 were excluded because of small sample size, inferior design, or a lack of long-term follow-up.

Later, an additional 38 articles were identified by the authors and deemed to be of sufficient merit for inclusion, including two randomized, controlled trials and other work published after the initial search date, which is added in the context of evolving evidence to better inform the issues addressed in the Melanoma Key Question 2 in Operative Standards for Cancer Surgery and for the purposes of this review.[16] The final 47 articles were selected for complete review and assigned strength of recommendation based on the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system.

FINDINGS AND DISCUSSION

For surgical oncologists to provide the best possible care to melanoma patients, integration of evidence with supporting best practices based on stage of disease in the context of individual patient factors and preferences should be used to inform discussion and shared decision-making. Regarding CLND for SLN-positive melanoma, key points to be addressed include survival, regional disease control, the diagnostic value of complete pathologic nodal staging on selection of adjuvant therapies and/or clinical trial enrollment, morbidity, quality of life, cost, and other pragmatic concerns, such as current evidence deficits.

Melanoma-Specific Survival

To provide context for the DeCOG-SLT and MSLT-II studies, review of the MSLT-I trial is helpful. MSLT-I accrued 2001 patients from 1994 to 2002 and randomized (3:2) patients with melanomas $\geq$ 1.2 mm to wide excision and SLNB followed by CLND for a positive SLN ("SLN arm") or wide excision alone with observation and delayed therapeutic node dissection for clinically evident nodal disease ("observation arm"). There was no statistically significant difference in 10-year, melanoma-specific survival (MSS) between the groups (81.4% vs. 78.3%, $P = 0.18$).[3] However, 10-year MSS was significantly better for SLN-positive patients who underwent immediate CLND than patients observed and were treated with node dissection for clinically evident nodal relapse (62.1% vs. 41.5%, $P = 0.006$). The conclusion of the investigators was that early treatment of clinically occult nodal metastatic disease in patients with intermediate thickness melanomas via SLNB with CLND improved survival versus observation (without SLNB) with subsequent LND for clinically evident disease. These findings are similar to the much earlier World Health Organization trial comparing elective LND to observation for clinically node-negative truncal melanoma patients. For node-positive patients, there was a 20% absolute 5-year survival benefit for elective LND: 47% versus 27%.[17]

DeCOG-SLT, a randomized, phase III trial of CLND versus close observation for SLN-positive melanoma included 473 assessable patients from 41 German skin cancer centers undergoing SLNB from 2006 to 2014.[13] After preoperative nodal basin ultrasound, FNA of suspicious nodes and exclusion of patients with FNA-positive metastases (who proceeded directly to LND), remaining patients with SLN metastases < 2 mm were randomized (1:1) to the two treatment arms (240 to CLND and 233 to observation). At 35 months median follow-up, there was no statistically significant difference between CLND and observation for the primary endpoint of 3-year distant

metastasis-free survival (DMFS) (74.9% vs. 77%, $P = 0.87$), nor for the secondary endpoints of recurrence-free survival (RFS) (66.8% vs. 67.4%, $P = 0.75$) or overall survival (OS) (81.2% vs. 81.7%, $P = 0.87$). The authors concluded that CLND should not be recommended for patients with SLN metastases measuring ≤ 1 mm.

Notable limitations to DeCOG-SLT include early trial closure secondary to low accrual, exclusion of head and neck primaries, and a statistical power of only 50%, based on higher than anticipated actual DMFS.

MSLT-II was a phase III multicenter, randomized trial of SLNB and CLND versus SLNB plus surveillance nodal basin ultrasound (OBS) in melanoma patients with either molecular (RT-PCR) or histopathological evidence of SLN metastases.[14] The primary endpoint was MSS. Secondary endpoints included same-basin nodal recurrence, disease-free survival (DFS), DMFS, and OS. From 2004 to 2014, 1939 patients were randomized 1:1 to CLND or OBS and 1755 patients were treated per protocol (824 CLND and 931 OBS). After 43 months median follow-up, there was no statistically significant difference in 3-year MSS between arms (86% vs. 86%, $P = 0.42$).

There are potential confounders in the MSLT-II trial. The majority of patients in both arms had only one positive SLN and low-volume disease (< 1 mm). The rate of positive non-SLNs (NSLN) in the CLND group was low (11.5%), potentially diluting any therapeutic effect and suggesting a component of enrollment bias. Exclusions included immunosuppressed patients and those with > 2 mapped nodal basins, SLN metastases with extracapsular extension, concomitant in-transit disease or primary tumor microsatellites. Finally, median follow-up was short and practical application of ultrasonography has been questioned. A summary comparison of key features of the two trials is presented in Table 1.

Regional Disease Control

A benefit of CLND for SLN-positive disease is improved nodal basin control through early detection and eradication of additional regional nodal disease. Nodal basin recurrence rates in two large prospective studies have been reported in < 5% of patients.[18,19] In different patient populations, DeCOG-SLT, the 3-year nodal relapse rate was 15% in the observation arm and 8% in the SLNB/CLND arm while in MSLT-II it was 22.9% and 6.5%, respectively.[13,14]

The dissected nodal basin failure rate in the two studies suggests an opportunity for better surgical standardization and quality improvement for CLND. The MSLT-II protocol described technical standards for CLND by anatomic region as well as a recommended minimum number of LNs evaluated per basin, including 15 for axillary dissection, 8 for superficial inguinal dissection, and 40 for modified radical neck dissection.[14] Data on total nodes removed with CLND in MSLT-II is not yet published. In DeCOG-SLT, only 36% of patients had > 10 LNs removed with CLND.[13]

In an effort to improve patient care, standardization of and quality indicators for melanoma surgery have been proposed. Proper performance of SLN surgery with lymphatic mapping and attention to each mapped basin is beyond the scope of this paper, but a key first step to ensure that the at-risk nodal basin is correctly identified. Regarding regional lymphadenectomy, proposed quality measures center on minimum acceptable LN counts per anatomic nodal basin similar to those outlined above and as summarized by Pasquali and colleagues.[20] One NCDB report found that for melanoma, only 32% of axillary dissections removed ≥ 10 nodes and only 48% of inguinal dissections removed ≥ 5 nodes.[21] Interestingly, at least one study shows NSLN positivity rates statistically significantly increase as the number of LNs removed at CLND increases, whereas another shows significantly higher nodal basin failure rates when LNDs remove fewer than 8 inguinal, 15 axillary or 20 cervical nodes, highlighting the importance of attention to surgical quality.[7,22]

Prognostic Value of Non-SLN Status

SLN status is the strongest predictor of disease recurrence and melanoma-specific death for clinically node-negative melanoma patients.[3,23–26] A second valuable prognostic component of SLN surgery is pathologic status of NSLNs obtained from CLND. Several studies have confirmed that a positive NSLN is a strong predictor of distant recurrence and MSS.[27–30] Furthermore, among patients with the same total number of positive nodes, a positive NSLN confers a worse prognosis than the same total positive number of SLNs. Within the CLND arm of the MSLT-II trial, a positive NSLN was associated with a significantly higher risk of melanoma-related death, hazard ratio 1.78 (1.19–2.67, $P = 0.005$).[14]

Prediction of Non-SLN Disease

Accurate estimation of the likelihood of a positive NSLN may help gauge the potential benefit of CLND. Various factors associated with NSLN status include primary tumor thickness, patient age, number of SLNs analyzed, number SLNs positive, and tumor burden within the SLN (including micrometastasis size, location within the LN, multifocality and extracapsular extension, or perinodal lymphatic invasion).[11,31–33]

In 2008, Gershenwald et al. developed a model to predict NSLN positivity that scored for tumor thickness (0 for ≤ 2 mm, 1 for > 2 mm), largest SLN metastatic focus (0

TABLE 1 Summary of two randomized trials evaluating CLND versus observation for SLN-positive melanoma

	DeCOG-SLT	MSLT-II
Randomization criteria	SLN met ≤ 2 mm	+ SLN
	≥ 1.0-mm thickness	Age 18–75 years
	Age 18–75 years	
	Nodal US screen-negative	
Notable exclusion criteria	Head and neck melanoma	Microscopic or gross satellitosis
# Randomized/screen enrolled[a]	483/1269	377/608[a]
# Withdrew after randomization	49	184
Number analyzed[b]	233 OBS	931 OBS
	240 CLND	824 CLND
Median patient age (yr)	56 OBS	54.9 OBS
	57 CLND	53.7 CLND
% (Proportion) one SLN +	91% (213/233) OBS	81% (754/931) OBS
	93% (222/240) CLND	82% (676/824) CLND
# SLN removed		
1	45% (105/233) OBS	NR
> 3	50% (120/240) CLND	
	11% (25/233) OBS	
	13% (32/240) CLND	
% Metastasis size ≤ 1 mm[b]	68% (158/233) OBS	65% (408/623) OBS
	63% (153/240) CLND	67% (378/566) CLND
Median metastasis size (mm)[c]	NR	0.67 OBS
		0.61 CLND
% SLN H&E +	62% OBS	NR
	58% CLND	
> 10 LN removed at CLND	36%	NR
% NSLN +	18%[d]	11.5%
Adjuvant therapy	65% OBS (IFN)	7% OBS
	57% CLND (IFN)	8% CLND
Imaging surveillance for observed patients	Regional nodal ultrasound q 3 months; whole body CT, MRI or PET-CT q 6 months	Regional nodal ultrasound q 4 months × 2 years; q 6 months × 3 years, then annually
Nodal relapse at 3 years	15% OBS	22.9% OBS
	8% CLND	6.4% CLND
Nodal relapse at 5 years	NR	26.1% OBS
		8.4% CLND

SLN sentinel lymph node; *CLND* completion lymph node dissection; *OBS* observation arm; *NR* not reported; *NSLN* nonsentinel lymph node; *IFN* interferon

[a]In MSLT-II, 608 of 3531 patients prescreened and randomized were SLN + among whom 377 were enrolled, whereas the remaining 1431 patients were directly enrolled at randomization

[b]Data are for intention-to-treat arms in DeCOG-SLT and per protocol arms in MSLT-II

[c]Longest diameter of largest SLN metastasis not available for 375 patients

[d]Pathologic nodal stage was unknown in 25% of DeCOG-SLT patients

for ≤ 0.5 mm, 1 for > 0.5 to ≤ 2 mm, 2 for > 2 to ≤ 10 mm, and 3 for > 10 mm), and number of SLNs harvested (0 for ≥ 3, 1 for 2, and 2 for 1).[11] The risk for positive NSLNs was zero for a total score of 0, 4.0% for 1–2, 22.2% for 3–4, and 46.7% for 5–6. Subsequently, the Non-Sentinel Node Risk Score (N-SNORE) model was

developed.[33] Integer scores were given for sex, primary tumor regression, proportion of metastatic SLNs, perinodal lymphatic invasion, and size of the largest SLN tumor deposit (maximum total score of 11). The risk for positive NSLNs ranged from zero for a score of 0 to 70–80% for a score ≥ 8. This model, with minor variations, has been independently validated in retrospective patient data sets, although it is unknown how often this prognostication influences treatment decisions.[34,35] Thus, consensus on an optimal algorithm for prediction of NSLN status and how it might be applied in clinical practice remains to be determined.

Morbidity

The rationale for SLNB is to accurately stage at-risk regional nodal basins with minimal morbidity. Complication rates from SLNB are approximately 5% versus approximately 20% for regional lymphadenectomy and vary with the anatomic location of the nodal basin.[36] Acute complications, while uncommon, include bleeding, wound infection, dehiscence, and lymphocele. Chronic morbidity can include neuropathy and lymphedema. Lymphedema rates following axillary dissection for melanoma are 8–14% and 17–20% following inguinal or ilioinguinal dissection.[37,38] Surgical expertise, technical advances, such as greater saphenous vein preservation with inguinal lymphadenectomy, and processes, such as enhanced recovery pathways, may partially mitigate these risks.[39] An analysis of morbidities in 225 MSLT-I trial participants who underwent CLND for a positive SLN versus 132 patients who underwent delayed LND after a clinical nodal basin recurrence showed a significantly lower rate of lymphedema with early CLND (12.4%) versus delayed LND (20.4%).[40] In the MSLT-II trial, 6.3% of patients in the OBS group versus 24.1% in the CLND group developed lymphedema, although it was graded as moderate/severe in only 3%, still inexplicably higher than the 12.4% rate reported with substantially longer follow-up in the comparable MSLT-1 CLND patient group noted above.[14] Interestingly, prospectively ascertained patient-reported outcomes from 490 patients in the Sunbelt Melanoma Trial showed no differences in short- and long-term quality of life and physical condition measures between patients treated with SLN surgery alone versus SLNB/CLND for micrometastatic melanoma, nor any differences by nodal basin anatomic location.[41]

Future Directions/Unanswered Questions

Longer-term follow-up of SLN-positive patients treated with SLN surgery alone and outcomes data on patients treated outside the clinical trial setting are lacking. Meaningful differences in MSS may not be evident for many years for favorable prognosis micrometastatic disease.[5] Therefore, applicability of the findings for patients with an otherwise anticipated long life expectancy may be limited.

At present, there are little data to help guide surgeons and patients on issues of cost, quality of life, or patient-reported outcomes for SLNB followed by CLND versus imaging surveillance for patients with micrometastatic nodal disease. Furthermore, there are no data on whether newly approved adjuvant immunotherapies and targeted therapies tested in Stage III melanoma patients treated with CLND also are efficacious in 1) patients treated with SLNB only or 2) patients with micrometastatic disease ≤ 1 mm treated with either SLNB or SLNB/CLND.[42–45] Molecular profiling of the primary melanoma and/or regional immune microenvironment (SLN and environs) is an area of active investigation that may further challenge current surgical treatment paradigms in the near future.[46–48] New predictive biomarkers may supersede disease burden in patient selection for adjuvant systemic therapies and/or surgical treatment options.

CONCLUSIONS

Current evidence supports a selective and individualized approach to the management of clinically node-negative, SLN-positive melanoma patients. It is important to note that these recommendations do not apply to patients presenting with clinically evident or recurrent nodal disease. For low-risk, low-volume micrometastatic disease, SLNB may be diagnostic and therapeutic, and either close clinical follow-up with imaging or CLND are reasonable options for appropriately selected patients. For higher-risk patients, omission of CLND requires careful consideration of the potential risks and benefits, relevant histopathology, and informed patient discussion. The latter should address patient comorbidities, estimated life expectancy, compliance with follow-up, likelihood of additional nodal disease, availability of imaging surveillance, prognostic value of complete nodal staging and its impact on adjuvant therapy recommendations or clinical trial participation, and the consequences of regional recurrence. Data on long-term outcomes, cost, and patient-reported quality of life measures are not yet available.

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