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Melanoma Patients with Positive Sentinel Nodes Who Did Not Undergo Completion Lymphadenectomy: A Multi-Institutional Study

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Background: Completion lymph node dissection (CLND) is considered the standard of care in melanoma patients found to have sentinel lymph node (SLN) metastasis. However, the therapeutic utility of CLND is not known. The natural history of patients with positive SLNs who do not undergo CLND is undefined. This multi-institutional study was undertaken to characterize patterns of failure and survival rates in these patients and to compare results with those of positive-SLN patients who underwent CLND.

Methods: Surgeons from 16 centers contributed data on 134 positive-SLN patients who did not undergo CLND. SLN biopsy was performed by using each institution's established protocols. Patients were followed up for recurrence and survival.

Results: In this study population, the median age was 59 years, and 62% were male. The median tumor thickness was 2.6 mm, 77% of tumors had invasion to Clark level IV/V, and 33% of lesions were ulcerated. The primary melanoma was located on the extremities, trunk, and head/neck in 45%, 43%, and 12%, respectively. The median follow-up was 20 months. The median time to recurrence was 11 months. Nodal recurrence was a component of the first site

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of recurrence in 20 patients (15%). Nodal recurrence–free survival was statistically insignificantly worse than that seen in a contemporary cohort of patients who underwent CLND. Disease-specific survival for positive-SLN patients who did not undergo CLND was 80% at 36 months, which was not significantly different from that of patients who underwent CLND.

Conclusions: This study underscores the importance of ongoing prospective randomized trials in determining the therapeutic value of CLND after positive SLN biopsy in melanoma patients.

Key Words: Melanoma—Sentinel lymph node biopsy—Completion lymphadenectomy—Recurrence—Survival.

Sentinel lymph node (SLN) biopsy has become widely accepted as a staging procedure for patients with primary cutaneous melanoma. SLN biopsy is a highly accurate procedure that uses well-characterized lymphatic mapping techniques. Histopathologic studies have validated the diagnostic utility of SLN biopsy, thus proving that the SLN accurately predicts the status of the regional nodal basin.[1] The presence of SLN metastasis has also been shown to be the most important prognostic factor in terms of clinical outcome in patients with clinical stage I or II melanoma.[2]

When SLN metastases are found, the current standard of care is completion lymph node dissection (CLND). Approximately 15% to 20% of patients are found to have additional disease in the CLND specimen. Prior studies have attempted to define uniform predictors of metastasis in non-SLNs to determine which patients are at high risk of further disease and should have CLND. Likewise, CLND could be abandoned if patients who have an exceedingly low risk of non-SLN metastasis could be reliably identified. Because accurate predictive factors have yet to be identified, CLND continues to be routinely performed in patients found to have a positive SLN.[2–6]

However, the therapeutic utility of CLND after positive SLN biopsy is unknown, both in terms of regional control and disease-specific survival (DSS). Very little is known about the natural history of patients with positive SLNs who do not undergo CLND. Nodal recurrences have been reported in up to 10% of patients after CLND for occult metastasis detected by SLN biopsy.[7] The risk of developing same-basin nodal recurrence if positive SLN biopsy is not followed by CLND has yet to be determined. Results from prospective randomized trials of elective lymph node dissection (ELND) have failed to demonstrate a survival advantage over observation and therapeutic lymph node dissection for patients with clinical stage I or II melanoma. In most of these studies, nodal basin recurrence rates were quite similar to the incidence of involved lymph nodes found at ELND. Because SLN biopsy potentially spares 80% of patients a negative ELND, a survival benefit may be seen given a more select population of patients undergoing CLND.

The potential benefit of CLND in the context of node positive selective lymphadenectomy is currently being investigated in the Multicenter Selective Lymphadenectomy Trial II, a large prospective randomized study that is open and actively accruing. Patients with positive SLNs are randomized to immediate CLND or close nodal observation. The observation arm of the trial involves interval follow-up and ultrasound examination of the involved regional nodal basin, with CLND if nodal metastases are detected at a later time.

This study represents a multi-institutional collaboration undertaken to characterize the natural history of patients with SLN metastases who did not undergo CLND. Aims of the study were to determine patterns of recurrence and to examine the effect on DSS of foregoing CLND. The experience of a contemporary cohort of patients from Memorial Sloan-Kettering Cancer Center (MSKCC) with positive SLNs who had CLND was used as a standard of comparison for patterns of recurrence and survival.

METHODS

We contacted 26 investigators from high-volume melanoma institutions regarding participation in this study. Investigators from 21 centers expressed interest in participating. Ultimately, patient data from 16 institutions were provided for analysis. Standardized data were requested for consecutive patients with SLN metastasis who did not undergo CLND, including patient, tumor, and SLN characteristics and follow-up information. Data were collected under the auspices of each center's institutional review board guidelines.

SLN biopsy was performed according to the individual surgeon's preferred mapping techniques.

Harvested SLNs were examined by using each institution's established histopathologic protocols for serial sectioning, hematoxylin and eosin staining, and immunohistochemistry (IHC) staining. Centralized pathology review was not performed. Micrometastatic disease was defined as detection of metastasis by histologic examination only. Patients with metastases found only with reverse transcriptase-polymerase chain reaction were not included in this analysis.

Reasons why CLND was not performed were elicited as part of the data collection. Data regarding other modalities of treatment, such as interferon alfa-2b or vaccine protocols, were not captured. Only patients with adequate prospective follow-up were eligible for inclusion in this study. Patients who refused CLND and did not return for follow-up were not included in this study. We allowed investigators to report patients seen as referrals after positive SLN biopsy at outside institutions. Patients with positive SLN who did not have CLND, but who presented to participating centers for treatment of recurrence, were excluded from analysis.

Clinical follow-up intervals were at the discretion of the individual surgeon. Data regarding methods of follow-up and subsequent detection of recurrent disease were not collected for this study. Each patient's clinical course was reported according to the site of disease recurrence, if any, and disease status at the time of last follow-up.

Recurrences were characterized as locoregional, defined as local or in-transit disease; nodal, defined as recurrences in the mapped basin; or systemic, defined as disease in all other sites. The recurrence rates and survival outcomes for patients with positive SLNs who did not undergo subsequent CLND were compared with results from a contemporary cohort of patients from MSKCC, the organizing center for this study, who had positive SLN biopsy followed by CLND. These patients were identified from a prospectively maintained database and represent consecutive patients treated between March 1992 and September 2004.

Statistical analyses were performed with SPSS software, version 12 (SPSS, Inc., Chicago, IL). Comparisons were made by using χ^2 analysis or Student's *t*-test, and estimated survival rates were calculated by the Kaplan-Meier method. The influence of CLND on outcome was evaluated by comparing the collected series with the MSKCC cohort and subjecting the combined group of patients to multivariable analysis with Cox regression analysis. $P < .05$ was considered significant.

RESULTS

The study population included 134 patients from 16 institutions with histologically positive SLNs who did not undergo CLND. It is interesting to note that investigators from four institutions indicated that they had no patients who elected observation after positive SLN biopsy. Clinicopathologic characteristics, including patient, tumor, and SLN factors, are listed in Table 1. In the vast majority of cases, the decision to forego CLND was made by the patient alone or by the patient and physician jointly (Table 2). Nearly half of patients refused CLND. When the decision for nodal observation was made between the patient and physician, commonly cited reasons included medical comorbidities, findings of an interval/in-transit positive SLN, or enrollment to a clinical trial where nodal observation was selected.

The median follow-up for the entire group was 20 months. The median time to recurrence was 11 months. For patients without recurrent disease, the median follow-up was 18 months. Recurrent disease was reported in 49 (37%) patients. Patterns of first recurrence are listed in Table 3. In the study population, local or in-transit recurrences were seen as sites of first recurrence in seven (14%) patients. Systemic disease was seen as a component of initial recurrence in 51% of patients (25 of 49) who had recurrences. Recurrent disease in the previously mapped nodal basin was seen either alone (14 of 134 patients; 10%) or as a component of first recurrence (20 of 134; 15%). Concomitant presentation with both nodal and systemic recurrence was reported in three patients. Of note, one patient presented with systemic metastases as a site of first recurrence but later developed a recurrence in the nodal basin.

Among 14 patients with a nodal-only recurrence, 10 underwent successful salvage lymphadenectomy. Of those patients, four remain free of disease, four have died of disease, and two were alive with disease at time of last follow-up. Among the 10 patients who did not have salvage lymphadenectomy for some type of nodal recurrence, 5 were alive with disease and 5 were dead of disease at the last reported follow-up.

The estimated nodal recurrence–free survival for positive-SLN patients who did not undergo CLND, as calculated by the Kaplan-Meier method, is shown in Fig. 1. Comparison to a contemporary series of 164 melanoma patients with positive SLNs who had CLND was made by using the prospectively maintained melanoma database at MSKCC. The clinicopathologic characteristics of this group of patients

TABLE 1. *Clinicopathologic characteristics of melanoma patients with positive SLN biopsy results*

Variable	Multi-institutional study population: SLN^+ patients who did not undergo CLND (n = 134)	MSKCC cohort: SLN^+ patients who underwent CLND (n = 164)	*P* value
Age, y (median)	59	56	.29
Sex			
Male	83 (61.9%)	105 (64%)	.71
Female	51 (38.1%)	59 (36%)	
Tumor thickness, mm (median)	2.6	2.85	.11
Tumor location			
Head/neck	16 (11.9%)	14 (8.5%)	.62
Trunk	57 (42.5%)	67 (40.9%)	
Extremity	60 (44.8%)	80 (48.8%)	
Unknown/other	1 (.7%)	3 (1.8%)	
Clark level			
II	2 (1.5%)	0	.07
III	20 (14.9%)	11 (6.7%)	
IV	87 (64.9%)	119 (72.6%)	
V	16 (11.9%)	26 (15.9%)	
Unknown	9 (6.7%)	8 (4.9%)	
Ulceration			
Present	44 (32.8%)	82 (50%)	.003
Absent	79 (59.0%)	64 (39%)	
Unknown/not reported	11 (8.2%)	18 (11%)	
Method of disease detection			
IHC only (micrometastatic disease)	38 (28%)	15 (9.1%)	< .0001
H&E	96 (72%)	149 (90.9%)	
Number of positive nodes			
Single positive SLN	106 (79%)	117 (71.3%)	.13
Multiple positive SLNs	28 (21%)	47 (28.7%)	

SLN, sentinel lymph node; CLND, completion lymph node dissection; MSKCC, Memorial Sloan-Kettering Cancer Center; IHC, immunohistochemistry; H&E, hematoxylin and eosin.

TABLE 2. *Reasons CLND was not performed after positive SLN biopsy results (n = 134)*

Reason	n (%)
Patient refusal	65 (49)
Patient/physician decision	64 (48)
Unknown	5 (4)

CLND, completion lymph node dissection; SLN, sentinel lymph node.

from MSKCC with SLN metastasis are largely comparable to those of the study population (Table 1), except that the study population had fewer patients with ulceration of the primary tumor, a lower proportion of melanoma primary tumors with invasion to Clark level IV or V (not statistically significant), and more patients with micrometastatic disease in the SLN, as detected by IHC. Taking these tumor and SLN characteristics into account, the group of patients who underwent CLND seems to have an overall poorer set of prognostic indicators.

The median follow-up for the MSKCC cohort of patients was 36 months—somewhat longer than the 20 months in the study group. Patterns of recurrence are listed in Table 3. The nodal recurrence–free survival at 36 months was 88% in the MSKCC cohort, compared with 80% in this study population (Fig. 1). There was a statistically insignificant trend toward worse nodal recurrence–free survival when CLND was not performed ($P = .07$; log rank).

The estimated DSS in patients with positive SLN biopsy results is shown in Fig. 2A. The DSS at 3 years was 80%. The overall DSS of patients with positive SLNs who did not undergo CLND was no different from that of positive SLN-patients who had CLND (Fig. 2B), as seen on log-rank analysis ($P = .65$).

The results of Cox regression analysis (univariable and multivariable) of clinicopathologic factors with respect to nodal recurrence–free survival and DSS are as seen in Table 4. The two groups of patients were combined for the purposes of this analysis (n = 298). Age and tumor thickness were analyzed as continuous variables. Factors included in the multiple covariate analysis included significant variables from the univariate analysis (up to $P < .1$) and the major factor of interest in this study (CLND vs. nodal observation). On multivariable analysis, the only factor predictive of decreased nodal recurrence–free survival was age ($P = .04$), although a trend toward

TABLE 3. *Patterns of first recurrence*

Variable	Study population: SLN^+ patients who did not undergo CLND (49/134; 37%)	MSKCC cohort: SLN^+ patients who underwent CLND (85/164; 52%)
Median follow-up (mo)	20	36
Type of recurrence		
Locoregional only	7 (14.3%)	29 (34.1%)
Nodal only	14 (28.6%)	12 (14.1%)
Nodal ± locoregional	17 (34.7%)	14 (16.5%)
Nodal as a component	20 (40.8%)	17 (20.0%)
Systemic as a component	25 (51.0%)	42 (49.4%)

SLN, sentinel lymph node; CLND, completion lymph node dissection; MSKCC, Memorial Sloan-Kettering Cancer Center.

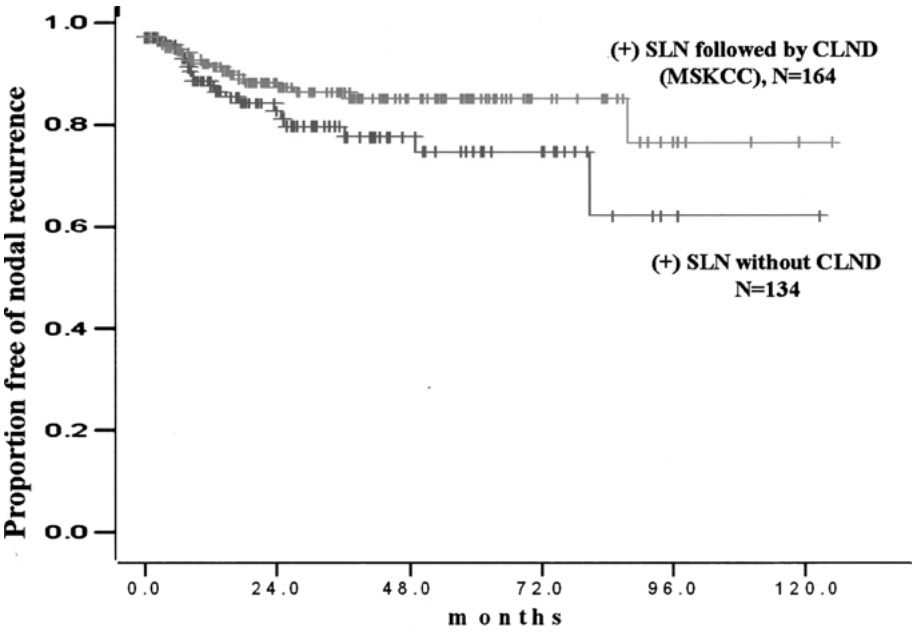

FIG. 1. Nodal recurrence-free survival for melanoma patients with positive sentinel lymph nodes (SLNs; $P = .07$; log-rank analysis). CLND, completion lymph node dissection; MSKCC, Memorial Sloan-Kettering Cancer Center.

significance was seen for CLND with regard to decreased nodal recurrence.

Factors predictive of decreased DSS were increasing age and tumor thickness ($P < .001$ and $P = .002$, respectively). Whether a patient had CLND or nodal observation after positive SLN biopsy was not a significant predictor of DSS on either univariable or multivariable analysis.

DISCUSSION

SLN biopsy is a valuable diagnostic procedure that is associated with low false-negative rates and highly accurate staging. Patients with positive SLNs have a significantly higher risk of recurrence and death than those without SLN metastasis.[2] Because there is no reliable way to predict the absence of further disease in the CLND specimen with certainty, the currently accepted practice is to perform CLND for positive-SLN patients. However, the therapeutic utility of CLND and the natural history of positive-SLN melanoma patients who did not undergo CLND are unknown. This series reports a multi-institutional experience of 134 patients who did not undergo CLND after positive SLN biopsy. A better understanding of this group of patients is essential to assess the importance of ongoing prospective randomized trials designed to compare observation of involved nodal basins with CLND.

We found 20 (15%) patients who had nodal recurrence as a component of their first recurrence. This is quite similar to the incidence of positive non-SLNs had these patients undergone CLND. The median time to recurrence was 11 months. With a median follow-up of 20 months, we believe that most, but not all, of the nodal recurrences have been observed.

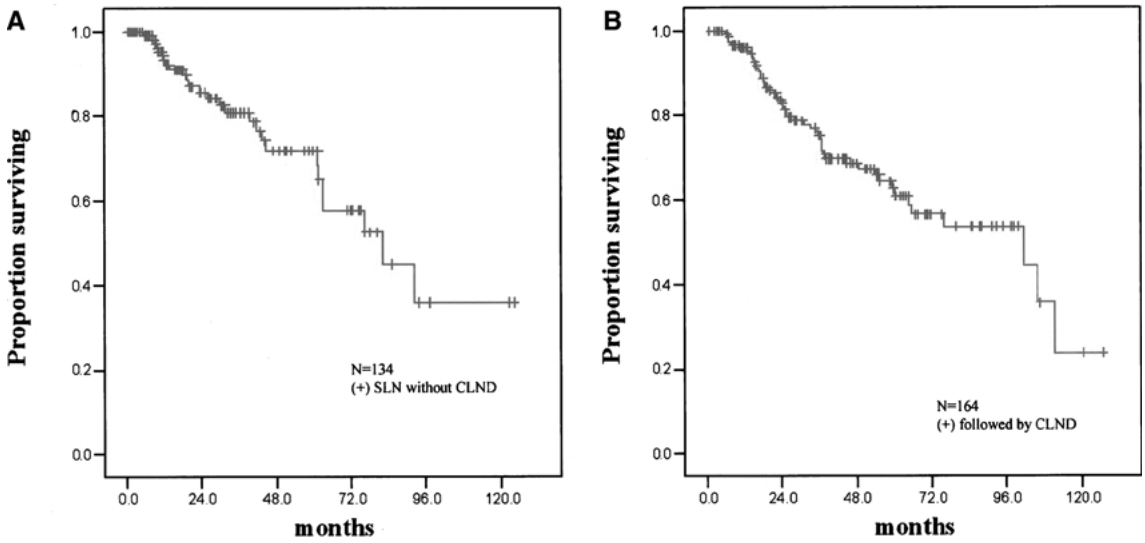

FIG. 2. (**A**) Disease-specific survival (DSS) for melanoma patients with positive sentinel lymph nodes (SLNs) who did not undergo completion lymph node dissection (CLND; present multi-institutional study). The 3-year DSS was estimated at 80%. (**B**) DSS for melanoma patients with positive SLNs who underwent CLND (Memorial Sloan-Kettering Cancer Center cohort). The 3-year DSS was estimated at 74%. There was no difference in DSS between the two groups ($P = .65$; log-rank analysis).

Recurrent disease in the nodal basin after ELND has been reported in 4% to 16% of patients.[8–11] Consistent with the MSKCC cohort, the incidence of same-basin nodal recurrence after CLND for positive SLN results in contemporary series from other institutions range from 2.6% to 12% in the literature.[7,9,12,13] The median time to nodal basin recurrence after therapeutic lymph node dissections or after CLND for positive SLN has previously been reported to be 13 to 14 months.[7] When the nodal recurrence–free survival of the study population was compared with that of the MSKCC cohort, the patients who did not undergo CLND demonstrated a statistically insignificant trend toward poorer nodal recurrence–free survival. When both groups of patients were combined for a Cox regression analysis, CLND (compared with nodal observation) also demonstrated a statistically insignificant trend toward decreased nodal recurrence (Table 4). Taking into account the difference in median follow-up (20 vs. 36 months), this trend toward increased nodal recurrences in the group who did not have CLND could become statistically significant with longer follow-up if a few more nodal recurrences are seen.

Twenty patients had nodal recurrence either alone or as a component of their initial recurrence. Ten of 14 patients in this study with nodal-only recurrence underwent successful salvage CLND. At time of last follow-up, four of these patients were alive with no evidence of disease, and the remaining six were either alive with disease or dead of disease. It is conceivable that patients who do not undergo CLND are subjected to a higher risk of subsequent distant recurrences. Whether systemic recurrence and death in these cases are attributable to aggressive tumor biology or to delayed nodal intervention can be addressed only by a prospective trial. Four patients with nodal-only recurrences did not have CLND, and the reasons for this were not stated. Small numbers preclude extensive analysis, but there is certainly a risk of extensive nodal basin disease which is difficult to control with salvage lymphadenectomy.

The DSS for 134 node positive SLN patients who did not undergo CLND was remarkably similar to that of 164 node-positive MSKCC patients who underwent CLND. The 3-year DSS of 74% reported for MSKCC patients with positive SLNs who had CLND is similar to other reports in the literature. According to the experience at the M. D. Anderson Cancer Center, the 3-year DSS for positive SLN patients (CLND was performed) was 70% with a median follow-up of 40 months.[2] We compared this study population with a contemporary series of patients at MSKCC who had CLND after positive SLN biopsy. The groups were relatively well matched, but it seems that the group of positive-SLN patients who had CLND had more primary lesions with ulceration and fewer SLNs with micrometastatic disease, thus making them a population with a possibly poorer prognosis. The resulting concern would be that the benefit

TABLE 4. *Prognostic factors influencing disease-specific survival, all patients (n = 298)*

	Nodal recurrence–free survival			Disease-specific survival		
Clinicopathologic factor	Univariate (*P* value)	Multiple covariate (*P* value)	95% CI	Univariate (*P* value)	Multiple covariate (*P* value)	95% CI
Age[a,b]	.06	.04	1.00–1.04	< .001	.001	1.02–1.05
Sex	.7	–	–	.68	–	–
Thickness	.32	–	–	.002	.002	1.08–1.22
Tumor location[b]	.16	–	–	.33	–	–
Clark level	.82	–	–	.11	–	–
Ulceration	.28	–	–	.61	–	–
Detection of disease (H&E vs. IHC)	.43	–	–	.12	–	–
No. of positive SLNs[b]	.24	–	–	.06	.06	–
Underwent completion lymph node dissection[a,b]	.47	.09	–	.79	.5	–

CI, confidence interval; H&E, hematoxylin and eosin; IHC, immunohistochemistry; SLN, sentinel lymph node.
[a] Factors included in the multivariate model for nodal recurrence-free survival based on the *P* value from univariate analysis ($P < .1$).
[b] Factors included in the multivariate model for disease-specific survival based on the *P* value from univariate analysis ($P < .1$) or biological importance.

of CLND in reducing recurrences or improving survival may be mitigated by poorer clinicopathologic characteristics.

To examine this issue more carefully, a multiple covariate Cox regression analysis was performed to examine whether any prognostic factor was significantly predictive of DSS. We found that of those factors more prominent in the group of positive-SLN patients who underwent CLND, neither the method of histopathologic detection (hematoxylin and eosin vs. IHC) nor the presence of ulceration predicted decreased DSS. As expected, however, increasing age and tumor thickness were associated with a worse DSS for the group as a whole. It is clear that undergoing CLND after positive SLN biopsy is not a significant predictor of DSS on either univariate or multivariable analysis.

The findings of this study should not be taken as a treatise against SLN biopsy. The diagnostic and prognostic value of SLN biopsy should not be minimized. SLN biopsy is a minimally invasive, highly accurate staging procedure. The presence of SLN metastasis is the most important predictor of clinical outcome in patients with melanoma. No other variable provides the same independent level of prognostic information. If a positive SLN is found, the currently accepted practice, outside of a clinical protocol, is CLND. Although this trial was a retrospective analysis of a multi-institutional experience of a highly selected patient population, it is, to date, the most comprehensive reporting of the patterns of recurrence and clinical outcomes in patients with positive SLNs who did not undergo CLND. We report a statistically insignificant trend toward decreased nodal recurrence–free survival in the group of patients who did not undergo CLND but no difference in overall DSS compared with patients who underwent CLND.

Clinical equipoise, or the collective uncertainty over preferred treatment strategies, is the underlying ethical tenet of randomized clinical trials.[14] The results of this study strongly support the comparative therapeutic merit, or equivalency, of the observation arm of two ongoing randomized prospective trials for patients with SLN metastasis. Results from trials such as the regional Florida Melanoma Trial or the larger, national Multicenter Selective Lymphadenectomy Trial II[15] should help answer the question of whether CLND after positive SLN biopsy affects recurrence or improves survival. Our findings emphasize the importance of continued accrual to and completion of these clinical trials.

CONCLUSIONS

For patients with positive SLNs who did not undergo CLND, nodal recurrence was a component of the first site of recurrence in 15% of patients, and the 3-year DSS was 80%. With a median follow-up of 20 months, nodal recurrence–free survival and DSS seem similar to those seen in a contemporary cohort of patients after CLND for positive SLN biopsy. These findings underscore the importance of ongoing prospective, randomized trials in defining the therapeutic value of CLND after positive SLN biopsy in melanoma patients.

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