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Authors

Rios-Cantu, Andrei
Lu, Ying
Melendez-Elizondo, Victor
et al.

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Is the non-sentinel lymph node compartment the next site for melanoma progression from the sentinel lymph node compartment in the regional nodal basin?

Andrei Rios-Cantu[1,4,5], **Ying Lu**[2], **Victor Melendez-Elizondo**[1,4,5], **Michael Chen**[2,6], **Alejandra Gutierrez-Range**[1,4,5], **Niloofar Fadaki**[1], **Suresh Thummala**[1], **Carla West-Coffee**[1], **James Cleaver**[3], **Mohammed Kashani–Sabet**[1], and **Stanley P.L. Leong**[1]

[1]Center for Melanoma Research & Treatment, California Pacific Medical Center, 2340 Clay Street, 2nd Floor, San Francisco, CA 94115, USA

[2]Departments of Biomedical Data Science, Health Research and Policy, and Radiology, The Stanford Cancer Institute, Stanford University, Stanford, CA, USA

[3]Department of Dermatology, University of California, San Francisco, CA, USA

[5]Consorcio de Universidades Mexicanas (CuMEX), Pachuca, Mexico

[6]University of Nevada, Las Vegas, Las Vegas, NV, USA

Abstract

Melanoma patients with additional positive lymph nodes in the completion lymph node dissection (CLND) following a positive sentinel lymph node (SLN) biopsy would have a poorer prognosis than patients with no additional positive lymph nodes. We hypothesize that the progression of disease from the SLN to the non-SLN compartment is orderly and is associated with the worsening of the disease status. Thus, the SLN and non-SLN compartments are biologically different in that cancer cells, in general, arrive in the SLN compartment before spreading to the non-SLN compartment. To validate this concept, we used a large cohort of melanoma patients from our prospective SLN database in an academic tertiary medical center. Adult cutaneous melanoma patients (n = 291) undergoing CLND after a positive SLN biopsy from 1994 to 2009 were analyzed. Comparison of 5-year disease-free survival and 5-year overall survival between positive (n = 66) and negative (n = 225) CLND groups was made. The 5-year disease-free survival rates were 55% (95% CI 49–62%) for patients with no additional LN on CLND versus 14% (95% CI 8–26%) in patients with positive LN on CLND ($p < 0.0001$, log-rank test). The median disease-free survival time was 7.4 years with negative CLND (95% CI 4.4–15+ years) and 1.2 years with positive CLND (95% CI 1.0–1.8 years). The 5-year overall survival rates were 67% (95% CI 61–74%) for negative CLND versus 38% (95% CI 28–52%) for positive CLND ($p < 0.0001$, log-rank test). The median overall survival time was 12.1 years for negative CLND (95% CI 9.3–15+ years) and 2.5 years for positive CLND (95% CI 2.2–5.7 years). This study shows that CLND status is a significant prognostic factor for patients with positive SLNs undergoing CLND. Also, it suggests an orderly progression of metastasis from the SLN to the non-SLN compartment. Thus, the SLN

Correspondence to: Stanley P.L. Leong.

[4]Present Address: Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo Leon, Mexico

in the regional nodal basin draining the primary melanoma may serve as an important gateway for metastasis to the non-SLN compartment and beyond to the systemic sites.

Keywords

Cutaneous melanoma; Sentinel lymph node biopsy; Complete lymph node dissection; Overall survival; Disease free survival

Introduction

Since the introduction of the sentinel lymph node (SLN) biopsy procedure by Morton in 1992 [1], it has become the standard of treatment for melanoma patients with Breslow thickness equals or greater than 1.0 mm (stages IB through IIC) as recommended by current National Comprehensive Cancer Network (NCCN) guidelines [2]. Recent evidence shows that the indication may be expanded to less than 1 mm especially if the primary melanoma is associated with higher risk features such as ulceration and mitosis [3]. In general, SLN mapping and selective SLN dissection have become standard staging procedure for patients with primary melanoma with clinically negative nodal basins.

Despite the fact that patients with additional positive lymph nodes from the complete lymph node dissection (CLND) would have a worse outcome [4–15], there has been controversy surrounding the performance of immediate CLND in patients with tumor positive SLNs. The primary concern about CLND is related to morbidity related to the procedure, which consists primarily of lymphedema, as high as 25% with axillary dissection and 48% with inguinal dissection [16], seroma and wound infections. Several studies have reported much lower complication rates for SLN biopsy, ranging from 5 to 14% versus those for CLND, between 23 and 66% [17–22].

Since there is only a reported 20% chance of having non-sentinel lymph node (NSLN) positivity [23], after a positive SLN biopsy, there are some concerns about morbidity in patients who wouldn't otherwise benefit from a negative CLND procedure. Thus, some authors suggest only observation and CLND to be performed only in patients with clinical recurrence [24, 25]. One major reason why the outcome of patients with a positive SLN biopsy is not the same is probably because of the enormous heterogeneity of SLN micrometastasis relating to the size and location of micrometastasis within the SLN [6, 7, 9, 26–28], and anatomic locations of SLNs [10].

Recently some groups have tried to develop risk assessment scores to correctly identify patients with high risk of NSLN involvement and who would benefit the most from CLND [4–8], with an attempt to identify the subgroup of patients who would benefit from a CLND. Although certain factors are found to be statistically significant, none of these factors are specific enough to predict the result of the CLND for each patient to be useful to recommend each patient the need for a CLND. In a separate population-based study from the Surveillance Epidemiology and End Results Program registry, the likelihood of CLND is significantly associated with age, gender and geographic area [29].

We have followed our patients with a positive SLN biopsy undergoing CLND at least over 5 years. The overall survival and disease free survival between patients with positive and negative CLND status following a positive SLN biopsy have been analyzed and compared. The goal of this study is to demonstrate the clinical outcome of these 2 groups of patients and to evaluate the prognostic significance of CLND.

Materials and methods

The analyses were based on reviewing a prospective database of 2079 cutaneous melanoma patients undergoing SLN dissection, collected from a tertiary care referral center from 1993 to 2011. Out of 2109 of primary melanoma patients undergoing SLN biopsy, 353 patients (16.7%) had positive SLNs; of these, there were 293 in which CLND had been performed. After excluding 2 patients under age 18, a total of 291 adult cases is used for the analysis of this paper (Fig. 1). A positive node was considered when pathologic review of the specimen yielded a positive result on Hematoxilin and Eosin stain for melanoma cells, most of the times corroborated with inmunohistochemical staining (Melan-A, S100 and HMB-45). A sentinel node was considered as the one with the highest radioactive tracer activity, and every subsequent node which was at least higher than 10% of the highest count [30, 31].

Statistical calculations

For the purpose of this study we separated the group with a positive SLN from the rest, and then split the group between patients with positive and negative CLND results. Baseline difference between two groups were evaluated. Five-year disease-free survival was calculated from the date of SLN dissection to the first recurrence of melanoma (either local, regional or distant). Five-year overall survival was calculated as the interval between SLN dissection and death due to any cause.

Patients without such an event were censored at the date of the last follow-up visit or the date the patient was last known to be alive. Survival curves and estimated 5-year survival rates with 95% confidence interval (95% CI) between groups were generated using Kaplan–Meier non-parametric method and compared by log-rank test.

To determine if the difference in survival was due to possible effects of the baseline group difference, Cox regression model was performed to estimate the relative hazards ratio by group after adjustment for the baseline covariates that were significantly different at baseline.

P values of less than 0.05 were considered statistically significant.

Results

Of 291 patients in our analysis population, 182 were males (62.5%) and 109 were females (37.5%) with a mean age of 52.0 years (range 18–87). The anatomic locations involved were 34 head and neck (H&N) cases, 128 trunk, 43 upper extremities, and 86 lower extremities.

Table 1 compares differences between CLND positive and negative patients. As shown in this table, there were no significance difference between the two patient groups in age,

ethnicity, tumor regression, or mitotic rate. However, gender, Breslow thickness, Clark level, ulceration, lymphovascular invasion, and microsatellitosis were significantly different.

Site specific recurrence

Out of the 142 patients with a recurrence recorded, their first recurrence, 28 were local (19.7%), 26 regional (18.3%) which account for in-transit or satellite nodes, 10 were in a regional basin without previous dissection (7.0%), 15 in a regional basin with a previous dissection (10.6%), 59 in a distant site (41.5%), most of them in the lung, and 4 in an unspecified location (2.8%).

Five year disease-free survival and overall survival

Two hundred twenty-five (225) patients had negative CLND and 66 had positive CLND (22.7%). The 5-year disease-free survival rates were 55% (95% CI 49–62%) for patients with no additional LN on CLND versus 14% (95% CI 8–26%) in patients with positive LN on CLND ($p < 0.0001$, log-rank test). The median disease-free survival time was 7.4 years with CLND negative (95% CI 4.4–15+ years) and 1.2 years with CLND positive (95% CI 1.0–1.8 years) (Fig. 1).

The 5-year overall survival rates were 67% (95% CI 61–74%) for negative CLND versus 38% (95% CI 28–52%) for positive CLND ($p < 0.0001$, log-rank test). The median overall survival time was 12.1 years for CLND negative (95% CI 9.3–15+ years) and 2.5 years for CLND positive (95% CI 2.2–5.7 years) (Fig. 2).

A Cox proportional regression analysis was also calculated to estimate the relative hazards ratio between CLND group after adjustment of the difference in baseline covariates of gender, Breslow index, Clark's level, ulceration, lymphovascular invasion, and microsateliitosis that were significantly different in Table 1. The estimated hazards ratio for disease-free survival by CLND positive group is 2.40 with a 95% confidence interval (1.49, 3.86) ($p = 0.0003$, log-rank test). Similarly, the hazards ratio for overall survival is 2.15 with a 95% confidence interval (1.32, 3.50) ($p = 0.0022$, log-rank test).

Discussion

The concept that cancer cells from the microenvironment of the primary site would spread to the SLN(s) in the regional nodal basin [1] has been convincingly validated in melanoma [11] and breast cancer [32]. In the pre-SLN era, regional lymph node metastasis has been considered as an indicator rather than governor regarding cancer progression [33]. This concept may be challenged in the SLN era if micrometastasis in the SLN is merely an indicator of systemic disease or if it is being incubated within the SLN to become more aggressive to spread to the systemic sites. In most cases for melanoma [11] and breast cancer [32], perhaps, it is a spectrum of event from the initial arrival of cancer cells in the SLN, which functions like an incubator to allow the cancer cells to proliferate and then spread to the non-SLN compartment and the systemic sites. The tumor microenvironment of the SLN serves as a Darwinian selection force [34] as to allow the emergence of the “fittest clone” to spread to the distant sites. The SLN provides us with a unique opportunity to study the

progression of cancer cells in the nodal tissue from micrometastasis to macrometastasis and beyond to the distant sites.

Numerous studies have shown that melanoma patients with a positive CLND following a positive SLN biopsy have a worse prognosis than those with a negative dissection [4–15]. *One of the largest series by Rutkowski et al.* [15] *with 473 melanoma patients undergoing CLND following a positive SLN biopsy from a cohort of 1764 consecutive melanoma patients showed that 8 year overall survival rate in the entire group was 73.5%, 80% without SLN metastases and 50% in the SLN+ group ($p < 0.001$).* Leung et al. [35] have shown that non-SLN positivity is one of the most significatnt prognostic factors in Stage III melanoma patients with micrometastasis in SLN(s). Thus, they have proposed that non-SLN positivity should be used as an AJCC subclassification of nodal stage. An attempt was made by Roka et al. to identify the subgroup of patients with a positive NSLN status using clinicopathological features, but they were not able to find a difference between SLN-only metastasis and NSLN groups [36].

In general, solid cancer is a progressive disease, consistent with the spectrum theory of cancer progression [37], from the microenvironment of the primary site to the SLN gateway and beyond to the distant sites by way of the bone marrow and peripheral blood [38], perhaps in about 20% of the time. Thus, it is important to follow the SLN-negative patients for distant metastasis without local and/or regional recurrences as the cancer cells in these patients may have potentially spread from the primary site by hematogenous routes to distant sites.

The recently completed American College of Surgeons Oncology Group Z0011 trial, to examine whether CLND is necessary in early breast cancer patients with clinically non-palpable, but histopathology positive SLNs has shown that for such patients with no clinical palpable adenopathy but a positive SLN biopsy may not need an axillary lymph node dissection [39]. Thus, these findings suggest that when the SLN contains micrometastasis, the disease is probably limited to the SLN without further progression. The ultimate goal for cancer staging is to develop molecular biomarkers for cancer cells during their progression from the primary site to the regional nodes and beyond to the systemic sites [38, 40] so that therapy can be directed more precisely with personalized approaches based on molecular taxonomy.

Since micrometastasis is detected only occasionally in NSLNs from the CLND specimens, it has been argued that CLND is not required after a positive SLN biopsy. In general, each NSLN is examined by one hemotoxylin-eosin section. Thus, the lack of more extensive immunohistochemical staining of multiple sections for NLSNs has been assumed to result in low yield of positive NLSNs. Holt-kamp et al. have launched a study to examine a total of 21 tumor-negative CLND specimens from 20 patients with SLN micrometasis less than 0.1 mm in diameter using 5 additional sections stained with/for H&E, S-100, HMB45, Melan-A and H&E. One out of 20 patients was found to have additional micrometastasis in the NSLN. The authors admit that the risk of NSLN involvement with micrometastasis is low in this selective group of patients with SLN micrometastasis of only less than 0.1 mm, they maintain that nodal resection may be the safest alternative for patients with SLN

micrometastasis [41]. No such detailed studies with multiple sections for NSLNs for patients with SLN micrometastasis larger than 0.1 mm. Perhaps, the NSLN positivity rate may go up with increasing size of SLN micrometastasis.

Recently, the German Dermatologic Oncology Group (DeCOG)-SLT trial has completed a phase III study which randomized 483 patients with a positive SLN biopsy to either CLND or nodal observation. The results showed that CLND following a positive SLN biopsy did not pro-long distant metastasis-free, recurrence-free survival or improved overall survival in positive SLN patients when compared with the cohort having nodal observation only with a median follow-up of 35 months. Most of the patients in this study have a low tumor burden in SLNs not exceeding a diameter of 1 mm (311; 66%). Comparing observation versus CLND in patients with melanoma with single cells or micrometastases, the CLND group showed better regional nodal basin control. On the basis of the findings from the DeCOG-SLT trial, CLND may not be indicated in melanoma patients with micrometastases, at least those with single cells or mircometastases, 1 mm in size or smaller [42]. The DeCOG-SLT trial data may be criticized for lack of large number of enrolled patients and its median follow-up period is relatively short. The long-awaited MSLT II clinical trial results have just been published [43]. Although immediate CLND decreased the regional disease recurrence rate and provided useful prognostic information, it did not increase melanoma-specific survival among patients with sentinel-node metastases. One critique is that the SLN tumor burden was quite low with a median diamter of about 0.6 mm. In fact, about three quarters of the SLN-positive patients had a negative CLND, thus, potentially diluting the therapeutic effect. In addition to SLN status, other features such as primary melanoma sites, heterogeneity of micrometastases and melanoma thickness may influence recurrence and survival. Data from EORTC 1208 MiniTub registration study may shed additional light to these issues (EORTC protocol 1208-MG, NCT01942603).

In this study, we have shown that about 20% of the adult patients with a positive SLN biopsy undergoing CLND have additional lymph nodes in the NSLN compartment, which carry a worse prognosis. The orderly progression of metastasis from the SLN to the NSLN compartment [44] has been firmly established in this study. Thus, the SLN compartment in the regional nodal basin draining the primary melanoma may serve as an important gateway for metastasis to the non-SLN compartment and beyond to the systemic sites.

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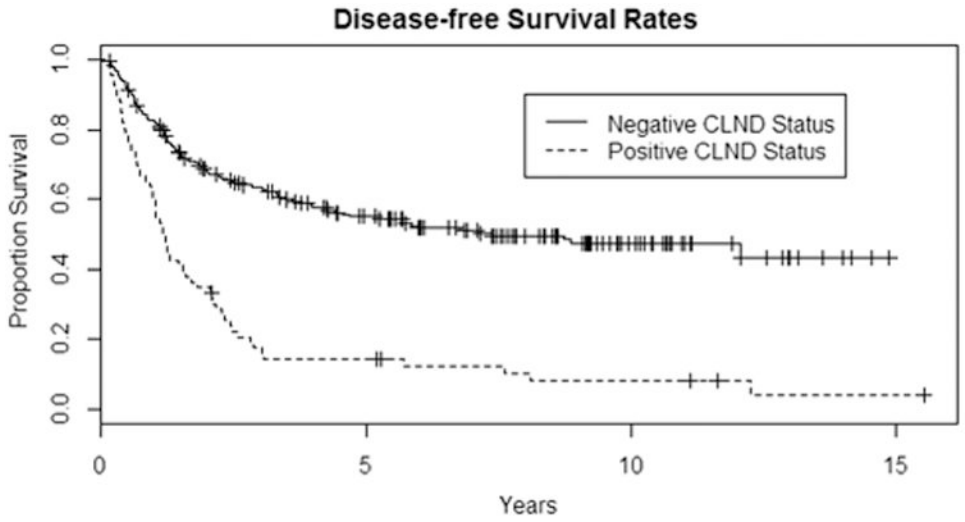

Fig. 1.

Kaplan–Meier curves to show that the negative-CLND group has a much better disease-free survival than the positive-CLND group ($p<0.0001$)

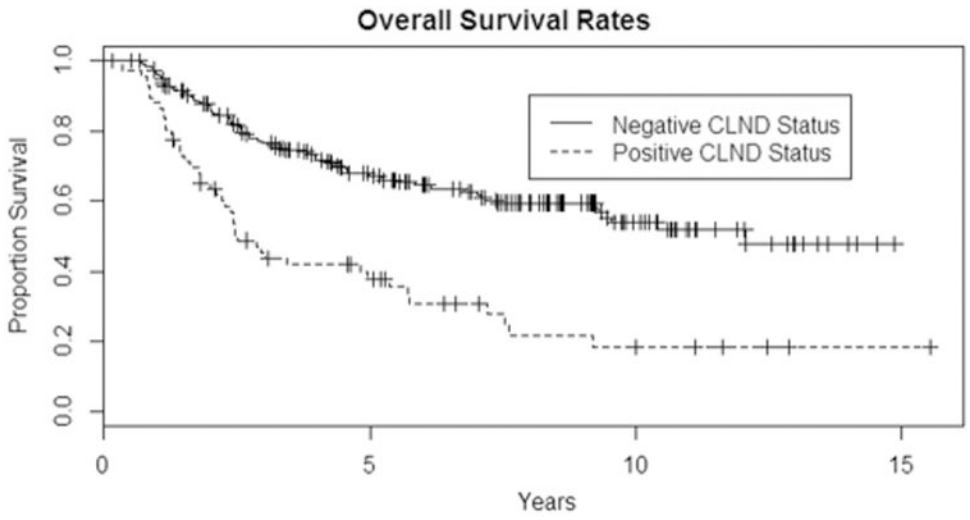

Fig. 2.

Kaplan–Meier curves to show that the negative-CLND group has a much better overall survival than the positive-CLND group (p = 0.0001)

Table 1
Clinical and histologic features comparing CLND positive and negative patients

	CLND− (N = 225)	CLND+ (N = 66)	Total (N = 291)	p value
Age				0.9284
Mean	52.1	51.9	52.0	
SD	15.7	15.9	15.7	
Range	18.1–87.2	18.3–82.4	18.1–87.2	
Age group				0.9371
<60	155 (69%)	47 (71%)	202 (69%)	
60–75	48 (21%)	13 (20%)	61 (21%)	
75+	22 (10%)	6 (9%)	28 (10%)	
Gender				0.0011
Male	152 (68%)	30 (45%)	182 (63%)	
Female	73 (32%)	36 (55%)	109 (37%)	
Ethnicity				0.1515
White	190 (84%)	53 (80%)	243 (84%)	
African-American	0 (0%)	1 (2%)	1 (0.3%)	
Asian	3 (1%)	0 (0%)	3 (1%)	
Other	1 (0.4%)	1 (2%)	2 (0.7%)	
Breslow thickness (mm)				<0.0001
Mean	2.93	4.75	3.32	
SD	2.35	3.15	2.64	
Range	0.5–9.6	0.7–6.0	0.5–9.6	
Breslow thickness group				0.0001
<2.00	69 (31%)	5 (8%)	74 (25%)	
2.00–2.99	41 (18%)	10 (15%)	51 (18%)	
3.00–3.99	17 (8%)	7 (11%)	24 (8%)	
≥4.00	37 (16%)	23 (35%)	60 (21%)	
Clark level group				0.0429
II/III	51 (23%)	8 (12%)	59 (20%)	
IV/V	149 (66%)	53 (80%)	202 (69%)	
Ulceration				0.0002
Present	71 (32%)	39 (59%)	110 (38%)	
Absent	110 (49%)	19 (28%)	129 (44%)	
Lymphovascular invasion				0.0052
Present	34 (15%)	22 (33%)	56 (19%)	
Absent	102 (45%)	25 (38%)	127 (44%)	
Tumor regression				0.4651
Present	16 (7%)	3 (5%)	19 (7%)	
Absent	126 (56%)	38 (58%)	164 (56%)	
Microsatellitosis				0.0369
Present	14 (6%)	11 (17%)	25 (9%)	

	CLND− (N = 225)	CLND+ (N = 66)	Total (N = 291)	p value
Absent	111 (49%)	35 (53%)	146 (50%)	
Mitotic rate				0.7916
<1.0	3 (1%)	1 (2%)	4 (1%)	
≥1.0	151 (67%)	37 (56%)	188 (65%)	

Not all patients had full complement of data points