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Patients with sentinel lymph node positive melanoma: Who needs completion lymph node dissection?

Darryl Schuitevoerder [a], Irvan Bubic [b], Jeanine Fortino [c], Kristen P. Massimino [a, c], John T. Vetto [a, c, *]

[a] Oregon Health & Science University, Department of Surgery, Portland, OR, USA
[b] Oregon Health & Science University, School of Medicine, Portland, OR, USA
[c] Oregon Health & Science University, Division of Surgical Oncology, Portland, OR, USA

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ABSTRACT

Introduction: Completion lymph node dissection (CLND) for melanoma after positive sentinel lymph node biopsy (SLNB) was recently shown to improve regional but not overall survival, likely due to the majority of patients harboring no further nodal disease. We sought to determine predictors of non-sentinel node (NSN) positivity.
Methods: Retrospective review of prospectively collected data on melanoma patients undergoing SLNB.
Results: 116 patients underwent 119 CLNDs. The incidence of NSN positivity was 17.6%; the average number of positive NSNs in those cases was 1.5. Cervical and inguinofemoral location were most likely to yield positive NSN(s) (40% each). Conversely, the axilla was least likely at 18% ($p < 0.001$). The average number of nodes harvested was 13 for NSN negative cases and 20 for NSN positive cases ($p = 0.005$). Tumor thickness increased the probability of positive NSN(s) (OR 1.2, $p = 0.02$).
Conclusions: Tumor thickness and nodal basin were predictors of NSN metastasis, factors that could help determine which patients may benefit from CLND. Further, CLNDs with fewer nodes may inadequately clear residual nodal disease.

1. Introduction

Since being introduced by Morton in the early 1990's, sentinel lymph node biopsy (SLNB) for cutaneous melanoma has become the standard of care. Sentinel lymph node status has been shown to be the most important prognostic factor and remains the mainstay for accurate staging and determination of further treatment.[1,2] The first Multicenter Selective Lymphadenectomy Trial (MSLT-I) confirmed the importance of SLNB as a staging test and demonstrated that biopsy-based management improves melanoma-specific survival for patients with positive sentinel nodes for intermediate-thickness (1.2–3.5 mm) or thick (>3.5 mm) primary lesions.[1] However, among patients with positive sentinel nodes, there continues to be a large discrepancy in survival rates, ranging from 30% to 90%.[3] Furthermore, van der Ploeg et al. found that the overall survival rate at 5 years for sentinel lymph node (SLN)-positive patients with minimal tumor burden (<0.1 mm) was nearly identical to that of SLN-negative patients (91% and 90%, respectively), suggesting that those patients would not benefit from a completion lymph node dissection (CLND).[4] Never the less up until recently CLND for positive SLNB has been the standard of care.

Recent publication of two randomized controlled trials, the DeCOG – SLT trial and the second Multicenter Selective Lymphadenectomy Trial (MSLT-II), have shown that CLND compared to observation in patients with positive SLNB was not associated with increased overall survival (OS).[5,6] However, the larger and more robust of the two trials, the MSLT-II, did show that CLND provides valuable prognostic information as well as improved regional disease control (improved disease free survival [DFS]). One important factor revealed by CLND is the pathologic status of non-sentinel lymph nodes, which was determined by MSLT-II to be a significant prognostic factor (hazard ratio for death, 1.78)[6]. Furthermore, while the difference in overall survival between dissection and observation groups was not significant, the trial did show that region-specific nodal recurrence was reduced by nearly 70% in the

* Corresponding author. Oregon Health & Science University, Department of Surgery, Division of Surgical Oncology, 3181 S.W. Sam Jackson Park Rd., Mail code L619, Portland, OR 97239, USA.
E-mail address: vettoj@ohsu.edu (J.T. Vetto).

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dissection group, which led to a decreased overall risk of recurrence.[6]

When considering CLND, the associated morbidity must be taken into account and carefully weighed against potential benefits. The reported incidence of complications after CLND varies widely, 11.5–73%,[6–11] and appears to be related the nodal basin dissected, with a higher rate of complications after CLND of the groin.[9,10,12] While the prognostic importance of non-sentinel lymph node (NSN) status has been established, the role of CLND continues to be defined. Our study sought to determine predictors of NSN positivity to aid in determining appropriate management, both surgical and medical, of patients with positive sentinel lymph nodes.

2. Methods

We performed a retrospective review of our prospectively collected, University-based database of melanoma patients undergoing SLNB (OHSU IRB #1108). All patients who underwent SLNB for cutaneous melanoma from 1999 to 2017 were included. The indication for SLNB was based on the National Comprehensive Cancer Network guidelines in accordance with the current standard of care. All patients with a positive SLNB were recommended to undergo CLND. Patients with clinically positive nodes as well as those patients with positive SLN(s) who did not undergo CLND were excluded.

Our process of identifying and removing sentinel nodes using a dual dye technique and the "10% rule has been previously described, as has our pathologic evaluation of the SLNB specimen[13] which is consistent with a modification of the Augsburg consensus.[14] It involves serial sectioning of the nodes followed by staining with both hematoxylin/eosin and immunohistochemical stains (S100, melanA, HMB45, Sox10, and Ki-67), using an automated immunostainer (Ventana Medical Systems, Tucson, AZ).

For statistical analysis we used SPSS version 22 (IBM, Armonk, NY). Student's T-test was used to compare continuous variables and either Chi-square or Fisher's exact test was used to compare categorical variables. Kaplan-Meier with log-rank test was used to determine a difference in overall and disease free survival between those patients with and without positive NSNs. Logistic regression analysis was performed to determine predictors of positive non-sentinel nodes.

3. Results

3.1. Positive lymph node rate

During the observed time period, 1271 patients underwent SLNB of which 142 (11.2%) had positive SLN(s). Excluding T1 lesions, the percentage of patients with positive SLNs increased to 16.7%. Of the 142 node positive patients, 116 (82%) underwent 119 CLNDs. The incidence of NSN positivity in the CLND specimen was 17.6%, and the average number of NSNs harboring metastasis in those cases was 1.5.

3.2. Determinants of positive NSNs

In those patients with positive NSNs, there were no statistical differences in patient age, sex, presence of ulceration, mitoses, regression or lymphovascular invasion in the primary tumor compared to those patients without positive NSNs. Conversely, patients with positive NSN(s) had thicker primary tumors (4.4 vs 3.1 mm, $p = 0.05$) compared to those without positive NSNs on CLND (Table 1). There was no statistically significant difference in the number of positive SLNs in patients with positive and negative NSNs (1.52 vs 1.29, $p = 0.13$). The regions most likely to yield positive NSN(s) were the cervical and inguinofemoral nodal basins at 40% each. Conversely, CLND specimens from axilla were least likely, with 18% yielding positive NSN(s) ($p < 0.001$ on univariable analysis). The average number of nodes harvested was 13 for NSN negative cases and 20 for NSN positive cases ($p = 0.005$) (Table 2). The size of this discrepancy was not significantly different between anatomic locations ($p = 0.85$), with the number of nodes harvested for positive NSN cases being greater than negative NSN in all 3 nodal basins examined.

Table 1
Patient demographics and tumor features; Negative NSN vs Positive NSN.

Characteristics	Negative NSN N = 98	Positive NSN N = 21	*p*-Value
Age	52.1	58	0.15[a]
Gender			
Male	45 (46%)	9 (45%)	0.8[b]
Female	53 (54%)	12 (55%)	
Breslow Thickness			
Average (mm)	3.1	4.4	0.05[a]
Ulceration			
Yes	41 (42%)	8 (36%)	0.72[b]
No	47 (48%)	11 (50%)	
Mitotic rate			
$<1/mm^2$	5 (5%)	0 (0%)	0.64[c]
$\geq 1/mm^2$	73 (74%)	7 (36%)	
Regression			
Yes	8 (8%)	2 (9%)	0.42[c]
No	23 (23%)	3 (14%)	
LVI			
Yes	6 (6%)	2 (9%)	0.36[c]
No	32 (33%)	5 (23%)	

NSN: Non-sentinel node; LVI: Lymphovascular invasion.
*Unknown values not included.
[a] Student's T-Test.
[b] Chi-square test.
[c] Fisher's exact test.

On multivariable logistic regression analysis, tumor thickness increased the probability of positive NSN(s) (OR 1.2, CI 1.02–1.46, $p = 0.02$). Additionally, CLND of axillary lymph nodes was less likely to yield positive NSN(s) than CLND of inguinofemoral nodes (OR 0.14, CI 0.03–0.71, $p = 0.017$) (Table 3). The remainder of patient, tumor, and nodal factors were not significantly different in patients with or without positive NSN(s) on multivariable analysis.

3.3. Survival

The average length of follow up was 5 years. The median OS for patients without NSN metastasis was 9.5 years compared to 4.3 for those patients with NSN metastasis. However, this did not reach statistical significance ($p = 0.244$ on log rank test [Fig. 1a]). Patients with negative NSNs were more likely to have regional recurrence (14 vs 5%), while patients with NSN metastases were more likely to have distant recurrence (13 vs 33%). However, this difference was not significant ($p = 0.14$). Median disease free survival for patients without NSN metastasis was not reached, while the median DFS for patients with positive NSN was 3 years. Similarly to OS, this difference did not reach statistical significance ($p = 0.305$ on log rank test [Fig. 1b]).

4. Discussion

The MSLT-II trial, which randomized melanoma patients with a positive sentinel node to get or not get a CLND, showed no impact of CLND on OS. As noted by the MSLT-II authors, the ability of the CLND arm of that study to show such an effect was diluted by the

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