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ORIGINAL ARTICLE – MELANOMA

# Characteristics Associated with Pathologic Nodal Burden in Patients Presenting with Clinical Melanoma Nodal Metastasis

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## ABSTRACT

**Background.** Nodal observation is safe for patients with microscopic melanoma metastasis in a sentinel lymph node (LN). Complete LN dissection (CLND) remains the standard of care for patients with clinically evident LN (cLN) metastases, even though about 40% have only one pathologic LN (pLN). We sought to identify clinical features associated with having one pLN among patients with cLNs.

**Methods.** Patients at three melanoma centers who underwent CLND for cLNs were identified. Clinicopathologic and imaging characteristics associated with one pLN were determined by multivariable logistic regression and classification tree analysis.

**Results.** Of 190 patients, 90 (47.4%) had one pLN and 100 (52.6%) had more than one pLN. By multivariable logistic regression, extremity versus truncal primary (odds ratio [OR] 2.15, $p = 0.012$), axillary versus superficial inguinal location (OR 3.89, $p = 0.009$), and preoperative cross-sectional imaging demonstrating more than one versus one cLN (OR 17.1, $p < 0.001$) were associated with more than one pLN. The negative predictive value for additional pathologic nodal disease of preoperative imaging was 70.9%, increasing to 74.4% for positron emission tomography/computed tomography. In the subgroup of patients with one cLN, the classification tree identified two groups with $< 10\%$ risk of additional pLNs: (1) Breslow thickness $> 6.55$ mm ($n = 17$); and (2) if unknown primary or Breslow thickness $\leq 6.55$ mm, then LN diameter $> 1.8$ cm in the inguinal location ($n = 22$).

**Conclusion.** The majority of patients with one cLN from melanoma by preoperative imaging will harbor no additional pathologic nodes on CLND. Safety of nodal observation after clinical nodal excision in these patients, particularly in an era of effective adjuvant therapies, deserves prospective evaluation.

The surgical management of regional lymph node (LN) metastasis in stage III melanoma has evolved in recent years. Historically, complete LN dissection (CLND) was routinely recommended for all patients with melanoma nodal metastases; however, CLND can be associated with significant morbidity that negatively impacts quality of life, including pain, decreased mobility, psychological distress, and chronic lymphedema.[1–5]

In patients with clinically occult nodal disease detected by sentinel LN biopsy (SLNB), two randomized trials recently showed no overall survival (OS) benefit with immediate CLND compared with nodal observation.[2,6]

Minyoung Kwak, Yun Song, Craig L. Slingluff Jr., and Giorgos C. Karakousis have contributed equally to the completion of this study.

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Thus, guidelines from the National Comprehensive Cancer Network now support observation rather than CLND for these patients;[7] however, CLND is still routinely recommended for patients with macroscopic, clinically evident LN (cLN) metastases.[7] Approximately 40% of patients with cLNs have only one pathologic LN (pLN) on CLND[8,9] and are therefore at low risk for subsequent recurrence. Moreover, there are limited data supporting a survival benefit with a more extensive lymphadenectomy in patients with cLNs. Practice changes in the management of patients with a positive SLNB demonstrate that in the absence of a survival benefit, clinicians are willing to accept a 15–20% risk of additional occult in-basin nodal disease when patients are being closely monitored in order to spare a majority of patients the morbidity of unnecessary surgery. Similarly, there may be subgroups of patients with cLNs with relatively low risk of harboring additional occult metastases for whom close nodal observation after removal of clinically evident disease may be a reasonable option, particularly in an era of effective systemic therapies.

The purpose of the current study was to identify preoperative characteristics associated with one pLN among patients presenting with clinically evident melanoma nodal metastases. We hypothesized that using preoperative cross-sectional imaging, along with other clinicopathologic factors, patient groups at low risk of more than one pLN can be identified.

## METHODS

### *Data Source and Patient Selection*

Patients 18 years of age or older diagnosed with resectable cLNs who underwent CLND between 1993 and 2017 at three academic melanoma centers were identified. Clinical nodal disease was defined as macroscopic LN metastasis diagnosed by physical examination, imaging, cytology, or core or excisional biopsies. CLNDs were performed by specialized surgical oncologists at each institution. For patients with groin metastases, superficial or ilioinguinal dissections were performed at the discretion of the surgeons. Patients with microscopic nodal disease identified by SLNB were excluded. Additionally, patients were excluded for the following reasons: (1) no preoperative cross-sectional imaging (computed tomography [CT] or positron emission tomography [PET]/CT); (2) previous CLND in the same nodal basin; (3) previous positive SLNB in the same LN basin for which a CLND was not performed; (4) neoadjuvant immune checkpoint (ICB) or BRAF/MEK (BRAF/MEKi) pathway inhibitors prior to CLND; and (5) insufficient or missing clinical data. The study was reviewed and approved by the Institutional Review Board at each institution. All de-identified data were compliant with the Health Insurance Portability and Accountability Act.

### *Variables Analyzed*

The criteria, defined a priori, for identifying cLNs as suspicious included fluorodeoxyglucose (FDG) avidity on PET/CT, or LN cross-sectional diameter $\geq$ 0.95 cm on CT. FDG avidity and diameter were extracted from the original radiology report, or measured by the authors if the information was missing. The primary binary outcome was the presence of one, or more than one, pLNs. The number of pLNs was extracted from pathology reports and included the total number of metastatic LNs removed by excisional biopsy (if performed) and in the CLND specimen.

Clinicopathologic variables analyzed included age at the time of CLND, sex, primary tumor characteristics (primary site or unknown primary, Breslow thickness, ulceration, mitotic rate, tumor-infiltrating lymphocytes, regression, and lymphovascular invasion or neurotropism), previous SLNB, LN basin involved, timing of clinical nodal disease presentation (initial diagnosis or recurrence), preoperative imaging modality utilized, imaging characteristics (LN dimensions, standardized uptake value [SUV]), and preceding or concurrent in-transit disease. LN cross-sectional area was estimated as an ellipse if two dimensions were available, and as a circle if only one dimension was provided. Missing data for demographic, clinicopathologic, and imaging characteristics were included as a separate category.

Disease-free survival (DFS) was defined as the time (in months) from CLND to disease recurrence. Patients who had no recurrences were censored at the time of last follow-up. OS was defined as the time from CLND to death related to any cause, with censoring at the time of last follow-up for patients who were alive.

### *Statistics*

Categorical variables are described with frequencies, and continuous variables are described with medians and interquartile ranges (IQRs). Univariate comparisons used Pearson's Chi-square or Fisher's exact test, as appropriate, for categorical variables, and the Wilcoxon rank-sum test for continuous variables. Multivariable logistic regression was used to identify factors associated with finding one versus more than one pLN. The initial model utilized all available clinicopathologic factors, with sequential removal of non-significant variables ($p > 0.05$), to arrive at the final reduced logistic regression model. Model

goodness of fit was tested with the Hosmer–Lemeshow test using five groups. Because preoperative imaging was strongly associated with pathologic outcome, further risk stratification was performed in the subgroup of patients with one cLN using recursive partitioning to develop a classification tree. Primary tumor Breslow thickness (as a continuous variable), tumor-infiltrating lymphocytes, regression, LN basin involved, preoperative imaging modality, largest LN dimension (grouped in tertiles), largest LN area (grouped in tertiles), SUV (grouped in tertiles), and in-transit disease were entered into the initial classification tree analysis. Constraints used included (1) a group must contain $\geq$ 20 patients to be a candidate for splitting; (2) each of the two groups resulting from a split must include $\geq$ 10 patients; and (3) the tree was limited to three levels to avoid overfitting. DFS and OS curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Statistical analyses were performed using R version 3.5.1.[10] Salford Predictive Model version 8.2,[11] and SAS/STAT® software.[12] *P* values $< 0.05$ were considered statistically significant, and all tests were two-sided.

## RESULTS

### *Baseline Characteristics*

Of the 190 study patients, 90 (47.4%) had one pLN and 100 (52.6%) had more than one pLN (Table 1). The median (IQR) age at the time of CLND was 62 years (52–73). Most patients (61.1%) presented with recurrent nodal disease, while 38.9% of patients had evidence of LN metastasis at the initial melanoma diagnosis. Approximately 23.7% of patients had an unknown primary, and thus unknown primary tumor characteristics. On preoperative CT or PET/CT, 110 (57.9%) patients had one suspected cLN and 80 (42.1%) had more than one cLN. Additionally, 16.3% of patients had preceding or concurrent in-transit disease, which was treated with curative intent by surgical resection or isolated limb perfusion/infusion.

### *Characteristics Associated with Pathologic Nodal Burden*

Findings on preoperative imaging were strongly associated with pathologic outcome. Among patients with more than one cLN, 85.0% had more than one pLN on histopathologic evaluation of the CLND specimen. In contrast, 29.1% of patients with one cLN had additional nodal disease ($p < 0.001$), for a negative predictive value (NPV) of 70.9% (78/110 patients). By PET/CT, the NPV was 74.4% (64/86 patients). By multivariable logistic regression, more than one versus one cLN on imaging (odds ratio [OR] 17.1, 95% confidence interval [CI] 8.03–39.9, $p < 0.001$), extremity versus truncal primary (OR 4.26, 95% CI 1.40–13.9, $p = 0.012$), and axillary versus superficial inguinal basin (OR 3.89, 95% CI 1.43–11.3, $p = 0.009$) were associated with more than one pLN (Table 2). Other factors, such as primary tumor thickness, mitotic rates, and regression, were not associated with the outcome by multivariable analysis. Goodness of fit of the reduced multivariable logistic regression model was confirmed using the Hosmer–Lemeshow test with $p = 0.54$, indicating no evidence of poor fit.

### *Identification of Very-Low-Risk Subgroups*

The subgroup of 110 patients with one cLN on preoperative imaging was evaluated for characteristics associated with an even lower risk of additional pLNs (Fig. 1). The classification tree identified two subgroups of patients with a $< 10\%$ rate of finding more than one pLN: (1) primary tumor Breslow thickness $> 6.55$ mm ($n = 17$; 5.9% with more than one pLN, 95% CI 0.1–28.7%); and (2) if unknown primary or thickness $\leq 6.55$ mm, then LN size $> 1.8$ cm in the inguinal basin ($n = 22$; 9.1% with more than one pLN, 95% CI 1.1–29.2%). Together, these two subgroups accounted for 39 (35.5%) patients with one cLN, of whom only three (7.7%, 95% CI 1.6–20.9%, 90% CI 2.1–18.7%) patients had additional pLNs (mean 2.3 LNs [range 2–3]). In contrast, among the other 71 patients, 29 (40.8%) had more than one pLN, with a mean of 4.4 LNs (range 2–17).

### *Recurrence and Survival*

After a median follow-up time of 30.8 months (IQR 14.0–66.0), 119 (62.6%) patients developed a recurrence. The first recurrence site was the same LN basin in 26 (13.7%) patients, while the other 93 (48.9%) developed in-transit or distant disease first. The median DFS time was 13.2 months from CLND, and the 3-year DFS rate was 32.8% (95% CI 26.3–41.0%). The median OS time was 136.8 months, and the 3-year OS rate was 70.9% (95% CI 64.0–78.6%). Compared with patients with more than one cLN on preoperative imaging, those with only one cLN had a significantly longer DFS (log-rank $p = 0.008$), including a lower incidence of in-transit and distant metastases as the first event following CLND (log-rank $p = 0.043$) (Fig. 2). Patients with one cLN also experienced significantly longer OS than those with more than one cLN (log-rank $p = 0.037$).

**TABLE 1** Characteristics of 190 patients with clinically evident melanoma nodal metastases, stratified by the number of pathologic lymph nodes at the time of complete lymph node dissection

| Variable | Overall ($N$ = 190) | One pLN [$N$ = 90 (47.4%)] | More than one pLN [$n$ = 100 (52.6%)] | $p$ value |
|---|---|---|---|---|
| *Patient characteristics* | | | | |
| Age, years [median (IQR)] | 62 (52–73) | 61 (52–74) | 64 (53–72) | 0.66 |
| Sex | | | | |
| Female | 73 (38.4) | 39 (43.3) | 34 (34.0) | 0.24 |
| Male | 117 (61.6) | 51 (56.7) | 66 (66.0) | |
| *Primary tumor characteristics* | | | | |
| Primary lesion site | | | | |
| Extremity | 60 (31.6) | 25 (27.8) | 35 (35.0) | 0.64 |
| Trunk/axial | 58 (30.5) | 29 (32.2) | 29 (29.0) | |
| Head/neck | 27 (14.2) | 12 (13.3) | 15 (15.0) | |
| Melanoma of unknown primary | 45 (23.7) | 24 (26.7) | 21 (21.0) | |
| Thickness (mm) | | | | |
| $\leq$ 1.0 | 23 (12.1) | 9 (10.0) | 14 (14.0) | 0.54 |
| $>$ 1.0–2.0 | 35 (18.4) | 14 (15.6) | 21 (21.0) | |
| $>$ 2.0 | 73 (38.4) | 36 (40.0) | 37 (37.0) | |
| Unknown primary/not reported | 59 (31.1) | 31 (34.4) | 28 (28.0) | |
| Ulceration | | | | |
| Absent | 61 (32.1) | 30 (33.3) | 31 (31.0) | 0.94 |
| Present | 60 (31.6) | 28 (31.1) | 32 (32.0) | |
| Unknown primary/not reported | 69 (36.3) | 32 (35.6) | 37 (37.0) | |
| Mitoses | | | | |
| Not mitogenic | 6 (3.2) | 3 (3.4) | 3 (3.0) | 0.93 |
| Mitogenic ($\geq$ 1 per mm$^2$) | 107 (56.3) | 52 (57.8) | 55 (55.0) | |
| Unknown primary/not reported | 77 (40.5) | 35 (38.9) | 42 (42.0) | |
| Tumor-infiltrating lymphocytes | | | | |
| Absent | 20 (10.5) | 11 (12.2) | 9 (9.0) | 0.58 |
| Present | 87 (45.8) | 38 (42.2) | 49 (49.0) | |
| Unknown primary/not reported | 83 (43.7) | 41 (45.6) | 42 (42.0) | |
| Regression | | | | |
| Absent | 89 (46.8) | 47 (52.2) | 42 (42.0) | 0.23 |
| Present | 16 (8.4) | 5 (5.6) | 11 (11.0) | |
| Unknown primary/not reported | 85 (44.7) | 38 (42.2) | 47 (47.0) | |
| Lymphovascular invasion or neurotropism | | | | |
| Absent | 95 (50.0) | 50 (55.6) | 45 (45.0) | 0.060 |
| Present | 18 (9.5) | 4 (4.4) | 14 (14.0) | |
| Unknown primary/not reported | 77 (40.5) | 36 (40.0) | 41 (41.0) | |
| Previous sentinel LN biopsy | 65 (34.2) | 28 (31.1) | 37 (37.0) | 0.48 |
| *Clinical nodal disease* | | | | |
| Presentation | | | | |
| Nodal metastasis at initial melanoma diagnosis | 74 (38.9) | 37 (41.1) | 37 (37.0) | 0.67 |
| Nodal recurrence | 116 (61.1) | 53 (58.9) | 63 (63.0) | |
| Time to nodal recurrence, months [median (IQR)] ($N$ = 116 with recurrence) | 20.5 (10.9–59.7) | 20.5 (11.0–66.2) | 20.6 (11.4–50.2) | 0.97 |
| LN basin | | | | |
| Axillary | 75 (39.5) | 33 (36.7) | 42 (42.0) | 0.38 |

**TABLE 1** continued

| Variable | Overall ($N$ = 190) | One pLN [$N$ = 90 (47.4%)] | More than one pLN [$n$ = 100 (52.6%)] | $p$ value |
|---|---|---|---|---|
| Superficial inguinal | 64 (33.7) | 34 (37.8) | 30 (30.0) | |
| Deep inguinal/pelvic | 11 (5.8) | 3 (3.3) | 8 (8.0) | |
| Cervical and/or parotid | 40 (21.1) | 20 (22.2) | 20 (20.0) | |
| Method of diagnosis | | | | |
| Imaging only | 22 (11.6) | 10 (11.1) | 12 (12.0) | 0.65 |
| Cytology or core biopsy | 119 (62.6) | 54 (60.0) | 65 (65.0) | |
| Excisional biopsy | 49 (25.8) | 26 (28.9) | 23 (23.0) | |
| Imaging modality | | | | |
| CT | 41 (21.6) | 17 (18.9) | 24 (24.0) | 0.50 |
| PET/CT | 149 (78.4) | 73 (81.1) | 76 (76.0) | |
| Number of clinically evident LNs | | | | |
| 1 | 110 (57.9) | 78 (86.7) | 32 (32.0) | < 0.001 |
| > 1 | 80 (42.1) | 12 (13.3) | 68 (68.0) | |
| Largest LN size, cm | | | | |
| < 1.8 | 47 (24.7) | 25 (27.8) | 22 (22.0) | 0.59 |
| 1.8–3.0 | 53 (27.9) | 22 (24.4) | 31 (31.0) | |
| ≥ 3.0 | 72 (37.9) | 33 (36.7) | 39 (39.0) | |
| Not reported | 18 (9.5) | 10 (11.1) | 8 (8.0) | |
| Largest LN area ($cm^2$) | | | | |
| < 2.0 | 46 (24.2) | 26 (28.9) | 20 (20.0) | 0.31 |
| 2.0–5.4 | 56 (29.5) | 22 (24.4) | 34 (34.0) | |
| ≥ 5.4 | 70 (36.8) | 32 (35.6) | 38 (38.0) | |
| Not reported | 18 (9.5) | 10 (11.1) | 8 (8.0) | |
| Highest SUV | | | | |
| < 8.8 | 38 (20.0) | 16 (17.8) | 22 (22.0) | 0.67 |
| 8.8–13.8 | 31 (16.3) | 17 (18.9) | 14 (14.0) | |
| ≥ 13.8 | 44 (23.2) | 19 (21.1) | 25 (25.0) | |
| Not reported/PET not performed | 77 (40.5) | 38 (42.2) | 39 (39.0) | |
| Preceding or concurrent in-transit metastasis | 31 (16.3) | 11 (12.2) | 20 (20.0) | 0.21 |

Data are expressed as $n$ (%) unless otherwise specified

*IQR* interquartile range, *CT* computed tomography, *PET* positron emission tomography, *SUV* standardized uptake value, *pLN* pathologic lymph nodes, *LN* lymph node

## DISCUSSION

Identifying clinical factors associated with pathologic nodal burden in patients with clinically evident stage III melanoma introduces a novel opportunity for risk stratification, and potentially sparing those with a low nodal disease burden from a potentially morbid operation. Evaluating patients with melanoma cLNs from three academic institutions, the present study found preoperative imaging, among other clinical factors, to be strongly associated with pathologic outcome. Furthermore, among those with only one cLN by imaging, patients at even lower risk of additional pathologic disease may be identified.

Predictors of sentinel LN status have been extensively studied, identifying younger age, increasing thickness, ulceration, lymphovascular invasion, and mitotic rate to be associated with nodal positivity.[13–17] To the authors' best knowledge, no studies have specifically evaluated characteristics associated with the extent of pathologic nodal burden in patients with cLN metastases. Using multivariable logistic regression, preoperative imaging was identified to be strongly associated with pathologic outcome. The overall NPV for additional pathologic nodal disease was 70.9%, increasing to 74.4% if a PET/CT was obtained. Furthermore, the number of cLNs on imaging has significant prognostic value and was associated with DFS and OS.

**TABLE 2** Univariable and reduced multivariable logistic regression analyses for identifying more than one pathologic lymph node

| Variable | Univariable [OR (95% CI)] | *p* value | Multivariable [OR (95% CI)] | *p* value |
|---|---|---|---|---|
| Age (years) | | | | |
| < 65 | Reference | | | |
| ≥ 65 | 1.22 (0.69–2.18) | 0.50 | | |
| Sex | | | | |
| Female | Reference | | | |
| Male | 1.48 (0.83–2.68) | 0.19 | | |
| Primary site | | | | |
| Trunk/axial | Reference | | Reference | |
| Extremity | 1.40 (0.68–2.91) | 0.36 | 4.26 (1.40–13.9) | 0.012 |
| Head/neck | 1.25 (0.50–3.17) | 0.63 | 2.15 (0.35–14.4) | 0.41 |
| Unknown primary | 0.88 (0.40–1.91) | 0.74 | 1.33 (0.47–3.79) | 0.59 |
| Primary Breslow thickness (mm) | | | | |
| ≤ 1.0 | Reference | | | |
| > 1.0–2.0 | 0.96 (0.32–2.82) | 0.95 | | |
| > 2.0 | 0.66 (0.25–1.70) | 0.40 | | |
| Unknown primary/not reported | 0.58 (0.21–1.53) | 0.28 | | |
| Ulceration | | | | |
| Absent | Reference | | | |
| Present | 1.11 (0.54–2.26) | 0.78 | | |
| Unknown primary/not reported | 1.12 (0.56–2.24) | 0.75 | | |
| Mitoses | | | | |
| Absent | Reference | | | |
| Present (≥ 1 mitoses) | 1.06 (0.19–5.94) | 0.95 | | |
| Unknown primary/not reported | 1.20 (0.21–6.84) | 0.83 | | |
| Tumor-infiltrating lymphocytes | | | | |
| Absent | Reference | | | |
| Present | 1.58 (0.59–4.28) | 0.36 | | |
| Unknown primary/not reported | 1.25 (0.47–3.41) | 0.65 | | |
| Tumor regression | | | | |
| Absent | Reference | | | |
| Present | 2.46 (0.82–8.35) | 0.12 | | |
| Unknown primary/not reported | 1.38 (0.76–2.52) | 0.29 | | |
| Lymphovascular invasion or neurotropism | | | | |
| Absent | Reference | | | |
| Present | 3.89 (1.29–14.5) | 0.024 | | |
| Unknown primary/not reported | 1.27 (0.69–2.32) | 0.44 | | |
| Previous sentinel LN biopsy | | | | |
| No | Reference | | | |
| Yes | 1.30 (0.71–2.39) | 0.39 | | |
| Presentation | | | | |
| Clinical LN metastasis at initial presentation | Reference | | | |
| Clinical LN recurrence | 1.19 (0.66–2.14) | 0.56 | | |
| LN basin | | | | |
| Superficial inguinal | Reference | | Reference | |
| Deep inguinal/pelvic | 1.44 (0.74–2.83) | 0.28 | 1.88 (0.37–11.2) | 0.46 |
| Axillary | 3.02 (0.79–14.8) | 0.12 | 3.89 (1.43–11.3) | 0.009 |
| Cervical and/or parotid | 1.13 (0.51–2.51) | 0.76 | 2.04 (0.37–10.8) | 0.40 |

**TABLE 2** continued

| Variable | Univariable [OR (95% CI)] | *p* value | Multivariable [OR (95% CI)] | *p* value |
|---|---|---|---|---|
| Method of diagnosis | | | | |
| Imaging only | Reference | | | |
| Cytology or core biopsy | 1.00 (0.39–2.50) | > 0.99 | | |
| Excisional biopsy | 0.74 (0.26–2.02) | 0.55 | | |
| Imaging modality | | | | |
| CT | Reference | | | |
| PET/CT | 0.74 (0.36–1.48) | 0.39 | | |
| Number of clinically evident LNs on imaging | | | | |
| 1 | Reference | | Reference | |
| > 1 | 13.8 (6.8–30.1) | < 0.001 | 17.1 (8.03–39.9) | < 0.001 |
| Largest LN size (cm) | | | | |
| < 1.8 | Reference | | | |
| 1.8–3.0 | 1.60 (0.73–3.56) | 0.24 | | |
| ≥ 3.0 | 1.34 (0.64–2.82) | 0.43 | | |
| Not reported | 0.91 (0.30–2.71) | 0.86 | | |
| Largest LN area ($cm^2$) | | | | |
| < 2.0 | Reference | | | |
| 2.0–5.4 | 2.01 (0.92–4.49) | 0.084 | | |
| ≥ 5.4 | 1.54 (0.73–3.29) | 0.26 | | |
| Not reported | 1.04 (0.34–3.12) | 0.94 | | |
| Highest reported SUV | | | | |
| < 8.8 | Reference | | | |
| 8.8–13.8 | 0.60 (0.23–1.55) | 0.29 | | |
| ≥ 13.8 | 0.96 (0.40–2.31) | 0.92 | | |
| Not reported/no PET-CT | 0.75 (0.34–1.63) | 0.47 | | |
| Preceding/concurrent in-transit metastasis | | | | |
| No | Reference | | | |
| Yes | 1.80 (0.82–4.11) | 0.15 | | |

*OR* odds ratio, *CI* confidence interval, *CT* computed tomography, *PET* positron emission tomography, *SUV* standardized uptake value, *LN* lymph node

In further risk stratification of patients with one cLN by imaging, subgroups with even lower rates of more than one pLN were identified. These subgroups included patients with primary tumors > 6.55 mm and, if unknown primary or < 6.55 mm, then LN size > 1.8 cm in the inguinal basin. These results may seem counterintuitive as greater primary thickness and LN size are often viewed as poor prognostic factors. However, it should be noted that the classification tree only included patients thought to have one cLN; thus, the outcome evaluated was not total pathologic nodal burden per se, but rather additional factors that would make the imaging findings more or less reliable. This is a subtly different question than the one typically presented in the literature. That is, thickness and larger LN size among the select group with one cLN by imaging may serve as factors that strengthen the verity of the imaging findings. It is quite possible that although patients with very thick primaries[18] and larger tumor burden within LNs (e.g. macroscopic vs. microscopic metastases)[19] are at higher risk overall, that risk may be declared early as distant metastases or extensive nodal disease. Finding only one cLN on imaging may therefore counter intuitively be more concordant with pathologic outcome in this subgroup. An advantage of using the classification tree is that the recursive partitioning algorithm identifies the best cut-points based on data distribution, and thus does not rely on the investigators' preconceptions, allowing for potentially novel findings.

Appropriate risk stratification of patients with melanoma cLNs would allow for more informed preoperative discussions and potentially identify patients who could safely avoid additional surgery in the form of CLND. Similar to the evolution in care that has followed the MSLT-2 and DeCOG trials for patients with positive sentinel LNs,[2,6] it

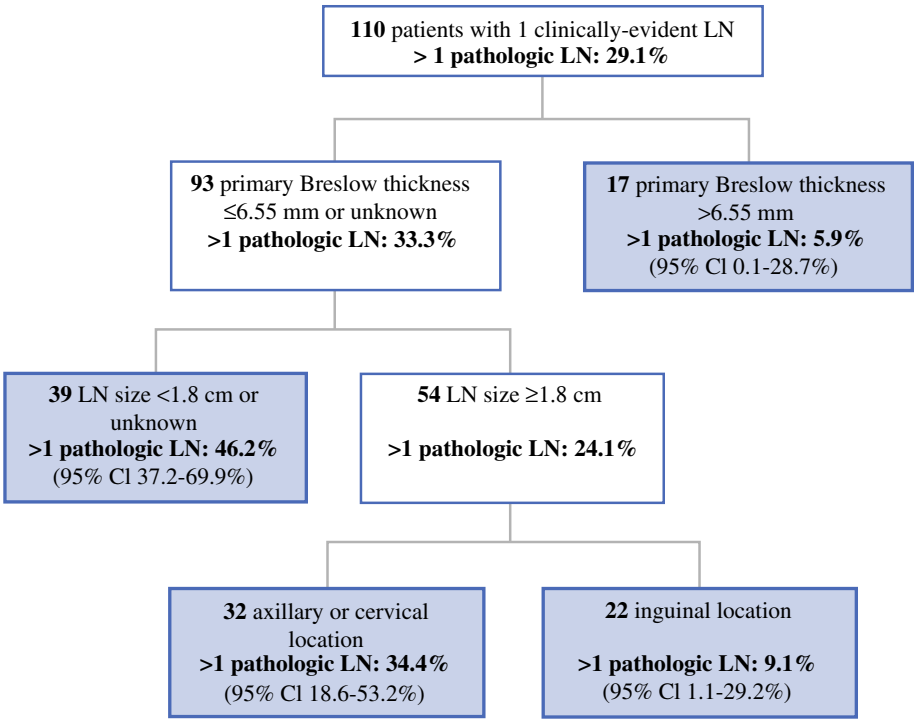


**FIG. 1** Classification tree identifying factors associated with one pathologic LN in the subgroup of patients with one clinically evident melanoma LN metastasis. *LN* lymph node, *CI* confidence interval

may be time to reconsider whether CLND is appropriate for all patients with cLNs. In patients with inguinal metastases, studies have shown that ilioinguinal compared with superficial inguinal dissection may provide prognostic information but does not appear to add survival benefit.[20,21] Therefore, selective lymphadenectomy is essentially already in practice for patients with cLNs limited to the superficial inguinal basin, and may be possible for disease in other nodal basins. Furthermore, ICB and BRAF/MEKi have demonstrated significant survival benefits in stage III melanoma.[22–25] Neoadjuvant sequencing of these novel therapies is feasible for clinically evident disease, and, in a subset of patients, can result in a complete pathologic response.[26–28] As the trend continues toward less extensive locoregional surgery for melanoma, it must be balanced with a better understanding of risk patterns for recurrence in the context of novel systemic therapies.

Several study limitations should be noted, including those inherent to a retrospective design and modest patient cohort size. Because of the cohort size, the results of the classification tree in the 110 patients with one cLN had relatively large CIs and should be considered preliminary. Further validation with a larger dataset is needed. While the current study utilized routine, readily available clinical data to allow for greater generalizability, integration of genomic or immunologic analysis of the tumor and LN microenvironments could provide more precise risk estimates. Additionally, there was substantial 'missing' information in primary tumor factors due to the large proportion of patients with unknown primaries. Inclusion of these missing data not only allowed for the treatment of those with unknown primaries as a potentially biologically separate group but also reduced available comparisons among the known subgroups. Additionally, pathologic evaluation of CLND specimens was not centralized and variation could exist among institutions in the methodology of nodal tissue assessment. This may, however, allow for greater generalizability of the results across institutions.

## CONCLUSIONS

In patients presenting with melanoma cLNs, preoperative imaging is strongly associated with pathologic status. Among patients with one cLN by imaging, additional clinical factors may allow for further risk stratification, and warrants further evaluation. Towards the goal of defining the optimal population of patients with clinical stage III melanoma that may be safely spared the morbidity of CLND, a prospective study is planned to validate the current findings.

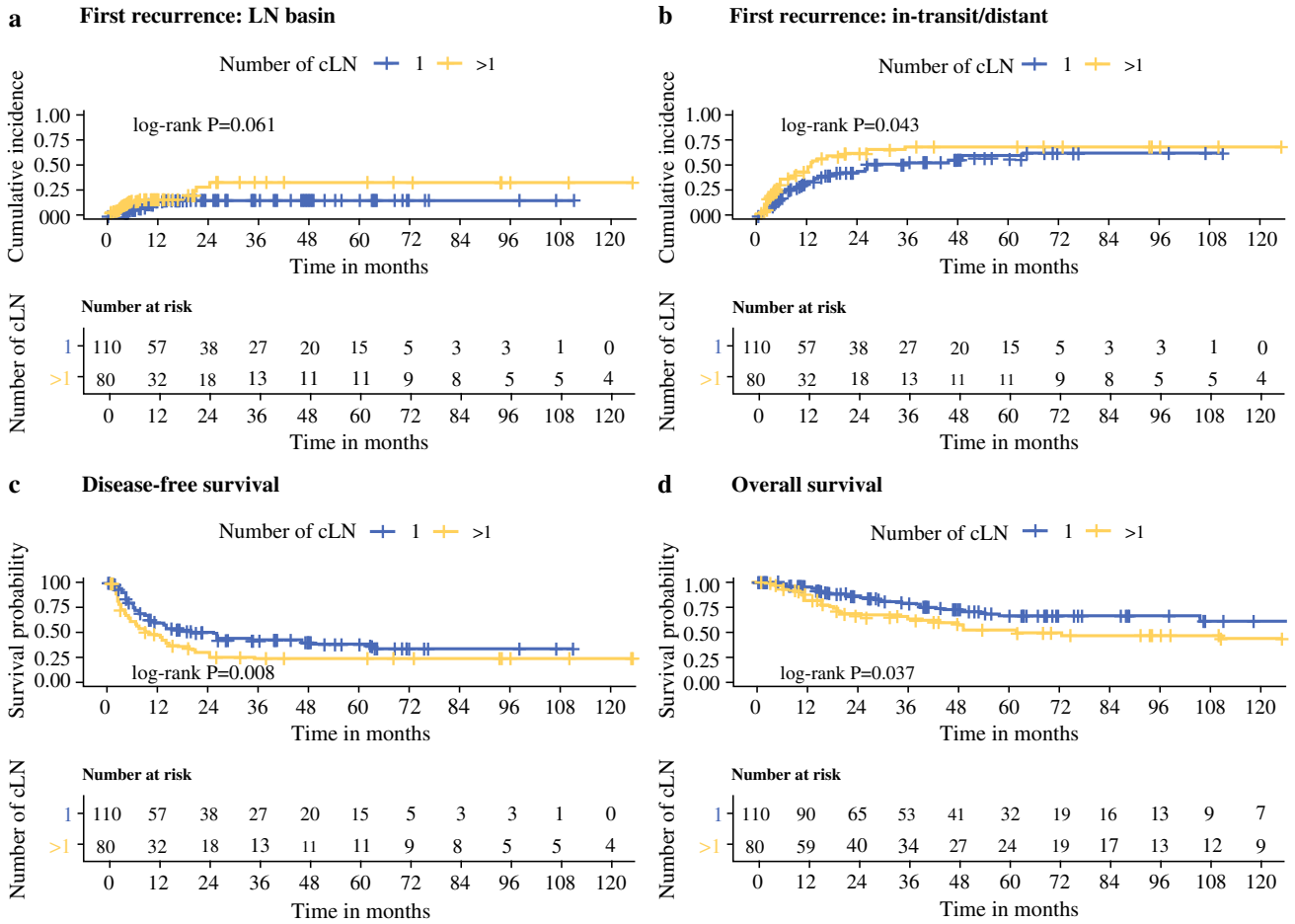


**FIG. 2** Kaplan–Meier recurrence and survival curves stratified by the number of cLNs on preoperative imaging. Cumulative incidence of the first recurrence event **a** in the same LN basin and **b** as in-transit and distant metastases. **c** Disease-free survival and **d** overall survival. *cLNs* clinically evident lymph nodes, *LN* lymph node

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