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Regional Node Basin Recurrence in Melanoma Patients: More Common After Node Dissection for Macroscopic Rather than Clinically Occult Nodal Disease

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ABSTRACT

Background. Recommended treatment for patients with sentinel lymph node (SLN)-positive melanoma has recently changed. Randomized trials demonstrated equivalent survival with close observation versus completion lymph node dissection (CLND), but increased regional node recurrence. We evaluated factors related to in-basin nodal recurrence after lymphadenectomy (LND) for SLN-positive or macroscopic nodal metastases.

Methods. An institutional database and the first Multicenter Selective Lymphadenectomy Trial (MSLT-I) were analyzed independently. Exclusions were multiple primaries, multi-basin involvement, or in-transit metastases. Patient demographics, primary tumor thickness and ulceration, lymph nodes retrieved, and use of adjuvant radiotherapy were analyzed. Multivariate analyses were performed to determine factors predicting in-basin nodal recurrence (significance $p \leq 0.05$).

Results. The retrospective cohort (577 patients) showed an in-basin failure rate of 6.6% after CLND for a positive SLN and 13.1% after LND for palpable disease ($p = 0.001$). This recurrence risk persisted after adjustment for patient, tumor, and LND factors [hazard ratio (HR) 2.32; $p = 0.004$]. In the MSLT-I cohort (326 patients), the failure rate after CLND following SLNB was 6.2%, but 10.1% after LND for palpable recurrence in observation patients. After adjustment for other factors, macroscopic disease was associated with an increased risk of recurrence after LND (HR 2.24; $p = 0.05$).

Conclusion. After LND for melanoma, in-basin recurrence is infrequent, but a clinically significant fraction will fail. Failure is less likely if dissection is performed for clinically occult disease. Further research is warranted to evaluate the long-term regional control and quality of life associated with nodal basin observation, which has now become standard practice.

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The first Multicenter Selective Lymphadenectomy Trial (MSLT-I) demonstrated that early removal of nodal metastases in intermediate-thickness melanoma led to improved melanoma-specific survival (MSS) compared with lymph node dissection (LND) at the time of palpable recurrence.[1] The second MSLT trial (MSLT-II) recently demonstrated that this survival benefit does not require a completion lymph node dissection (CLND) after a positive sentinel lymph node biopsy (SLNB), and established nodal observation including ultrasound as an acceptable option for patients with sentinel lymph node (SLN) metastases.[2] One concern regarding observation, whether with clinical examination or with ultrasound, has been the potential for 'loss of regional control' in patients who develop nodal recurrence during observation after SLN biopsy (SLNB). Patients in the MSLT-II study who were observed had a higher rate of clinically apparent (ultrasound detected) nodal recurrence at 3 years compared with those managed by CLND (23% vs. 8%). Data regarding long-term regional disease control are currently limited, and there is debate regarding whether the development of macroscopic nodal metastases in observed patients makes regional disease control more difficult to achieve. We evaluated factors related to in-basin nodal recurrence after LND, including the impact of the extent of nodal disease, by comparing patients undergoing a CLND after a positive SLNB or an LND after detection of palpable disease.

METHODS

Two data sources were used for this study: a large institutional database of melanoma patients, and the MSLT-I database. Institutional Review Board approval was obtained for analysis of all patient data. The melanoma database at the John Wayne Cancer Institute (JWCI) has been prospectively maintained for over 40 years. Patients entered into the database or enrolled in MSLT-I provided written consent to provide clinical data. Approval from the Institutional Review Board was obtained, and the informed consent requirement was waived for this analysis. We queried the institutional and MSLT-I databases to identify all patients who underwent LND, either after a positive SLN biopsy (defined as CLND) or after presentation with macroscopic nodal disease. The institutional database included patients treated from 1972 to 2012, and the MSLT-I database spanned patients treated from 2004 to 2012.

Patients with mucosal melanoma, multiple primary melanomas, multiple basin involvement, or in-transit metastases were excluded, as were patients who did not have a recorded indication for LND. Variables queried from the databases included age, sex, primary tumor thickness, primary tumor ulceration, number of lymph nodes removed upon LND, and timing of radiotherapy if administered. Univariate and multivariate analyses using Cox proportional hazards regression examined factors related to in-basin nodal recurrence. Patients with incomplete data were excluded from multivariable analyses. Survival curves for recurrence after LND were constructed using the Kaplan–Meier method and compared using the log-rank test. Significance was set at $p \leq 0.05$.

RESULTS

Retrospective Cohort (John Wayne Cancer Institute Database)

Five hundred and seventy-seven patients with positive lymph nodes in the cervical (n = 116), axillary (n = 288) and inguinal (n = 173) basins were identified (Fig. 1, Table 1), representing 4.8% of patients reported in this database. The mean age at the time of initial diagnosis was 48.3 years and 68.1% were male. The indications for initial LND were similar between basins, with 57.7% overall performed for a positive SLN (CLND) and 42.3% for macroscopic disease. A modified radical neck dissection was performed on all cervical basins, and a level I through III dissection for axillary basins. Groin LNDs involved superficial dissections only for 46 (27%) patients, and superficial and deep dissections for 77 (45%) patients, while 50 (29%) patients did not have extent of dissection recorded. Patients with macroscopic groin disease were more likely to undergo a deep dissection compared with patients undergoing CLND (52% vs. 38%; p = 0.04). The thickness distribution was also similar between basins, as was ulceration of the primary site. The mean number of lymph nodes removed was higher for cervical basins

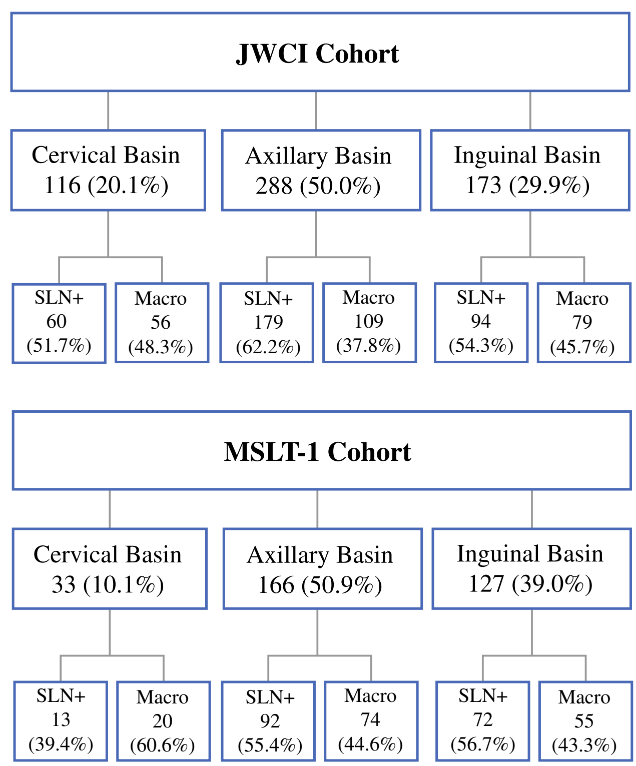


FIG. 1 Patient cohorts. *JWCI* John Wayne Cancer Institute, *MSLT* Multicenter Selective Lymphadenectomy Trial, *SLN+* dissection after a positive sentinel lymph node, *Macro* dissection for macroscopic (palpable) nodes

TABLE 1 Demographics of lymph node dissection patients at the John Wayne Cancer Institute

	Cervical (*n* = 116)	Axillary (*n* = 288)	Inguinal (*n* = 173)	Total (*n* = 577)
Mean age, years	50.3	48.0	47.5	48.3
Sex				
Male	96 (82.8)	203 (70.5)	94 (54.3)	393 (68.1)
Female	20 (17.2)	85 (29.5)	79 (45.7)	184 (31.9)
Primary tumor thickness				
T1	6 (5.2)	31 (10.8)	9 (5.2)	46 (8.0)
T2	25 (21.6)	67 (23.3)	30 (17.3)	122 (21.1)
T3	42 (36.2)	96 (33.3)	60 (34.7)	198 (34.3)
T4	20 (17.2)	65 (22.6)	49 (28.3)	134 (23.2)
Tx	23 (19.8)	29 (10.1)	25 (14.5)	77 (13.3)
Ulceration				
No	68 (58.6)	167 (58.0)	89 (51.4)	324 (56.2)
Yes	34 (29.3)	92 (31.9)	70 (40.5)	196 (34.0)
Unknown	14 (12.1)	29 (10.1)	14 (8.1)	57 (9.9)
Indication				
SLN+	60 (51.7)	179 (62.2)	94 (54.3)	333 (57.7)
Macroscopic	56 (48.3)	109 (37.8)	79 (45.7)	244 (42.3)
Mean nodes, initial LND	29	20	18	21
Nodes excised				
0–9	26 (22.4)	59 (20.5)	43 (24.9)	128 (22.2)
10–20	14 (12.1)	109 (37.8)	80 (46.2)	203 (35.2)
> 21	76 (65.5)	120 (41.7)	50 (28.9)	246 (42.6)
Radiotherapy use after relapse				
No	82 (70.7)	243 (84.4)	131 (75.7)	456 (79.0)
Yes	34 (29.3)	45 (15.6)	42 (24.3)	121 (21.0)
In-basin recurrence				
No	98 (84.5)	272 (94.4)	153 (88.4)	523 (90.6)
Yes	18 (15.5)	16 (5.6)	20 (11.6)	54 (9.4)

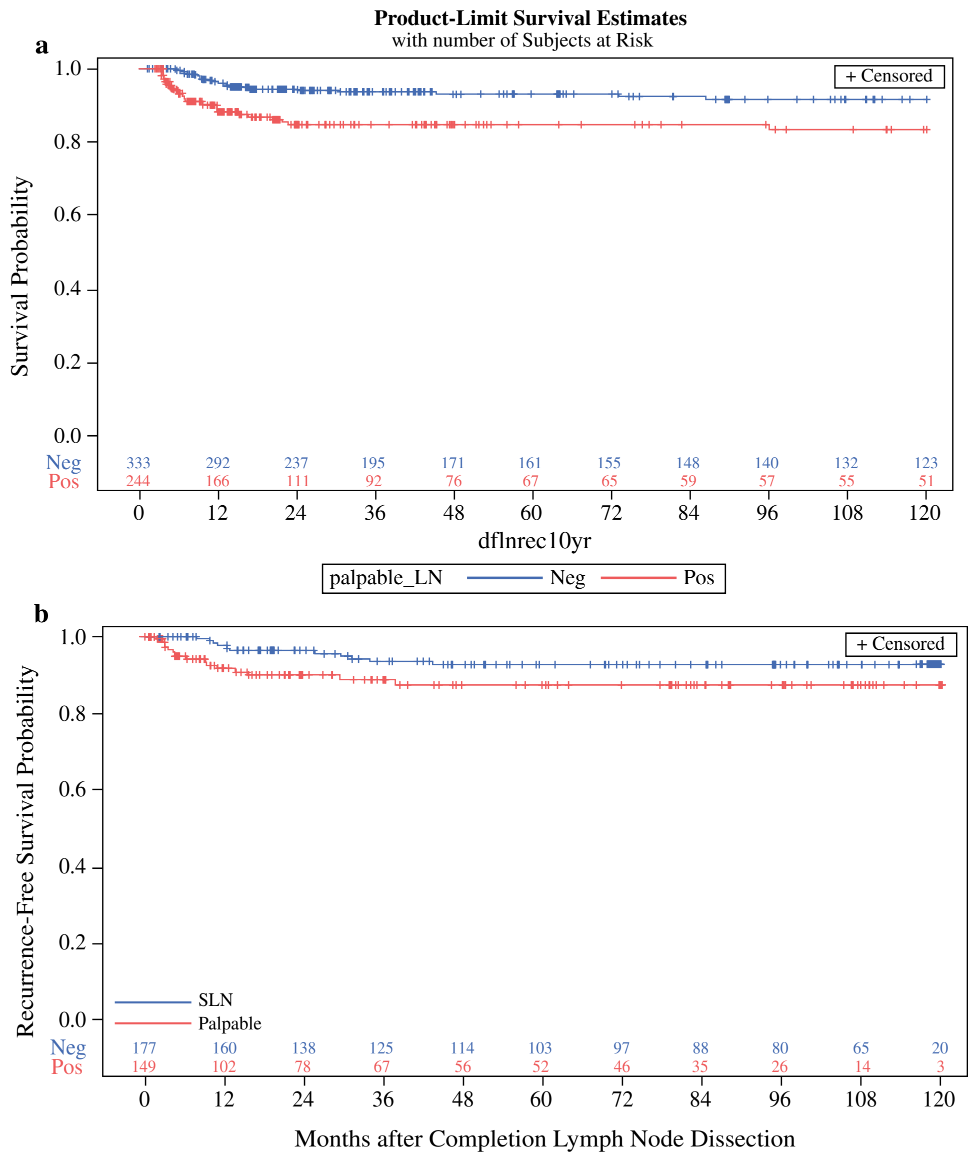
Data are expressed as *n* (%) unless otherwise specified

SLN+ positive sentinel lymph node, *LND* lymph node dissection

compared with axillary and inguinal basins (29, 20, and 18, respectively). Median follow-up was 41.8 months. In-basin recurrence after CLND was 6.6% after 10 years, compared with 13.1% after LND for palpable disease ($p = 0.001$) (Fig. 2a). Axillary basins had a lower percentage of recurrence after CLND than groin or neck basins (3.9% vs. 9.6% and 10.0%, respectively). Cervical basins with palpable disease had the highest percentage of recurrences after LND (21.4% vs. 8.9% for groin and 8.3% for axilla). The majority of recurrences after LND were within the first 2 years, regardless of initial indication. No cervical basin recurrences were recorded more than 3 years after LND in patients with SLNB-positive or palpable disease, and only one recurrence occurred in the axillary basin after 3 years.

In the overall population, macroscopic (palpable) disease was associated with in-basin recurrence after adjustment for other risks factors, including primary tumor thickness, primary tumor ulceration, and age [hazard ratio (HR) 2.32; $p = 0.004$] (Table 2). Characteristics of the primary, including thickness and ulceration, were not independently associated with recurrence. Lymph node basins had differing recurrence risks: groin and cervical basins had higher recurrence rates than axillary basins (HR for groin 2.22, $p = 0.02$; HR for cervical 3.29, $p = 0.001$). Radiotherapy was excluded from the multivariate model as it was primarily administered for salvage therapy after recurrence, and only two patients received radiotherapy prior to the event. Forty-two percent of patients were treated with adjuvant therapy, including 3.8% treated with interferon and 40% treated with vaccine or other on-trial regimens. Of the 54 patients with in-basin recurrence after LND, 45 (83.3%) underwent salvage dissections. Twenty

FIG. 2 **a** In-basin recurrence-free survival in the JWCI cohort. The percentage of patients with in-basin recurrence at 10 years was 6.6% for patients undergoing CLND after SLN versus 13.1% after CLND for palpable disease (p = 0.001). **b** In-basin recurrence-free survival in the MSLT-I cohort. The percentage of patients with in-basin recurrence at 10 years was 6.2% for patients undergoing CLND after SLN versus 10.1% after LND for palpable disease (p = 0.06). *JWCI* John Wayne Cancer Institute, *MSLT* Multicenter Selective Lymphadenectomy Trial, *CLND* completion lymph node dissection, *SLN* sentinel lymph node, *Neg* negative, *Pos* positive



inguinal lymph node recurrences were recorded, three were deep recurrences. There was no difference in rates of salvage dissections between patients with initially macroscopic disease compared with those with undergoing CLND for a positive SLNB (84% vs. 81%; p = 0.9).

Multivariable analysis of individual basins identified different significant associations for recurrence for each basin (Table 2). Regional recurrence in cervical lymph node basins was independently associated with palpable nodes (HR for palpable nodes 4.13; p = 0.02). Groin lymph node recurrence was related only to sex (HR for females 0.34; p = 0.04). Age, number of nodes removed, primary tumor thickness, and primary tumor ulceration were not related to recurrence risk for any basin. Of the 577 patients in this cohort, 417 (72.3%) died of any cause during follow-up. The majority (327, 78.4%) died of melanoma. Forty-four (82%) of the 54 patients with an in-basin recurrence subsequently developed distant disease, and 39 (72%) died of melanoma. Of the 523 patients who did not have an in-basin recurrence, 275 (52.6%) had a distant recurrence, with 253 (92.0%) deaths within 10 years. Only 58 (23.4%) of the 248 patients without distant recurrence died of non-melanoma causes within 10 years.

Multicenter Selective Lymphadenectomy Trial (MSLT)-I Cohort

In the MSLT-I cohort, 326 patients with positive lymph nodes in the cervical (n =33), axillary (n =166), and inguinal (n =127) basins were identified (Fig. 1, Table 3). This represented 16.5% of all patients in the MSLT-I trial. Mean age was 51.8 years and 57.7% were male, similar to

TABLE 2 Factors associated with lymph node recurrence at the John Wayne Cancer Institute, by basin and in the overall population (multivariate model)[a]

	Cervical		Axillary		Inguinal		Total[b]	
	HR	*p* Value	HR	*p* Value	HR	*p* Value	HR	*p* Value
Age	1.01	0.43	0.98	0.37	1.01	0.50	1.00	0.92
Sex								
Male	Ref		Ref		Ref		Ref	
Female	1.28	0.71	0.25	0.07	0.34	0.04	0.46	0.03
Primary tumor thickness								
T1	Ref		Ref		Ref		Ref	
T2	1.72	0.66	0.40	0.38	1.26	0.84	0.86	0.81
T3	2.38	0.46	1.35	0.72	1.26	0.83	1.30	0.64
T4	2.52	0.46	0.53	0.55	0.68	0.73	0.81	0.74
Tx	2.28	0.48	1.66	0.59	0.82	0.88	1.21	0.76
Ulceration								
No	Ref		Ref		Ref		Ref	
Yes	0.98	0.97	2.44	0.12	1.34	0.56	1.47	0.21
Unknown	1.04	0.96	2.50	0.22	2.42	0.23	2.09	0.07
LND indication								
SLN+	Ref		Ref		Ref		Ref	
Macroscopic	4.13	0.02	2.18	0.14	1.76	0.25	2.32	0.004
Nodes excised								
0–9	Ref		Ref		Ref		Ref	
10–20	1.16	0.85	4.72	0.15	1.29	0.62	1.47	0.28
> 20	0.38	0.14	2.66	0.37	0.31	0.15	0.60	0.18
LN basin								
Axilla							Ref	
Groin							2.22	0.02
Cervical							3.29	0.001

HR hazard ratio, *SLN+* positive sentinel lymph node, *LND* lymph node dissection, *LN* lymph node

[a]Multivariate models for each basin and total cohort are listed separately. All listed variables were used for each model

[b]Model of the total population includes lymph node basin as an independent variable

the JWCI cohort. Mean numbers of lymph nodes removed were 31, 21, and 14 for the cervical, axillary, and inguinal basins, respectively. The levels of dissection within each basin were not recorded for patients with macroscopic disease, precluding comparisons between groups. Median follow-up was 59.3 months. There was an overall 6.2% failure rate after CLND and a 10.1% failure rate after LND for macroscopic disease ($p = 0.06$) (Fig. 2b). Failure rates after neck CLND were 7.7%, versus 10.0% after LND for macroscopic disease ($p = 0.73$), 9.7% versus 3.6% ($p = 0.39$) after groin dissections, and 3.3% versus 14.9% ($p = 0.003$) for axillary dissections. No recurrences were identified in any basin more than 4 years following LND, regardless of indication.

In the overall MSLT-I population, an association between macroscopic (palpable) disease and in-basin recurrence was observed after adjustment for other risk factors, including primary tumor thickness, primary tumor ulceration, and age (HR 2.24; $p = 0.05$) (Table 4) in multivariable analysis. Primary tumor stage and ulceration were not associated with lymph node basin recurrence. There was no significant difference in recurrence risk in axillary versus other basins. Radiotherapy was excluded from the multivariable model due to its limited use in this cohort. Adjuvant treatment was used in only 10 (3.1%) patients. Of the 26 patients with in-basin recurrence after dissection, 7 (27%) underwent salvage dissection, and 17 (65%) ultimately developed a distant recurrence. Of the 326 patients in this cohort, 159 (48.8%) died of any cause, and 146 (91.8%) deaths were due to melanoma. Of the 300 patients without in-basin recurrence after LND, 145 (48.3%) had a distant recurrence, and 126 (86.9%) of these had died by the end of follow-up. The majority of patients (155, 51.7%) did not have an in-basin recurrence after LND, and only 13 (8.4%) deaths were reported in this subset.

TABLE 3 Demographics of lymph node dissection patients in the MSLT-I study

	Cervical (n = 33)	Axillary (n = 166)	Inguinal (n = 127)	MSLT-I total (n = 326)
Mean age, years	53.2	50.7	52.7	51.8
Sex				
Male	24 (72.7)	114 (68.7)	50 (39.4)	188 (57.7)
Female	9 (27.3)	52 (31.3)	77 (60.6)	138 (42.3)
Primary tumor thickness				
T1	0 (0.0)	4 (2.4)	5 (3.9)	9 (2.8)
T2	10 (30.3)	44 (26.5)	39 (30.7)	93 (28.5)
T3	20 (60.6)	83 (50.0)	47 (37.0)	150 (46.0)
T4	3 (9.1)	35 (21.1)	36 (28.3)	74 (22.7)
Tx	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ulceration				
No	23 (69.7)	90 (54.2)	66 (52.0)	179 (54.9)
Yes	9 (27.3)	61 (36.7)	54 (42.5)	124 (38.0)
Unknown	1 (3.0)	15 (9.0)	7 (5.5)	23 (7.1)
Indication for LND				
SLN+	13 (39.4)	92 (55.4)	72 (56.7)	177 (54.3)
Macroscopic	20 (60.6)	74 (44.6)	55 (43.3)	149 (45.7)
Mean nodes, initial LND	31	21	14	19
Nodes excised				
0–9	2 (6.1)	5 (3.0)	31 (24.4)	38 (11.7)
10–20	8 (24.2)	96 (57.8)	80 (63.0)	184 (56.4)
> 21	23 (69.7)	65 (39.2)	16 (12.6)	104 (31.9)
Radiotherapy use after relapse				
No	31 (93.9)	163 (98.2)	126 (99.2)	320 (98.2)
Yes	2 (6.1)	3 (1.8)	1 (0.8)	6 (1.8)
In-basin recurrence				
No	30 (90.9)	152 (91.6)	118 (92.9)	300 (92.0)
Yes	3 (9.1)	14 (8.4)	9 (7.1)	26 (8.0)

Data are expressed as n (%) unless otherwise specified

MSLT Multicenter Selective Lymphadenectomy Trial, *HR* hazard ratio, *SLN+* positive sentinel lymph node, *LND* lymph node dissection

DISCUSSION

Both MSLT-I and MSLT-II demonstrated a lower risk of regional node recurrence among patients who underwent early surgical treatment, while nodal disease was clinically occult. In MSLT-I, there was a 10% improvement in disease-free survival with SLN biopsy and CLND for positive SLN. This was predominantly due to a decreased risk of nodal recurrence with immediate surgery. In MSLT-II, the risk of regional basin recurrence was also markedly reduced (HR 0.31, 95 confidence interval 0.24–0.41; $p < 0.001$)[2] in the CLND arm. However, in both trials, it is possible that the same degree of long-term regional control could have been obtained if surgical treatment of regional nodal metastases was provided when macroscopic disease was identified. This question prompted our current analysis.

We know from MSLT-I that the mean number of involved nodes that are able to be identified more than doubles during the period of observation before clinical detection. We also know that the risk of lymphedema is higher when LND is performed for macroscopic nodal metastases. Our current study demonstrates, in two separate cohorts, that the risk of a regional recurrence is lower among patients treated with CLND prior to clinical presentation with macrometastases. In both databases, the risk of in-basin recurrence was increased approximately two-fold after LND for macroscopic disease (JWCI database: 13.1% vs. 6.6%; MSLT-I database: 10.1 vs. 6.2%). This effect was most evident in the cervical basin.

TABLE 4 Factors associated with lymph node recurrence in the MSLT-I study, by basin and in the overall population (multivariate model)[a,b,c]

	Inguinal		Axillary		Total[c]	
	HR	*p* Value	HR	*p* Value	HR	*p* Value
Age	1.00	0.92	0.99	0.66	0.99	0.50
Sex						
Male	Ref		Ref		Ref	
Female	4.06	0.13	1.82	0.34	1.60	0.27
Primary tumor thickness						
T1/T2	Ref		Ref		Ref	
T3	0.62	0.64	1.07	0.92	0.96	0.93
T4	1.87	0.48	0.86	0.85	1.25	0.68
Ulceration						
No	Ref		Ref		Ref	
Yes	2.07	0.42	0.29	0.12	1.07	0.89
Unknown	8.14	0.06	1.89	0.36	3.69	0.02
LND indication						
SLN+	Ref		Ref		Ref	
Macroscopic	0.54	0.44	6.67	0.008	2.24	0.05
Nodes excised						
0–9	Ref		Ref		Ref	
10–20	0.58	0.48	0.50	0.56	0.55	0.34
> 20	0.00	0.99	0.49	0.55	0.37	0.17
LN basin						
Axilla					Ref	
Inguinal					0.55	0.22
Cervical					1.28	0.71

HR hazard ratio, *SLN+* positive sentinel lymph node, *LND* lymph node dissection, *LN* lymph node

[a]Multivariate models for each basin and total cohort are listed separately. All listed variables were used for each model

[b]The cervical nodal basin model is not shown due to limited numbers preventing multivariate analysis

[c]Model of the total population includes lymph node basin as an independent variable

Evaluation of nodal recurrence rates at other institutions has demonstrated conflicting findings regarding the association with indication for LND[3–5]. Pidhorecky and colleagues reported that patients undergoing elective LND in the pre-sentinel node era had half the nodal basin recurrence risk compared with those undergoing dissection for palpable disease (14% vs. 28%)[3]. They identified primary site (head and neck), Breslow thickness, and nodal extracapsular extension as independent risk factors for recurrence. In our institutional cohort, cervical and groin basins had a higher risk of recurrence than axillary basins, but primary tumor characteristics were not independently associated with nodal recurrence risk. Calabro and colleagues identified a 16% nodal recurrence rate after LND, with increasing risk associated with the number of positive lymph nodes, but no association with the indication for dissection (elective vs. therapeutic);[4] however, only 7% of their cases underwent elective LND, limiting the power to detect a difference in nodal in-basin recurrence rates. Nathansohn and colleagues similarly found no difference in the risk of nodal recurrence after elective versus therapeutic LND, but their study assessed only 17 patients.[5] In all three studies, the extent of nodal tumor burden was associated with overall survival. Similarly, studies of prospective cohorts of node-positive melanoma patients have demonstrated that lymph node disease burden is predictive for both recurrence and 5-year survival.[6] Fisher evaluated nodal recurrence in patients with head and neck melanomas and reported a 55% regional recurrence rate after delayed LND performed for clinically palpable disease, compared with a 7.9% recurrence rate after immediate LND.[7] These data suggest, and our current study demonstrates, that performing LND for salvage after the development of macroscopic disease reduces the regional control rate substantially compared with early detection by SLNB of occult disease, and CLND.

Recent clinical trials of immunotherapy and BRAF/MEK inhibitors for melanoma have demonstrated both recurrence-free and overall survival benefits in patients with resected and unresectable stage III disease.[8,9] These advances appear likely to reduce the overall risk of regional nodal basin recurrence, with or without immediate dissection. Even in these trials, 9.4–14.0% of patients, all of whom had undergone immediate CLND, had locoregional recurrence without distant metastases. These outcomes indicate that locoregional recurrence continues to affect a clinically significant proportion of node-positive melanoma patients. In addition, since adjuvant therapy clinical trial subjects had all undergone immediate CLND, most often for stage IIIB–D disease, we do not yet know what the magnitude of the benefit of adjuvant therapy will be on patients who are observed after a positive SLNB.

Limitations of this study include the limitations of most retrospective analyses. Factors other than those analyzed may contribute to recurrence risk. Limited information on adjuvant therapies that were used after LND is available, although patients from both cohorts were treated before the advent of effective systemic targeted therapy or immunotherapy. In addition, we were unable to determine how often definitive regional control was able to be re-established in patients with post-LND recurrence. In many instances, salvage through additional later interventions may have been possible, and prospective evaluation may ultimately be needed to settle the issue definitively.

CONCLUSION

The incidence of in-basin recurrence after lymphadenectomy was higher in patients who underwent LND for palpable disease compared with those who underwent CLND after a positive SLNB. This risk was independent of the number of lymph nodes removed on CLND, patient demographics, and primary tumor characteristics. Further analysis might indicate relative risk based on the extent of tumor burden within regional draining nodes, but this remains to be demonstrated. Another factor that requires investigation is the quality of clinical and ultrasound follow-up of regional nodes after a positive SLNB for routine surveillance outside of the strict clinical trial conditions, as this might influence the timeliness of regional recurrence detection. Meanwhile, close surveillance of SLNB-positive melanoma patients electing observation is warranted to maintain locoregional control.

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