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ORIGINAL ARTICLE – MELANOMA

Utility of Level III Axillary Node Dissection in Melanoma Patients with Palpable Axillary Lymph Node Disease

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ABSTRACT

Background. The Multicenter Selective Lymphadenectomy Trial II results suggest that future radical axillary lymphadenectomy (ALND) will be performed for bulkier metastatic disease. The utility of level III lymph node (LN) dissection in melanoma patients with palpable metastatic axillary disease was assessed.

Methods. We performed a retrospective chart review of patients who underwent ALND (levels I–III) for metastatic melanoma from 2005 to 2017. We assessed the frequency of level III positive nodes in patients undergoing radical axillary lymphadenectomy (ALND) for metastatic melanoma as well as the prognostic role and factors predictive of level III LN positivity.

Results. A total of 190 patients underwent ALND during the study period. Of these, 85 patients had palpable axillary disease, of which 71 had separate level III pathologic assessment. Level III LNs were positive in 16.9% of patients with palpable disease versus 0% with positive sentinel LN. The 1-, 3-, and 5-year overall survival (OS) for patients with palpable disease was 82.9%, 58.9%, and 39.0%, respectively. Median disease-free survival was 26.8 months, and the axillary recurrence rate was 8.2%. High level I/II LN ratio, BRAF mutation, and total LN examined were significant predictors of level III positivity (all $p \leq 0.05$). Patients with positive level III LN had significantly worse OS (median 18.6 months vs. not reached, $p = 0.001$). No preoperative factors were predictive of level III LN positivity.

Conclusions. Level III axillary disease is not uncommon in melanoma patients with clinically palpable nodal disease and provides useful prognostic information for OS. We recommend that full level I–III ALND be considered in this patient cohort.

Lymph node metastases are a significant prognostic factor in cutaneous melanoma.[1] The recent Multicenter Selective Lymphadenectomy Trial (MSLT) II has already significantly changed nodal management for melanoma.[2,3] In this study, patients with a positive sentinel lymph node biopsy (SLNB) were randomized to receive either immediate completion lymph node dissection or serial nodal observation with ultrasonography. Patients who underwent immediate lymph node dissection had improved disease-free survival (DFS) secondary to increased locoregional control; however, the 3-year melanoma-specific survival rates were equivalent. Given these results, indications for completion axillary lymph node dissection (ALND) will shift to those with macroscopically positive lymphadenopathy detected either by serial imaging or physical examination. Macroscopic, palpable lymphadenopathy in melanoma has been shown to have significantly worse oncologic outcomes with regards to DFS and overall survival (OS).[4–6]

The utility of a full level I–III ALND has been debated in SLNB-positive melanoma. The frequency of positive level III disease in this patient population is very low in retrospective series (1.5–3%).[5,7] Another series of 270 SLNB positive patients who only underwent level I/II ALND reported a 5% regional recurrence rate, and only 1 patient had a documented level III recurrence.[8] While there

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is no direct comparison for melanoma, in breast cancer the addition of level III lymphadenectomy results in higher rates of lymphedema.[9–11]

The utility of a level III ALND in melanoma patients with palpable axillary disease is less clear.[5,12] While multiple guidelines recommend patients with palpable nodal metastases undergo an anatomically complete nodal dissection, they do not comment on level I–III versus level I-II alone, and the evidence for these recommendations is graded a C, because there is a relative dearth of studies focused on this specific population.[13,14] Additionally, factors predictive of level III disease in this patient population are unknown. The objective of this study was to determine the frequency of level III positivity for patients with palpable axillary disease. We also investigated the prognostic oncologic significance of level III positive nodes and preoperative tumor and patient characteristics that predicted level III positivity.

METHODS

A series of melanoma patients undergoing level I–III ALND for metastatic melanoma was identified from an Institution Review Board-approved, prospectively maintained melanoma database at the Brigham and Women's Hospital. Patient demographics, pathologic characteristics, and surgical and oncologic outcomes were obtained from hospital chart records. Palpable axillary lymph node disease was based on the surgeon's preoperative physical examination. Wound infection was defined as cellulitis requiring antibiotics. Lymphedema was identified either by physical examination or as documented elsewhere in surgical or oncology follow-up at least 3 months following surgery.

Descriptive and comparative statistics were performed using SPSS-24. Categorical variables were compared using Chi-square analysis and continuous variables using the *t* test. Assessment of factors related to level III positivity, local recurrence, overall recurrence, and death were compared utilizing univariate logistic regression. Kaplan–Meier survival curves were generated for overall survival, disease-free survival, and local recurrence-free survival with log-rank test used to assess for statistical significance. Statistical significance was defined as $p \leq 0.05$.

Three separate surgeons at a single institution used similar approaches to radical levels I–III ALND. Skin flaps were developed to the pectoralis major, latissimus dorsi, and the coracobrachialis. The dissection extended to the sixth or seventh intercostal space on the serratus anterior and to the subscapularis. All axillary lymphadenectomies removed level III axillary nodes; those that did not were excluded from the study. Most of the 85 lymphadenectomies (83.5%) removed level I-II nodes (including Rotter's nodes) separately from level III nodes, which were sent as a separate specimen. Level III nodes were designated as those in the specimen dissected medial to the pectoralis minor. The 14 specimens (16.5%) in which the level III nodes were removed en bloc with levels I-II nodes were excluded from level III positivity prediction analyses. A 15-French Blake drain was routinely placed in the axillary space before closure.

RESULTS

A total of 190 patients underwent radical levels I–III axillary lymph node dissection (ALND) for metastatic melanoma between 2005 and 2017 (Fig. 1). Of these, 98 underwent ALND for a positive sentinel lymph node (SLN), and the remaining 92 had palpable axillary lymphadenopathy. Seven patients with palpable disease were excluded for whom the surgery was palliative, resulting in 85 patients for analysis. Of these 85 patients, 71 had separate pathologic evaluation of the level III lymph nodes. Table 1 describes the patient and tumor characteristics. The back was the most common site for the primary lesion (41.2%), whereas 23 patients (27.1%) had disease from an unknown primary source. Symptoms were present in 19 patients (22.4%) preoperatively, most commonly mild axillary pain/discomfort.

The total rate of level III positivity was 16.9% for patients with palpable axillary disease and separate pathologic examination. None of the 79 patients who underwent ALND for positive sentinel lymph node with separate level III pathologic analysis had positive level III disease (Fig. 1). Table 1 includes pathologic ALND characteristics and postoperative outcomes for patients with palpable axillary disease. The median number of total lymph nodes harvested was 28 (range 7–72). Three patients had fewer than ten lymph nodes examined (3.5%). For patients with level III lymph nodes examined separately, the mean total level III nodes harvested was 7.5. The median pathologic size of the dominant level I/II node was 4.4 cm, and the dominant level III node was 1.1 cm. For patients with positive level III disease, the mean number of positive nodes was 2.83 (range 1–12). BRAF mutation status was tested in 55 patients and identified in 24 cases (43.6% of patients).

Many patients received adjuvant therapy (Table 1). Axillary radiotherapy was given to 36 patients (42.4%). Interferon was given to 12 patients (14.1%), chemotherapy to 9 patients (10.6%), and vaccines to 7 (8.2%). Thirty-three patients received at least one immunotherapy agent (38.8%), and another nine patients received a different targeted-therapy (10.6%). Chemotherapy was most often

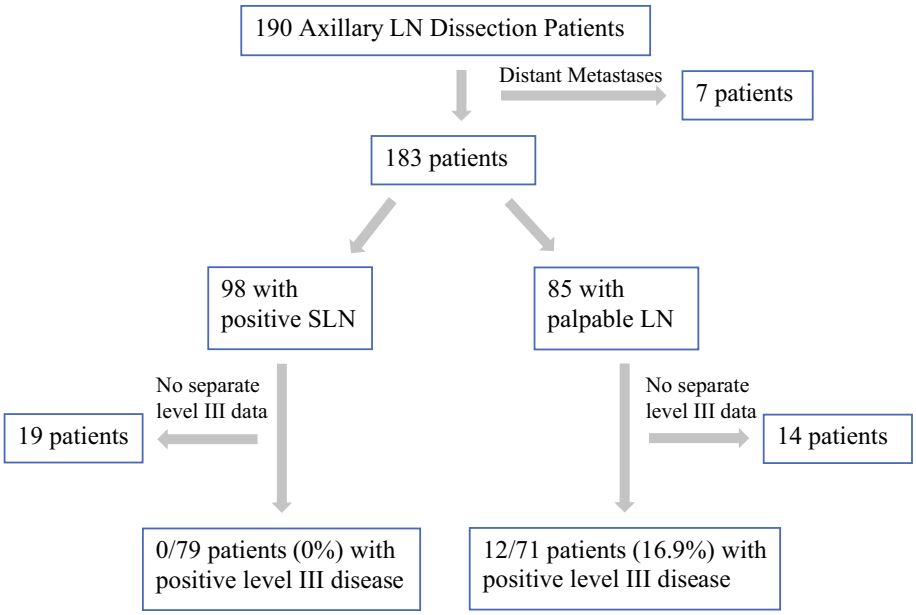


FIG. 1 Study flowchart

given after a recurrence and was significantly correlated with worse survival ($p = 0.001$). Receipt of targeted therapy was associated with increased recurrence and local recurrence ($p = 0.035$ and $p = 0.004$).

A total of 25 patients with palpable disease have died during follow-up (29.4%). The median follow-up of patients who died was 9.7 (range 1.2–54.1) months and 37.7 (range 0.6–144) months for surviving patients. The median overall survival (OS) was not reached (Fig. 2a). The 1-year, 3-year, and 5-year OS was 82.9%, 58.9%, and 39.0%, respectively. Recurrence was seen in 38 patients (44.7%) with a median disease-free survival (DFS) of 26.8 months (Fig. 2b). The 1-year, 3-year, and 5-year DFS was 58.3%, 39.0%, and 25.5%, respectively. Local axillary recurrence was seen in seven patients (8.2%), with a 1-year, 3-year, and 5-year local recurrence rate of 4.7%, 19.4%, and 30.4%, respectively. The median local-recurrence free survival was not reached (Fig. 2c). For the seven patients with a local recurrence, three subsequently died (at 4, 20, and 44 months). The median time to local recurrence was 13.5 (range 1.2–21.9) months. Of note, the patient with the one month time to local recurrence had a positive axillary vein margin. Six of the patients with a local recurrence had separate level III analysis, one of whom had positive level III disease. Four of the patients presented with synchronous recurrences at other sites as well (2 lung, 1 brain, and 1 skin). Only one patient who eventually developed an axillary recurrence had received adjuvant axillary radiotherapy.

Lymphedema was seen in 26.9% of patients, the majority (23.5%) of whom had slight or mild lymphedema. Only two patients (2.4%) had moderate lymphedema. Axillary radiotherapy significantly increased rates of lymphedema (38.9% vs. 16.3%, $p = 0.025$). Other complications included four patients with an infected seroma or abscess (4.7%), three patients with a seroma requiring drain replacement (3.5%), and five patients with a surgical site infection requiring antibiotics (5.9%). One patient each suffered a hematoma, upper extremity deep venous thrombosis, and *Clostridium difficile* infection (1.2%). Complications are represented in Table 1.

Table 2 shows univariate analysis for predictors of level III positivity, local recurrence, any recurrence, and death. The only factors found to be significantly predictive of level III positivity were higher lymph node ratio of levels I/II [odds ratio(OR) 5.967, $p < 0.001$], BRAF mutation (OR 1.386, $p = 0.05$), and higher total number of lymph nodes examined (OR 1.052, $p = 0.05$). Patients with primary melanomas with deeper Breslow thickness (OR 1.633, $p = 0.012$) and higher lymph node ratios (OR 2.8, $p = 0.023$) were significantly more likely to develop a recurrence, whereas patients with unknown primary tumors were less likely to recur (OR 0.244, $p = 0.013$). No factor was significantly predictive of local recurrence on univariate analysis. Patients with positive level III lymph nodes were significantly more likely to die than those with pathologically negative level III nodes (OR 1.861, $p = 0.007$). Lymph node ratio (OR 4.0001, $p = 0.002$) and any recurrence (OR 3.004, $p < 0.001$) were the only other factors significantly associated with death on univariate analysis. Kaplan–Meier overall survival curves stratified on level III positivity (log-rank, $p = 0.001$) and lymph node ratio category (log-rank, $p < 0.001$) are shown in Fig. 3. Median OS for patients with positive level III disease was 18.6 months (median was not reached in patients with negative level III disease).

TABLE 1 Preoperative characteristics, operative outcomes, adjuvant treatment, and complication rates

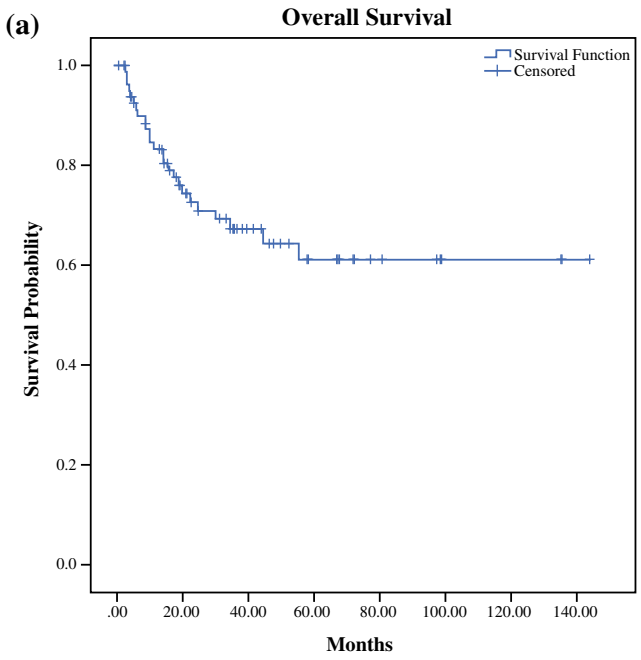
Variable	
Median age (range)	61 (25–91)
Male sex	66 (77.6%)
Site of primary lesion	
Back	35 (41.2%)
Chest	5 (5.9%)
Arm/shoulder	18 (21.2%)
Abdomen/flank	4 (4.7%)
Unknown primary	23 (27.1%)
Histology	
Superficial spreading	19 (22.4%)
Nodular	15 (17.6%)
Spindle cell	2 (2.4%)
Desmoplastic	2 (2.4%)
Unknown/unspecified	24 (28.2%)
Breslow depth	
In situ	2 (2.4%)
≤ 1 mm	17 (20%)
1.01–2.00 mm	13 (15.3%)
2.01–4.00 mm	11 (12.9%)
> 4 mm	15 (17.6%)
Clark level	
In situ	2 (2.4%)
II	2 (2.4%)
III	6 (7.1%)
IV	43 (50.6%)
V	3 (3.5%)
Ulceration	21 (24.7%)
Symptomatic LN disease	19 (22.4%)
In-transit disease	5 (5.9%)
Preoperative LN size on imaging	
≤ 2 cm	6 (7.1%)
2.01–4 cm	37 (43.5%)
> 4 cm	35 (41.2%)
Median level I/II total nodes (mean)	20 (21.2)
Median level III total nodes (mean)	7 (7.5)
Median total nodes harvested (range)	28 (7–72)
Mean number of positive nodes	4.35
Lymph node ratio	
≤ 0.1	56 (65.9%)
0.11–0.25	13 (15.3%)
> 0.25	16 (18.8%)
Pathological size level I/II	
Median	4.4 cm
≤ 2 cm	15 (18.5%)
2.01–4 cm	23 (28.4%)
> 4 cm	43 (53.1%)
Pathological size level III	
Median	1.1 cm
≤ 2 cm	9 (75%)
> 2 cm	3 (25%)
Pathologic nodal stage	
N1	25 (29.4%)
N2	23 (27.1%)
N3	37 (43.5%)
Extranodal extension	36 (42.4%)
BRAF mutation	
Yes	24 (28.2%)
No	31 (36.5%)
Not tested	30 (35.3%)
Adjuvant therapy	
Axillary radiotherapy	36 (42.4%)
Immunotherapy	33 (33.8%)
Chemotherapy	9 (10.6%)
Interferon	12 (14.1%)
Targeted therapy	9 (10.6%)
Vaccine therapy	7 (8.2%)
Lymphedema	
None	63 (74.1%)
Mild	20 (23.5%)
Moderate	2 (2.4%)
Other complications	
Abscess/infected seroma	4 (4.7%)
Seroma requiring drainage	3 (3.5%)
Surgical site infection	5 (5.9%)
Hematoma	1 (1.2%)
Clostridium difficile	1 (1.2%)
Upper extremity DVT	1 (1.2%)

LN lymph node; *DVT* deep venous thrombosis

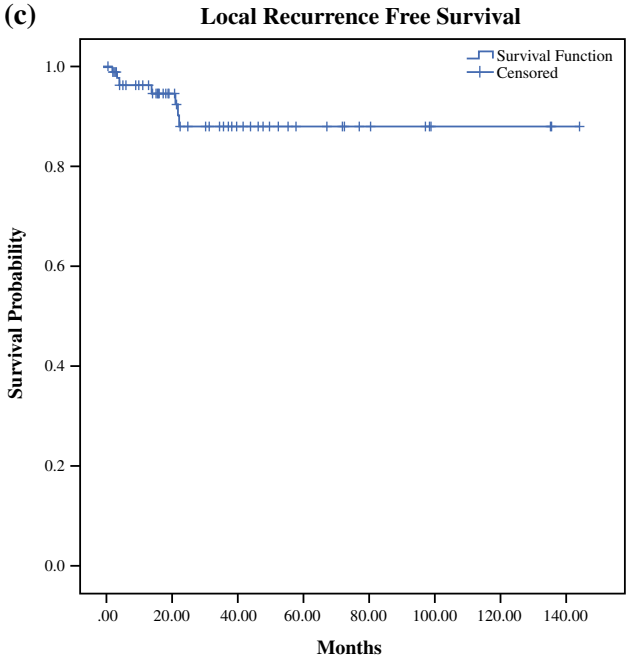
DISCUSSION

This study represents the largest to date specifically examining level III lymph node positivity in patients with palpable axillary lymphadenopathy from metastatic melanoma, an important patient cohort given the paradigm-shifting MSLT II results.[2]

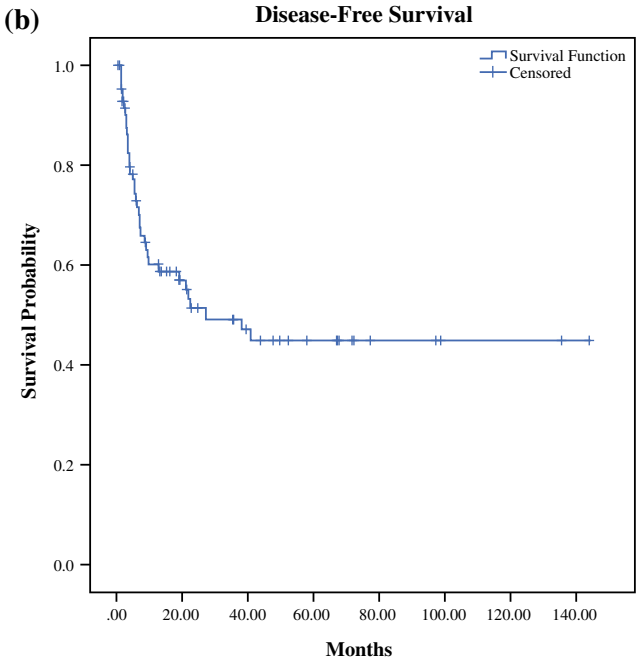
There has been minimal published data specifically examining level III positivity in patients with palpable axillary disease. A series of 117 patients with separate level III analysis, which included 44 patients with palpable disease, reported an 18% level III positivity rate for patients with clinically palpable disease preoperatively. These patients had a 11.4% axillary recurrence rate with a median DFS of 13.6 months. Similarly, patients with



Median OS	Not reached
1-year OS	63/76 (82.9%)
3-year OS	33/56 (58.9%)
5-year OS	16/41 (39.0%)



Median LRFS	Not Reached
1-year LRFS	61/64 (95.3%)
3-year LRFS	31/38 (81.6%)
5-year LRFS	16/23 (69.6%)



Median DFS	26.8 months
1-year DFS	42/72 (58.3%)
3-year DFS	23/59 (39.0%)
5-year DFS	13/51 (25.5%)

FIG. 2 Kaplan–Meier curves for overall survival (**a**), disease-free survival (**b**), and local recurrence-free survival (**c**)

TABLE 2 Univariate logistic regression for level III positivity, local recurrence, any recurrence, and death

Variable	Level III positive		Local recurrence		Any recurrence		Death	
	OR	*p* value	OR	*p* value	OR	*p* value	OR	*p* value
Gender		0.823		0.681		0.196		0.737
BMI		0.989		0.94		0.987		0.675
Age		0.363		0.976		0.965		0.221
Nodular primary		0.273		0.779		0.721		0.256
Superficial spreading primary		0.321		0.942		0.842		0.557
Ulceration		0.615		0.739		0.052		0.607
Breslow depth		0.35		0.267	1.633	**0.012**		0.867
Clark level		0.381		0.541		0.411		0.729
Primary location		0.913		0.907		0.108		0.367
Unknown primary		0.789		0.998	0.244	**0.013**		0.146
Symptomatic		0.514		0.681		0.436		0.442
Preoperative size on imaging		0.363		0.61		0.25		0.573
Pathological size		0.626		0.479		0.339		0.923
Extranodal extension		0.474		0.263		0.122		0.247
BRAF mutation	1.386	**0.05**		0.965		0.508		0.927
LN ratio I/II	5.967	< **0.001**		0.199	2.8	**0.023**	4.001	**0.002**
Total nodes harvested	1.052	**0.05**		0.763		0.185		0.543
Level III positive				0.987		0.133	1.861	**0.007**
Local recurrence						0.999		0.421
Any recurrence							3.004	< **0.001**

Bold values indicate statistical significance ($p < 0.05$)

OR odds ratio, *BMI* body mass index

positive level III disease had significantly worse outcomes, with 3-year OS of 13.3% versus 57.8% ($p < 0.001$).[5] A series of 19 patients with clinically palpable nodes in a separate study noted a 31.6% rate of level III positivity.[12] These data are consistent with our results demonstrating 16.9% level III positivity for patients with palpable axillary disease; furthermore, level III disease correlated significantly with worse outcomes with median OS of 18.6 months.

The MSLT II reported 23% regional recurrence with a positive SLNB and nodal observation at 3 years.[2] In one large series that included 1251 patients undergoing ALND (78% of whom had palpable lymphadenopathy), regional recurrence was the first site of recurrence in 11% of patients.[6] A similar 13% locoregional first recurrence rate was reported in a series of 57 ALND for palpable disease.[15] In a multisite series, including 441 patients with macroscopic stage III disease of any lymph node basin, the 5-year survival was 43% (compared with 67% in patients with nodal micrometastatic disease, $p < 0.001$).[16] Similarly, 5-year survival for macroscopically positive disease in another large series was 24–46%, with worse survival with increasing number of positive nodes.[1] Our series reported similar 5-year OS rate of 39% with a favorable overall axillary recurrence rate of 8.2%.

The median number of lymph nodes excised in this study was 28 with 96.5% of patients having at least 10 lymph nodes examined. Removal of at least 10 lymph nodes has been suggested as a quality marker for melanoma ALND based on tenth percentile, expert opinion, as well as survival analysis.[17,18] A National Cancer Data Base study recently showed only 31.6% adherence to this Commission on Cancer quality metric nationally.[19] The higher number of lymph nodes excised has been shown to be an independent positive prognostic factor and allowed for proper stratification.[20] Inadequate surgical clearance results in higher rates of understaging and can lead to subsequent undertreatment with adjuvant therapies.[21] The overall number of positive lymph nodes, similar to other cancers, also carries prognostic significance in melanoma.[1,22]

Lymph node ratio is defined as the number of positive lymph nodes to total number of lymph nodes removed during lymphadenectomy. A lower lymph node ratio is independently associated with improved melanoma-specific survival.[23–25] Lymph node ratio has also been shown to stratify prognosis within each N-stage; for example, the 5-year survival was 47% for N3 patients with a ratio of $\leq 10\%$ versus 20% with a ratio $> 25\%$.[23] The prognostic value of lymph node ratio is worse when minimum threshold lymph node retrieval numbers are not met.[26] In

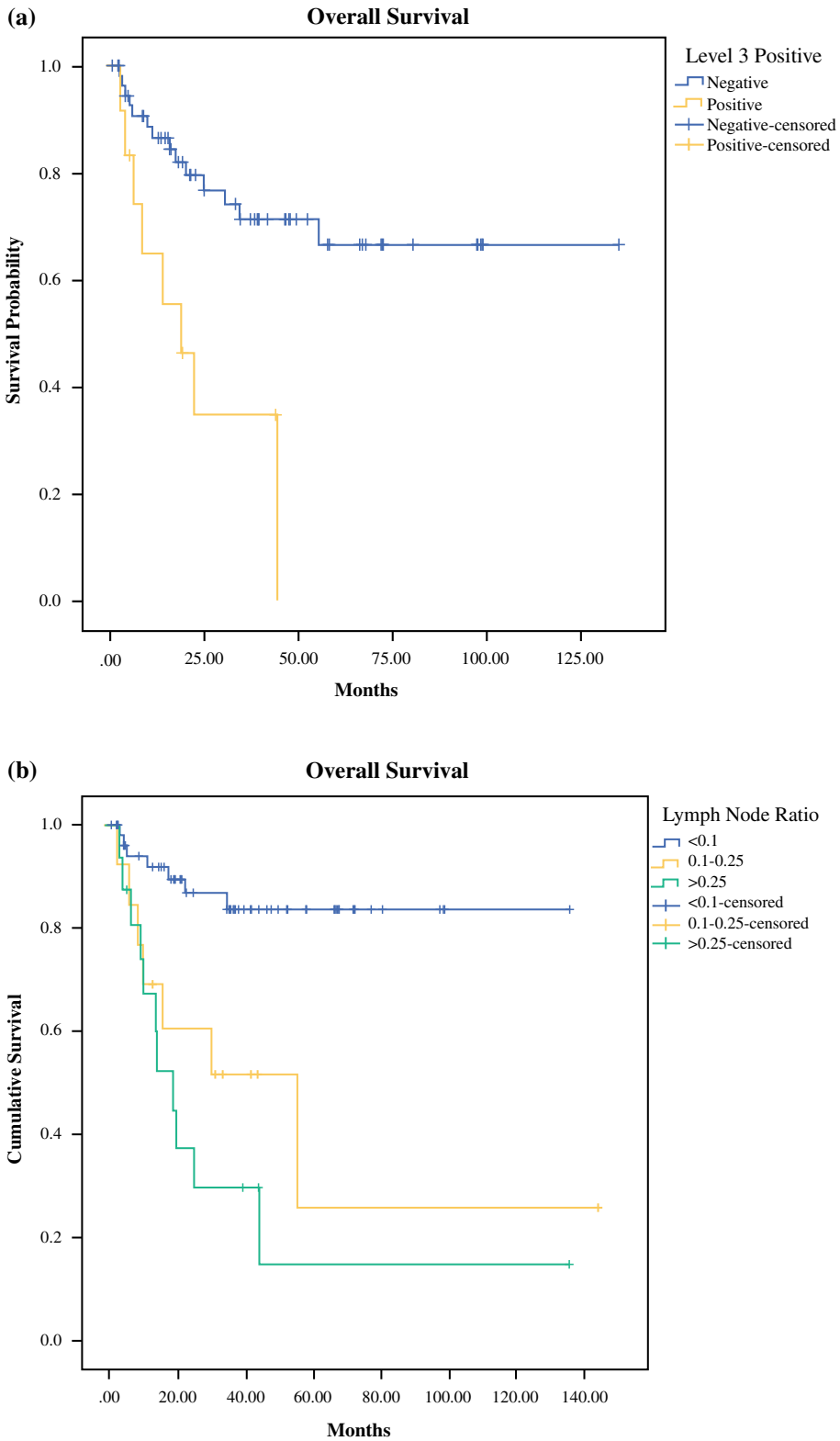


FIG. 3 Overall survival stratified by level 3 positivity (**a**) (log-rank, $p = 0.001$) and lymph node ratio category (**b**) (log-rank, $p < 0.001$)

our study, we similarly show that higher lymph node ratios were associated with worse OS and DFS. Additionally, the lymph node ratio of levels I/II was associated with level III positivity.

Patients with melanomas harboring BRAF mutations were more likely to have level III disease in this study. Whole-genome sequencing of melanomas demonstrate activating mutations of the mitogen-associated protein

kinase (MAPK) pathway, with approximately 40–60% of tumors having constitutive activation of the BRAF kinase.[27] Without targeted therapy, BRAF-mutated melanomas are associated with reduced survival compared to BRAF-wildtype tumors.[28] However, recent phase 3 trials using a combination of BRAF- and MEK-inhibitors have shown improved survival in patients with BRAF-mutated metastatic melanoma.[29] Most patients in our cohort did not have BRAF mutation testing results at the time of lymphadenectomy; however, there is 19% discordancy between primary and metastatic BRAF mutation status.[30] Further study in a larger series of patients would be needed before recommending BRAF testing for surgical planning of ALND. The most common adverse event following ALND is lymphedema. Rates in large series are reported to be approximately 20–24%.[2,31] For melanoma, the addition of level III dissection is not likely to increase the risk of lymphedema significantly and subsequent regional recurrence in this area can be difficult to manage surgically.[32] In our patient population, most lymphedema cases were mild; only two patients (2.4%) reporting moderate symptoms.

Limitations of this study include its retrospective nature as well as lack of comparison to ALND involving only levels I/II, because level I–III ALND was routinely employed throughout the study period. While this study showed low rates of axillary recurrence with similar rates of lymphedema and other complications compared to other series, in the absence of a randomized comparison, one cannot definitively conclude that a less complete surgery could provide similar oncologic outcomes with reduced operative morbidity. The assessment of lymphedema was based on clinical examination and not strict objective criteria, making its evaluation less reliable. The recurrence and survival data in this study should be interpreted cautiously given the nonrandomized administration of various adjuvant therapies. Additionally, while no survival or recurrence differences were seen in this study with adjuvant targeted therapies, the modern adjuvant therapy era may alter these oncologic conclusions and surgical recommendations in the future.

CONCLUSIONS

We conclude that level I–III ALND for palpable axillary disease from melanoma is straight-forward to perform with similar postoperative complication rates and excellent levels of axillary control. Selective level III dissections cannot be recommended as level III positivity is not able to be predicted based on preoperative patient or primary tumor factors, with the exception of BRAF status in some circumstances. Finally, level III positive disease provides important prognostic information for patient overall survival.

DISCLOSURES David A. Mahvi, Mark Fairweather, Charles H. Yoon, and Nancy L. Cho has have nothing to disclose.

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