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Recurrence of Melanoma After a Negative Sentinel Node Biopsy: Predictors and Impact of Recurrence Site on Survival

Daniel C. Thomas, MD, MPH[1], Gang Han, PhD[2], Stanley P. Leong, MD, MS[3], Mohammed Kashani-Sabet, MD[3], John Vetto, MD[4], Barbara Pockaj, MD[5], Richard L. White, MD[6], Mark B. Faries, MD[7], Schlomo Schneebaum, MD[8], Nicola Mozzillo, MD[9], Kim J. Charney, MD[10], Vernon K. Sondak, MD[11], Jane L. Messina, MD[11], Jonathan S. Zager, MD[11], and Dale Han, MD[4]

[1]Yale School of Medicine, New Haven, CT; [2]Texas A and M University, College Station, TX; [3]California Pacific Medical Center, San Francisco, CA; [4]Oregon Health and Science University, Portland, OR; [5]Mayo Clinic, Phoenix, AZ; [6]Carolinas Medical Center, Charlotte, NC; [7]The Angeles Clinic-Cedars Sinai, Los Angeles, CA; [8]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [9]National Cancer Institute of Naples, Naples, Italy; [10]St. Joseph Hospital, Orange, CA; [11]Moffitt Cancer Center, Tampa, FL

ABSTRACT

Background. Factors that predict melanoma recurrence after a negative sentinel lymph node biopsy (SLNB) are not well-defined. We evaluated melanoma recurrence patterns, factors prognostic for recurrence, and the impact of recurrence on outcomes after a negative SLNB.

Methods. The Sentinel Lymph Node Working Group database was evaluated from 1996 to 2016 for negative SLNB melanoma patients. Clinicopathologic characteristics were correlated with recurrence, overall survival (OS), and melanoma-specific survival (MSS).

Results. Median follow-up was 32.1 months. Recurrences developed in 558 of 5351 negative SLN patients (10.4%). First-site of recurrence included a local or in-transit recurrence (LITR) in 221 cases (4.1%), nodal recurrence (NR) in 109 cases (2%), and distant recurrence (DR) in 220 cases (4.1%). On multivariable analysis, age, thickness, head/neck or lower extremity primary, and microsatellitosis significantly predicted for an LITR as first-site. Having an LITR as first-site significantly predicted for a subsequent NR and DR, and significantly predicted for worse OS and MSS. Furthermore, thickness and head/neck or lower extremity primary significantly predicted for an NR as first-site, while a prior LITR significantly predicted for a subsequent NR. Factors significantly predictive for a DR included thickness, head/neck or trunk primary, ulceration, and lymphovascular invasion. Patients with any type of locoregional recurrence were at higher risk for a DR.

Conclusions. Recurrences occur in 10.4% of negative SLN patients, with LITR and DR being the most common types. Importantly, having an LITR significantly predicts for a subsequent NR and DR, and is prognostic for worse survival after a negative SLNB.

Sentinel lymph node biopsy (SLNB) provides prognostic data in patients with localized disease. [1] Overall, 15–20% of melanoma patients will have nodal metastasis, and SLN status is the strongest prognostic marker for recurrence and melanoma-related death.[2–5] Specifically, positive SLN patients are at higher risk for recurrence and have worse 5-year survival, ranging from 59 to 78%.[4]

In contrast, negative SLN patients have more favorable outcomes, yet a proportion of negative SLN patients will experience disease recurrence.[6] Up to 8.9–16.0% of negative SLN cases will develop a recurrence, with DRs representing the most common type.[6–9] Importantly, negative SLN patients represent the large majority of patients

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D. Han, MD
e-mail: handal@ohsu.edu

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who undergo nodal staging (80–85%), and therefore the absolute number of patients who experience a recurrence is greatest in the negative SLNB population.

The literature describing predictors for recurrences after a negative SLNB is relatively limited, and many studies focus on nodal recurrences (NRs) or false-negative SLNB.[6,10,11] Furthermore, the impact of the type of recurrence that develops after a negative SLNB has not been well-defined. This study aimed to describe patterns of melanoma recurrence after a negative SLNB in order to identify clinicopathologic factors prognostic for disease recurrence. Moreover, we sought to evaluate the impact of disease recurrence and the type of recurrence on survival for negative SLN patients.

METHODS

Retrospective review of the multi-institutional Sentinel Lymph Node Working Group (SLNWG) [electronic supplementary Table 1] database identified all melanoma patients who underwent SLNB from 1996 to 2016. All contributing SLNWG members obtained Institutional Review Board approval, and each participating institution submitted data through an encrypted, password protected website. Patients < 18 years of age or with missing SLNB data were excluded from the study.

SLNB was performed according to the techniques reported in the literature, and the selection of patients for SLNB was in accordance with national guidelines.[12–14] Patients who were clinically node-negative and deemed medically fit for general anesthesia were treated with SLNB for cases with a thickness > mm. Patients with melanomas between 0.75 and 1 mm were offered SLNB. For cases with melanomas < 0.75 mm in thickness, SLNB was utilized when one or more of the following factors was present: ulceration, higher mitotic rate, lymphovascular invasion (LVI), inadequate staging of the primary site (e.g. positive deep biopsy margin), and younger age. Evaluation of pathology specimens was performed according to pathology guidelines from each individual participating institution.

Age was stratified in 15-year increments, with the median age included in the 50–64 year age reference group. Thickness was grouped in 1 mm increments, with cases > 3 mm combined and median thickness included in the 1.01–2.0 mm reference group. Multiple thickness cut-points and groupings were evaluated, and only thickness groups ≤ 1 mm, 2.01–3.0 mm, and anything > 3 mm demonstrated significant findings in the various analyses. The category > 3 mm was chosen as the last cut-point since significant differences were seen from > 3 mm onward, and this was the lowest thickness grouping in which differences became statistically significant in some analyses. Furthermore, there was a lower number of thick melanoma patients overall in the study (9%), which relatively limited the number of thick cases and recurrence events in some comparison groups. By using a > 3 mm cut-point, this allowed for more robust multivariable analyses between the various comparison groups to assess for predictors of recurrence. Because of these reasons, thickness groups ≤ 1 mm, 2.01–3.0 mm, and > 3 mm were chosen as comparison groups.

Recurrences were stratified by location: (1) local or in-transit recurrence (LITR); (2) NR; and (3) DR. Local and in-transit recurrences were combined due to the inability to clearly distinguish a primary tumor recurrence from an in-transit recurrence. For cases that had concurrent recurrences, each recurrence was counted and categorized in the appropriate recurrence type. Recurrence outcomes were examined in two manners: (1) first-site of recurrence; and (2) overall recurrence (except for overall LITRs due to the small difference in the number of cases between first-site and overall LITR). A false-negative SLNB was recorded if a patient had a negative SLNB and subsequently developed an NR as first-site, specifically in the previous SLNB basin.

Descriptive statistics were reported for both baseline variables and recurrence type. The false-negative rate (FNR) for SLNB was calculated using the following: # false-negative SLNB/(# positive SLNB + # false-negative SLNB)*100. For negative SLN patients, univariable analysis was performed using Pearson's Chi square test. For each recurrence type, multivariable logistic regression was used to examine the association of covariates and the first-site of a specific recurrence, and was reported as odds ratio (OR) with 95% confidence interval (CI). Multivariable analyses were also performed for each recurrence type for overall recurrence. Overall survival (OS) and melanoma-specific survival (MSS) were analyzed using the Kaplan–Meier method, and using the log-rank test to compare survival differences. The follow-up period began at the date of SLNB. Patients with < 1 month of follow-up or with incomplete data on SLNB date and date of death or last follow-up were excluded from the survival analyses. Multivariable Cox proportional hazard regression models were created to estimate the hazard ratio (HR) for death and to identify clinicopathologic factors associated with survival, with a significance of ≤ 0.20 used for inclusion into the models. Backward selection was used for multivariable models, and a p-value ≤ 0.05 was considered statistically significant in all analyses. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Overall Patients

Overall, 6305 patients were included in this study. SLNB was positive in 954 (15.1%) patients and negative in 5351 (84.9%) patients (electronic supplemental Fig. 1). The positive SLN rate in the head/neck was 10.8%, and 10.4% for upper extremity cases, 12.8% for truncal cases, and 25.6% for lower extremity cases. Overall median follow-up was 32.1 months. In total, 873 (13.9%) patients developed recurrences, with 558/5351 (10.4%) negative SLN patients and 315/954 (33.0%) positive SLN patients experiencing recurrences.

Clinicopathologic Characteristics of Negative Sentinel Lymph Node Biopsy (SLNB) Patients

For negative SLN patients, overall median age was 57 years, while overall median thickness was 1.3 mm. The majority of patients were male (56.8%), and the most common tumor location was the trunk (35.5%). Ulceration, LVI, and microsatellitosis (MS) were seen in 18.8, 3.5, and 1.5% of cases, respectively.

The median age of patients who had a recurrence (60 years) was older than those who did not recur (median 56 years, $p < 0.01$), and the recurrence rate increased significantly with increasing age group ($p < 0.01$) [Table 1]. A recurrence was seen in 11.7% of men, which was significantly higher than the recurrence rate seen in women (8.8%, $p < 0.01$). A significantly higher recurrence rate was also seen in patients who had tumors of the head/neck (15.1%) compared with other sites ($p < 0.01$).

Recurrent cases had thicker tumors (median 2.1 mm) compared with non-recurrent cases (median 1.2 mm, $p < 0.01$), and the recurrence rate significantly increased with increasing thickness group ($p < 0.01$). Recurrence rates for patients with ulceration (15.8%), LVI (22.3%), or MS (32.1%) were significantly higher compared with patients without ulceration (8.6%), LVI (9.8%), or MS (10.8%), respectively (all $p < 0.01$).

Recurrence After Negative SLNB

Among the 5351 negative SLN patients, first-site of recurrence included an LITR in 221 cases (4.1%), NR in 109 cases (2%), DR in 220 cases (4.1%), and an unknown site in 8 cases (0.2%). Overall, 225 cases (4.2%) developed an LITR, while 133 cases (2.5%) and 279 cases (5.2%) developed an NR and DR, respectively. Of the 558 recurrent cases, LITR was the most common first-site (39.6%), followed by DR (39.4%). The median times to an LITR as first-site, NR as first-site, and DR as first-site were 16.7 months, 18.6 months, and 31.2 months, respectively.

Predictors of Local or In-Transit Recurrence as First-Site Multivariable analysis revealed that age ≥ 80 years, head/neck or lower extremity primaries, thickness > 3 mm, and MS significantly predicted developing an LITR as first-site (all $p < 0.05$) [Table 2], with MS conferring the greatest risk (OR 3.8, 95% CI 1.9–7.8).

Predictors of Nodal Recurrence Multivariable analysis demonstrated that head/neck or lower extremity primaries, and thickness > 2 mm were significant predictors of developing an NR as first-site (all $p < 0.05$) [Table 2], with head/neck location giving the greatest risk (OR 2.9, 95% CI 1.5–5.5). In contrast, thickness ≤ 1 mm was associated with a lower risk for an NR as first-site (OR 0.2, 95% CI 0.1–0.5; $p < 0.05$). The FNR for SLNB was 10.3%. Three false-negative SLNB cases subsequently developed in-transit disease. In comparing false-negative SLNB cases with true positive SLNB cases, multivariable analysis showed that only head/neck location predicted for a false-negative SLNB.

Multivariable analysis revealed the same independent predictors for overall NR as was seen for NR as first-site (Table 2), however having a prior LITR (OR 3.6, 95% CI 2.0–5.5) also significantly predicted a subsequent NR.

Predictors of Distant Recurrence Significant predictors of DR as first-site on multivariable analysis included head/neck or truncal locations, thickness > 2 mm, ulceration, and LVI (all $p < 0.05$) [Table 2], with LVI showing the greatest risk (OR 2.3, 95% CI 1.3–3.8, $p < 0.05$). Thickness ≤ 1 mm was correlated with a lower risk for a DR as first-site (OR 0.5, 95% CI 0.3–0.8; $p < 0.01$).

Significant predictors of overall DR on multivariable analysis included head/neck or truncal primaries, thickness, ulceration, and LVI (all $p < 0.05$) [Table 2]. In addition, having a prior LITR (OR 3.1, 95% CI 2.1–4.7) or prior NR (OR 3.6, 95% CI 2.2–6.0) significantly predicted for developing a subsequent DR (all $p < 0.05$).

Survival After Negative SLNB

Overall, 4059 negative SLN patients with at least 1 month of follow-up and with complete data on SLNB date and date of death or last follow up were included in the survival analyses. Of these, 472 (11.6%) patients died, with 201 (5.0%) deaths due to melanoma. Five-year OS and MSS for all negative SLNB patients was 86.9% and

TABLE 1 Clinicopathologic characteristics by recurrence in negative SLNB patients [*N* = 5351]

	No recurrence [*N* = 4793]		Recurrence [*N* = 558]		*p*-value
	N	%	*N*	%	
Age, years					< 0.01
18–34	447	94.9	24	5.1	
35–49	1121	91.8	100	8.2	
50–64	1601	90.4	171	9.7	
65–80	1298	86.5	202	13.5	
≥ 80	326	84.2	61	15.8	
Sex					< 0.01
Female	2107	91.2	203	8.8	
Male	2686	88.3	355	11.7	
Location					< 0.01
Head/neck	905	84.9	161	15.1	
Trunk	1723	88.8	177	11.2	
Lower extremity	1043	90.7	131	9.3	
Upper extremity	1113	92.6	89	7.4	
Unknown	9	100.0	0	0.0	
Thickness, mm					< 0.01
0.1–1.0	1757	95.9	76	4.2	
1.01–2.0	1751	90.5	184	9.5	
2.01–3.0	588	83.5	116	16.5	
>3.0	609	78.9	163	21.1	
Unknown	88	82.2	19	17.8	
Ulceration					< 0.01
No	3157	91.4	298	8.6	
Yes	847	84.2	159	15.8	
Unknown	789	88.7	101	11.4	
LVI					< 0.01
No	2325	90.2	252	9.8	
Yes	146	77.7	42	22.3	
Unknown	2322	89.8	264	10.2	
Regression					0.14
No	1890	88.9	236	11.1	
Yes	570	91.6	52	8.4	
Unknown	2333	89.6	270	10.4	
Microsatellitosis					< 0.01
No	2402	89.2	290	10.8	
Yes	53	68.0	25	32.1	
Unknown	2338	90.6	243	9.4	

SLNB sentinel lymph node biopsy, *LVI* lymphovascular invasion

93.3%, respectively; median OS and MSS were not reached.

OS after a negative SLNB was significantly worse for patients who had an LITR or NR as first-site compared with patients who did not have a recurrence ($p < 0.01$) [Fig. 1a]. MSS after a negative SLNB was also significantly worse for patients who had an LITR or NR as first-site compared with patients who did not have a recurrence ($p < 0.01$) [Fig. 2a].

Five-year OS for patients who had an LITR as first-site versus patients with no LITR was 74.5% and 87.7%, respectively ($p < 0.01$) [Fig. 1b]. Five-year OS for patients who had an NR as first-site versus patients with no NR were 64.2% and 87.7%, respectively ($p < 0.01$) [Fig. 1c]. Five-year OS for patients who had a DR as first-site versus patients with no DR were 49.4% and 90.3%, respectively ($p < 0.01$) [Fig. 1d].

TABLE 2 Multivariable predictors of first-site of recurrence and overall recurrence at each site after a negative SLNB

		OR	95% CI	*p*-value		OR	95% CI	*p*-value
LITR as first-site								
Age, years	50–64	Ref						
	≥ 80	2.3	1.5–4.1	< 0.01				
Location	Upper extremity	Ref						
	Head/neck	1.8	1.2–2.7	< 0.01				
	Lower extremity	2	1.3–3.0	< 0.01				
Thickness, mm	1.01–2.0	Ref						
	> 3	2.1	1.5–2.9	< 0.01				
	No microsatellitosis	Ref						
	Microsatellitosis	3.8	1.9–7.8	< 0.01				
NR as first-site					*Overall NR*			
Location	Upper extremity	Ref			Upper extremity	Ref		
	Head/neck	2.9	1.5–5.5	< 0.01	Head/neck	2.3	1.3–4.1	< 0.01
	Lower extremity	2.2	1.1–4.2	0.02	Lower extremity	1.8	1.04–3.2	0.04
Thickness, mm	0.1–1.0	0.2	0.1–0.5	< 0.01	0.1–1.0	0.3	0.1–0.6	< 0.01
	1.01–2.0	Ref			1.01–2.0	Ref		
	2.01–3.0	2.3	1.4–3.8	< 0.01	2.01–3.0	2.3	1.5–3.7	< 0.01
	> 3	2.3	1.4–3.7	< 0.01	> 3	2.2	1.4–3.5	< 0.01
					No LITR	Ref		
					LITR as first-site	3.6	2.0–5.5	< 0.01
DR as first-site					*Overall DR*			
Location	Upper extremity	Ref			Upper extremity	Ref		
	Head/neck	2.0	1.1–3.6	0.02	Head/neck	1.5	1.04–2.2	0.04
	Trunk	1.8	1.2–2.7	< 0.01	Trunk	1.6	1.2–2.3	< 0.01
Thickness, mm	0.1–1.0	0.5	0.3–0.8	< 0.01	0.1–1.0	0.5	0.3–0.7	< 0.01
	1.01–2.0	Ref			1.01–2.0	Ref		
	2.01–3.0	1.7	1.2–2.5	< 0.01	2.01–3.0	1.7	1.3–2.5	< 0.01
	–> 3	1.8	1.2–2.6	< 0.01	> 3	1.8	1.3–2.5	< 0.01
	No ulceration	Ref			No ulceration	Ref		
	Ulceration	1.6	1.1–2.2	< 0.01	Ulceration	1.5	1.1–2.0	0.01
	No LVI	Ref			No LVI	Ref		
	LVI	2.3	1.3–3.8	< 0.01	LVI	1.9	1.1–3.1	0.02
					No LITR	Ref		
					LITR as first-site	3.1	2.1–4.7	< 0.01
					No NR	Ref		
					NR as first-site	3.6	2.2–6.0	< 0.01

SLNB sentinel lymph node biopsy, *OR* odds ratio, *CI* confidence interval, *Ref* reference group, *LITR* local or in-transit recurrence, *NR* nodal recurrence, *DR* distant recurrence, *LVI* lymphovascular invasion

Five-year MSS for patients who had an LITR as first-site was 82.4% compared with 94.0% for patients with no LITR ($p < 0.01$) [Fig. 2b]. Five-year MSS for patients who had an NR as first-site versus patients with no NR was 73.7% and 93.9%, respectively ($p < 0.01$) [Fig. 2c]. Five-year MSS for patients who had a DR as first-site versus patients with no DR was 55.2% and 96.6%, respectively ($p < 0.01$) [Fig. 2d].

On multivariable analysis, older age (≥ 65 years), thickness > 3 mm, ulceration, LITR, NR, and DR were significantly correlated with worse OS (all $p < 0.05$) [Table 3]. In contrast, female sex and thickness ≤ 1 mm were significantly correlated with improved OS (both $p < 0.05$). Multivariable analysis also showed that thickness 3 mm, LITR, NR, and DR were significantly correlated with worse MSS (all $p < 0.05$) [Table 3].

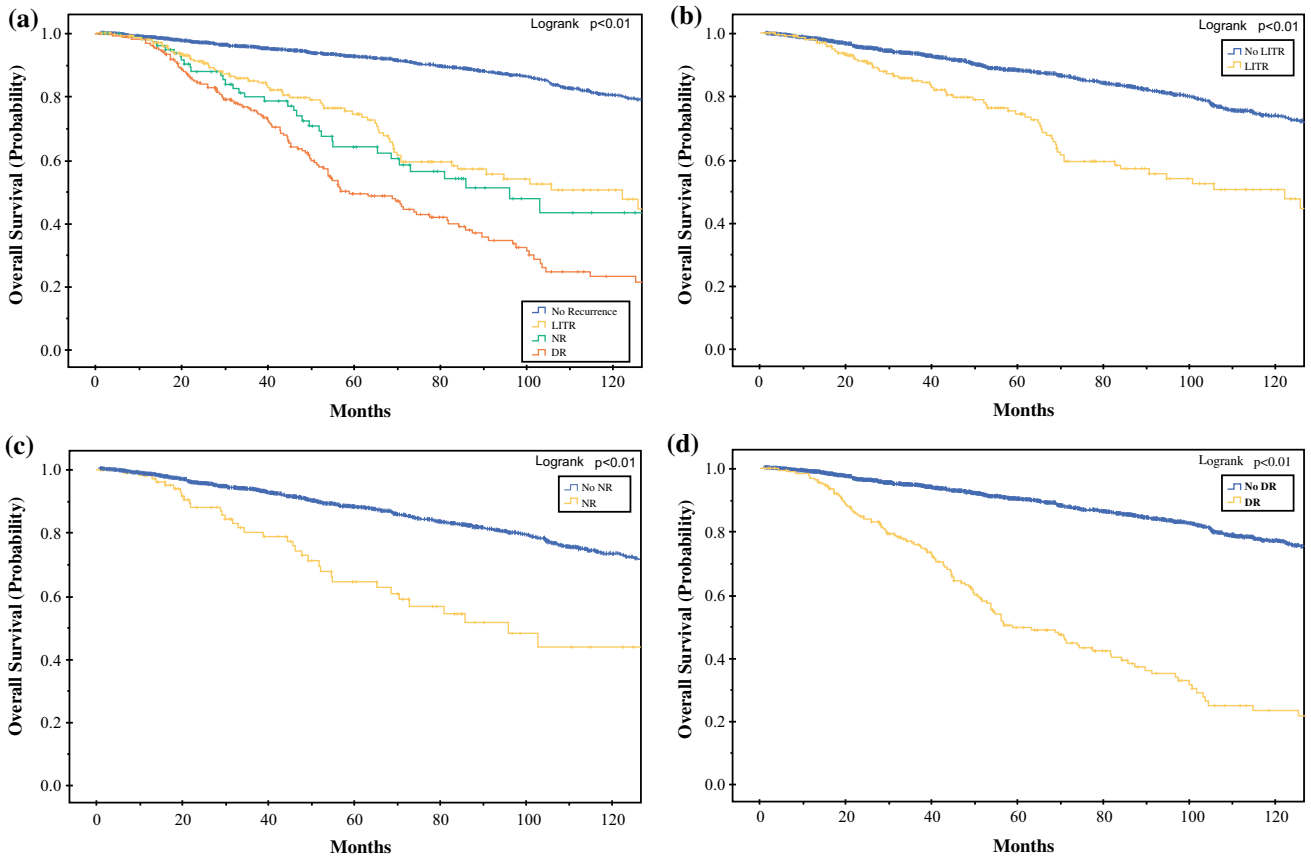

FIG. 1 **a** OS as stratified by recurrence type compared with patients who had no recurrence. **b** OS of patients who had an LITR as first-site compared with patients who had no LITR. **c** OS of patients who had an NR as first-site compared with patients who had no NR. **d** OS of patients who had a DR as first-site compared with patients who had no DR. *OS* overall survival, *LITR* local or in-transit recurrence, *NR* nodal recurrence, *DR* distant recurrence

DISCUSSION

SLN status is the strongest predictor for melanoma recurrence and melanoma-related death.[1] However, a proportion of negative SLN patients will still experience disease recurrence. Recurrence rates in negative SLN patients range from 7.7 to 16%, with DRs being the most common type at 4.6–11%.[7–9,15–17] Our results are consistent since 10.4% of negative SLN patients had disease recurrence, and LITR and DR were the most common types (4.1%). In addition, the FNR of SLNB in this study was 10.3%, which is consistent with a meta-analysis reporting a weighted FNR summary estimate of 12.5%.[5,18,19]

Certain factors were prognostic for each recurrence type after a negative SLNB. Our results demonstrated that thicker tumors were associated with all sites of recurrence, and this finding is consistent with prior studies evaluating factors associated with recurrence.[7, 10,15,17,18,20–22] Furthermore, thickness is a validated prognostic marker for survival in melanoma patients, and the current study also shows that thickness independently predicts for MSS and OS in negative SLN patients. However, it is important to note that recurrences were still seen in 4.2% of thin melanoma patients who had a negative SLNB.[23,24]

MS was found to significantly predict for only LITR in this negative SLNB population, supporting studies that show that MS appears to predict locoregional recurrence but not DR.[25,26] A significantly higher rate of LITR was also seen for lower extremity and head/neck tumors, and these locations are associated with the development of in-transit disease. In addition, older age was significantly associated with LITR in the current study. Although increasing age has been associated with overall recurrence, it has not been correlated with LITR alone.[17,27] One possible explanation may be that given the higher risk for wound issues in the lower extremity or in older patients, a higher percentage of these cases may have been treated with narrower margins, particularly for tumors 1–2 mm thick. However, the margins utilized for wide local excision (WLE) was not recorded in the SLNWG database, and we were unable to evaluate this variable. However, given the lack of consensus for resection margins in this group, and the fact that recurrences still develop despite utilizing

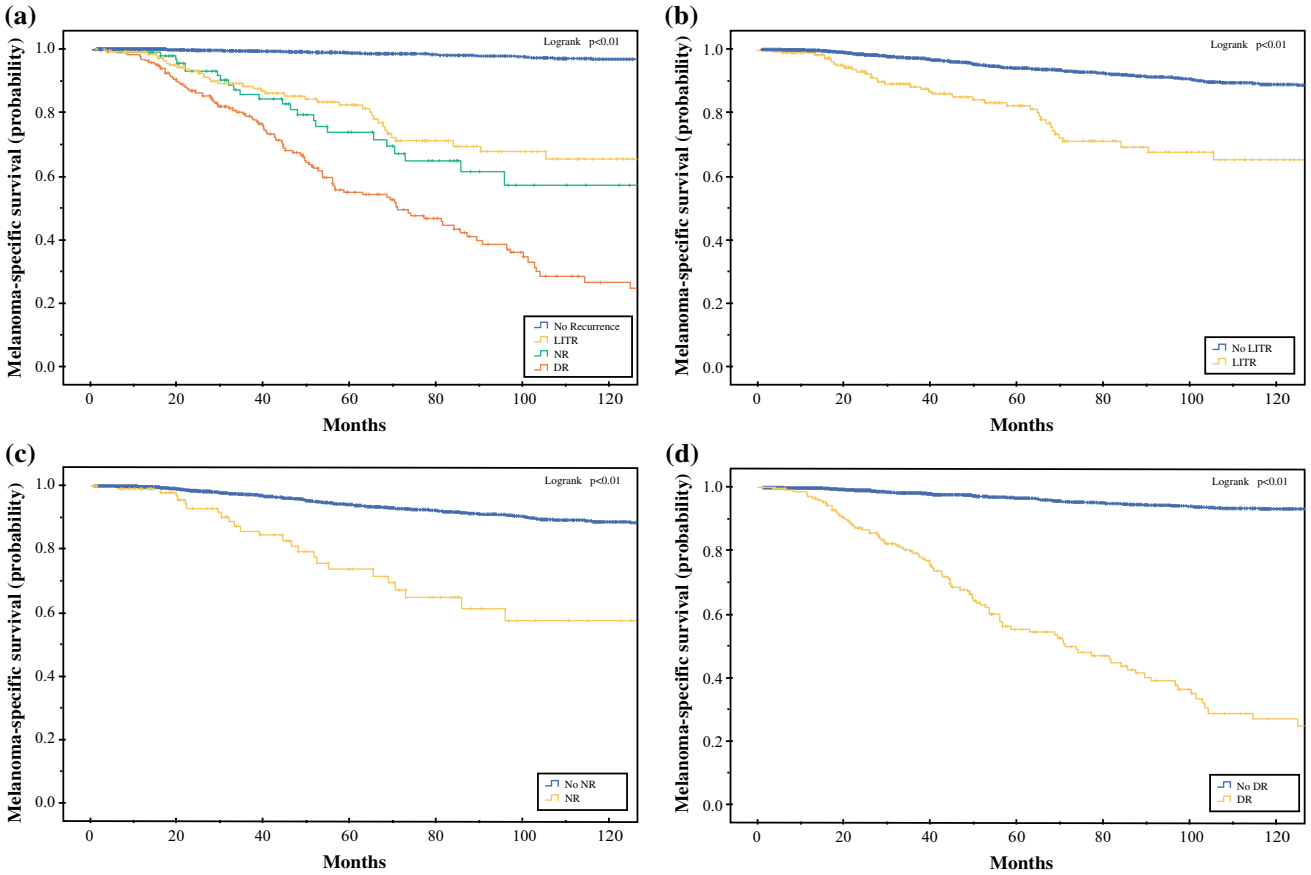

FIG. 2 **a** MSS as stratified by recurrence type compared with patients who had no recurrence. **b** MSS of patients who had an LITR as first-site compared with patients who had no LITR. **c** MSS of patients who had an NR as first-site compared with patients who had no NR. **d** MSS of patients who had a DR as first-site compared with patients who had no DR. *MSS* melanoma-specific survival, *LITR* local or in-transit recurrence, *NR* nodal recurrence, *DR* distant recurrence

recommended margins, it is likely that LITR is affected more by tumor biology rather than margins utilized. In addition, sun damage may also damage lymphatic vessels, thereby potentially increasing the risk for LITR while decreasing the risk for nodal metastasis.[28]

Multivariable analyses found that head/neck primaries were independently predictive of all sites of recurrence, while a truncal primary significantly predicted a DR, which confirms previously described findings.[6,7,20,29] Of note, in comparing false negative with true positive SLN cases, the only significant factor on multivariable analysis was a head/neck tumor location, a finding that has been previously reported.[30] It is possible that the correlation between a false-negative result and a head/neck location may be related to a lower positive SLN rate for head/neck cases (10.8%), such that a missed SLN with micrometastatic disease develops into a later NR. Although the upper extremity had a comparable positive SLN rate (10.4%) but did not significantly predict for a false negative result, the upper extremity was used as the reference group in the multivariable analyses, and head/neck location remained as a significant predictor for an NR after a negative SLNB. Interestingly, having a tumor on the lower extremities was also associated with an NR, in contrast to prior studies that have found no significant association. While the mechanisms behind the association between head/neck, truncal or lower extremity melanomas and disease recurrence are unclear, it may in part be a result of the complex and varying lymphatic drainage patterns in these regions, potentially more aggressive tumor biology in these locations, and more technically difficult nodal dissections in these basins.[6,31]

Additional factors predictive of recurrence included ulceration and LVI, both of which predicted a DR in negative SLN patients. Ulceration is a well-validated prognostic marker in melanoma, and other studies have reported that LVI is associated with recurrence.[7] However, there is very little data reported on the risks for developing subsequent metastases after an LITR. We found that developing an LITR significantly increased the risks for developing a subsequent NR and DR.

TABLE 3 Multivariable predictors of overall and melanoma-specific survival in negative SLNB patients

	HR	95% CI	*p*-value
Overall survival			
Age, years			
35–49	0.7	0.4–0.9	0.01
50–64	Ref		
65–80	1.8	1.4–2.2	< 0.01
> 80	5.0	3.7–6.6	< 0.01
Sex			
Male	Ref		
Female	0.8	0.6–0.9	< 0.01
Thickness, mm			
0.1–1.0	0.6	0.5–0.9	< 0.01
1.01–2.0	Ref		
> 3	1.5	1.2–1.9	< 0.01
No ulceration	Ref		
Ulceration	1.5	1.2–1.9	< 0.01
No LITR	Ref		
LITR as first-site	2.4	1.9–3.3	< 0.01
No NR	Ref		
NR as first-site	3.9	2.7–5.5	< 0.01
No DR	Ref		
DR as first-site	6.6	5.3–8.3	< 0.01
Melanoma-specific survival			
Thickness, mm			
1.01–2.0	Ref		
> 3	1.9	1.4–2.7	< 0.01
No LITR	Ref		
LITR as first-site	15.0	9.5–23.8	< 0.01
No NR	Ref		
NR as first-site	18.4	10.8–31.3	< 0.01
No DR	Ref		
DR as first-site	42.2	28.5–62.5	< 0.01

SLNB sentinel lymph node biopsy, *HR* hazard ratio, *CI* confidence interval, *Ref* reference group, *LITR* local or in-transit recurrence, *NR* nodal recurrence, *DR* distant recurrence

Negative SLN patients who developed a DR had a 5-year MSS of only 55.2%, while those with an NR had an MSS of 73.7%. Importantly, this study also showed the significantly negative impact of LITR on survival. In-transit disease has been correlated with worse survival, however the impact of a local recurrence (LR) by itself is not well-defined. The Intergroup trial, which assessed margin width in melanoma WLE, showed that patients who had an LR had significantly worse survival compared with patients who did not have an LR.[32] The current study shows that patients who had either a local or in-transit recurrence had significantly worse OS and MSS compared with patients with no LITR, with a 5-year MSS of 82.4%.

This study has several limitations. The high proportion of missing values for some variables, such as for histologic subtype of melanoma, limits the interpretation of these data. Furthermore, institutional variations in pathology evaluation may impact the results of this study, particularly in the assessment and reporting of tumor characteristics such as regression.[33] In addition, the high proportion of missing data on the type of treatments utilized following a melanoma recurrence prevented analysis of the impact of these specific treatments on OS and MSS. Finally, the median follow-up period was relatively short at 32.1 months, which may have limited the number of recurrences captured.

CONCLUSIONS

This large study demonstrates that recurrences after a negative SLNB occur in 10.4% of patients after a median follow-up of 32.1 months. LITR and DR are the most common recurrence types, and the FNR for SLNB is 10.3%. Specific factors are prognostic for the development of an LITR, NR, and DR, which may allow for stratification of patients who are at greater risk for recurrence after a negative SLNB. Importantly, our data show that having an LITR significantly predicts for a subsequent NR and DR, and that the development of an LITR is associated with worse survival.

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REFERENCES

1. Han D, Thomas DC, Zager JS, Pockaj B, White RL, Leong SP. Clinical utilities and biological characteristics of melanoma sentinel lymph nodes. *World J Clin Oncol.* 2016;7(2):174–88.
2. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med.* 2006;355(13):1307–17.
3. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med.* 2014;370(7):599–609.
4. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol.* 2009;27(36):6199–206.
5. Valsecchi ME, Silbermins D, de Rosa N, Wong SL, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in patients

with melanoma: a meta-analysis. *J Clin Oncol.* 2011;29(11):1479–87.
6. Zogakis TG, Essner R, Wang HJ, Foshag LJ, Morton DL. Natural history of melanoma in 773 patients with tumor-negative sentinel lymph nodes. *Ann Surg Oncol.* 2007;14(5):1604–11.
7. Jones EL, Jones TS, Pearlman NW, et al. Long-term follow-up and survival of patients following a recurrence of melanoma after a negative sentinel lymph node biopsy result. *JAMA Surgery.* 2013;148(5):456–61.
8. O'Connell EP, O'Leary DP, Fogarty K, Khan ZJ, Redmond HP. Predictors and patterns of melanoma recurrence following a negative sentinel lymph node biopsy. *Melanoma Res.* 2016;26(1):66–70.
9. Wagner JD, Ranieri J, Evdokimow DZ, et al. Patterns of initial recurrence and prognosis after sentinel lymph node biopsy and selective lymphadenectomy for melanoma. *Plast Reconstr Surg.* 2003;112(2):486–97.
10. Gershenwald JE, Colome MI, Lee JE, et al. Patterns of recurrence following a negative sentinel lymph node biopsy in 243 patients with stage I or II melanoma. *J Clin Oncol.* 1998;16(6):2253–60.
11. Scoggins CR, Martin RCG, Ross MI, et al. Factors associated with false-negative sentinel lymph node biopsy in melanoma patients. *Ann Surg Oncol.* 2010;17(3):709–17.
12. Coit DG, Andtbacka R, Anker CJ, et al. Melanoma version 22013 featured updates to the NCCN guidelines. *J Natl Compr Canc Netw.* 2013;11(4):395–407.
13. Wong SL, Balch CM, Hurley P, et al. Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guideline. *Ann Surg Oncol.* 2012;19(11):3313–24.
14. Morton DL, Thompson JF, Essner R, et al. Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. *Ann Surg.* 1999;230(4):453–53.
15. Gambichler T, Scholl L, Bechara FG, Stockfleth E, Stucker M. Worse outcome for patients with recurrent melanoma after negative sentinel lymph biopsy as compared to sentinel-positive patients. *Eur J Surg Oncol.* 2016;42(9):1420–26.
16. Yee VSK, Thompson JF, McKinnon JG, et al. Outcome in 846 cutaneous melanoma patients from a single center after a negative sentinel node biopsy. *Ann Surg Oncol.* 2005;12(6):429–39.
17. Clary BM, Brady MS, Lewis JJ, Coit DG. Sentinel lymph node biopsy in the management of patients with primary cutaneous melanoma: review of a large single-institutional experience with an emphasis on recurrence. *Ann Surg.* 2001;233(2):250.
18. Chao C, Wong SL, Ross MI, et al. Patterns of early recurrence after sentinel lymph node biopsy for melanoma. *Am J Surg.* 2002;184(6):520–24.
19. Jansen L, Nieweg OE, Peterse JL, Hoefnagel CA, Olmos RA, Kroon BB. Reliability of sentinel lymph node biopsy for staging melanoma. *Br J Surg.* 2000;87(4):484–89.
20. Saltman BE, Ganly I, Patel SG, et al. Prognostic implication of sentinel lymph node biopsy in cutaneous head and neck melanoma. *Head Neck.* 2010;32(12):1686–92.
21. Balch CM, Soong S, Murad T, Ingalls A, Maddox W. A multifactorial analysis of melanoma. II. Prognostic factors in patients with stage I (localized) melanoma. *Surgery.* 1979;86(2):343–51.
22. Bello DM, Han G, Jackson L, et al. The prognostic significance of sentinel lymph node status for patients with thick melanoma. *Ann Surg Oncol.* 2016;23 Suppl 5:938–45.
23. Han D, Zager JS, Shyr Y, et al. Clinicopathologic predictors of sentinel lymph node metastasis in thin melanoma. *J Clin Oncol.* 2013;31(35):4387–93.
24. Han D, Yu D, Zhao X, et al. Sentinel node biopsy is indicated for thin melanomas $\geq$ 0.76 mm. *Ann Surg Oncol.* 2012;19(11):3335–42.
25. Shaikh L, Sagebiel RW, Ferreira CM, et al. The role of microsatellites as a prognostic factor in primary malignant melanoma. *Arch Dermatol.* 2005;141(6):739–42.
26. Kelly JW, Sagebiel RW, Calderon W, Murillo L, Dakin RL, Blois MS. The frequency of local recurrence and microsatellites as a guide to reexcision margins for cutaneous malignant melanoma. *Ann Surg.* 1984;200(6):759–63.
27. Balch CM, Soong S-J, Thompson JF, et al. Age as a predictor of sentinel node metastasis among patients with localized melanoma: an inverse correlation of melanoma mortality and incidence of sentinel node metastasis among young and old patients. *Ann Surg Oncol.* 2014;21(4):1075–81.
28. Sawane M, Kajiya K. Ultraviolet light-induced changes of lymphatic and blood vasculature in skin and their molecular mechanisms. *Exp Dermatol.* 2012;21 Suppl 1:22–5.
29. Fadaki N, Li R, Parrett B, et al. Is head and neck melanoma different from trunk and extremity melanomas with respect to sentinel lymph node status and clinical outcome? *Ann Surg Oncol.* 2013;20(9):3089–97.
30. Lee DY, Huynh KT, Teng A, et al. Predictors and survival impact of false-negative sentinel nodes in melanoma. *Ann Surg Oncol.* 2016;23(3):1012–18.
31. McDonald K, Page AJ, Jordan SW, et al. Analysis of regional recurrence after negative sentinel lymph node biopsy for head and neck melanoma. *Head Neck.* 2013;35(5):667–71.
32. Balch CM, Soong S-J, Smith T, et al. Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1–4 mm melanomas. *Ann Surg Oncol.* 2001;8(2):101–8.
33. Rubinstein JC, Han G, Jackson L, et al. Regression in thin melanoma is associated with nodal recurrence after a negative sentinel node biopsy. *Cancer Med.* 2016;5(10):2832–40.