Research Article

The Natural History of Thin Melanoma and the Utility of Sentinel Lymph Node Biopsy[1]

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Synopsis:

This study examines the natural history of thin melanoma, 0.75 – 0.99 mm Breslow depth, assesses the likelihood for regional nodal disease, and identifies high-risk features to guide future patient selection for sentinel lymph node biopsy (SLNB).

Abstract

Background and Objectives: Current literature may overestimate the risk of nodal metastasis from thin melanoma due to reporting of data only from lesions treated with SLNB. Our objective was to define the natural history of thin melanoma, assessing the likelihood of nodal disease, in order to guide selection for SLNB.

Methods: Retrospective review. The primary outcome was the rate of nodal disease. Clinicopathologic factors were evaluated to find associations with nodal disease.

Results: 512 lesions, follow up available for 488 (median: 48 months). Lesions treated with WLE/SLNB compared to WLE alone were more likely to have high-risk features. The rate of nodal disease was higher in the WLE/SLNB group (24 positive SLNB, 5 false-negative SLNB with nodal recurrence: 10.2%) compared to WLE alone (4 nodal recurrences: 2.0%). Univariate analysis showed age ≤ 45, Breslow depth ≥ 0.85 mm, mitotic rate >1/mm^2, and ulceration were associated with nodal disease. Multivariate analysis confirmed the association of age ≤ 45 and ulceration.

Conclusions: SLNB for melanoma 0.75 – 0.99 mm should be considered in patients age ≤ 45, Breslow depth ≥ 0.85 mm, mitotic rate > 1/mm^2, and/or with ulceration. Thin melanoma < 0.85 mm without high-risk features may be treated with WLE alone.

Key Words: melanoma, thin melanoma, sentinel lymph node biopsy

Main Text:

Introduction:

Thin melanoma is defined as invasive melanoma with Breslow depth < 1.0 mm and generally has an excellent prognosis.[1,2] While the risk of nodal and distant metastasis from thin melanoma is low, optimizing treatment is important as an estimated 40,000 new cases of thin melanoma are diagnosed annually in the United States alone, representing the majority of new cases.[3]

Robust data support the utility of sentinel lymph node biopsy (SLNB) for melanoma ≥ 1.0 mm Breslow depth.[4-9] Data regarding SLNB for thin melanoma (< 1.0 mm), in contrast, is limited by retrospective and often conflicting reports of what constitutes high-risk features for nodal metastasis and thus selection criteria for performance of SLNB.[10,11] The 2016 National Comprehensive Cancer Network (NCCN) guidelines recommend "discussion and consideration" of SLNB for melanoma 0.76-1.0 mm, particularly for lesions with high-risk histologic features.[8] High-risk features can include increasing Breslow depth, ulceration, lymphovascular invasion, and a high mitotic rate.[8] Other reports have included young age, positive deep margin on biopsy, Clark level IV/V, vertical growth phase, regression, and lack of tumor infiltrating lymphocytes as adverse prognosticators.[12-25]

The purpose of our study was to define the natural history of thin melanoma 0.75 – 0.99 mm, identify features associated with a higher risk for regional nodal disease, and thus determine patient selection criteria for SLNB in the future. We evaluated a cohort of consecutive patients with melanoma 0.75 – 0.99 mm treated at a single institution concordant with NCCN guidelines with either WLE plus SLNB or WLE alone. By analyzing all patients, rather than only patients treated with WLE plus SLNB as in the majority of reports in the literature, we aimed to more

completely define the natural history through recurrence outcomes and to identify high-risk features associated with regional nodal disease not simply SLN positivity.

Materials and Methods:

Study approval was granted by the University of Michigan Medical School Institutional Review Board for Human Subject Research. Our prospectively collected database was queried for melanoma Breslow depth 0.75 – 0.99 mm, diagnosed and treated at the University of Michigan between January, 2005 and July, 2015. Cases were excluded if subsequent excisional biopsy or WLE specimen contained melanoma ≥1.0 mm or if the patient had a known second primary Breslow depth ≥ 1.0 mm. Demographic, clinical, and outcome measures were confirmed via the electronic medical record and by phone contact with the patient or referring physician's office. The follow up time for each patient was calculated as the difference between initial biopsy date and date of last contact, with the median follow-up time reported. The follow up period ended April 15, 2016.

All patients were seen in the Multidisciplinary Melanoma Clinic for consultation and discussion regarding melanoma treatment. SLNB was considered for all patients based on Breslow depth 0.75-0.99 mm, concordant with NCCN guidelines.[26] The presence of additional features considered higher risk for occult regional lymph node metastasis based on current literature included: increasing Breslow depth, ulceration, lymphovascular invasion, high(er) mitotic rate and young(er) age, regression (defined as partial or complete replacement of melanoma with a variable host response, as previously described),[27] and positive deep margin on biopsy. Patients were treated with WLE or WLE plus SLNB based on the discussion of potential risks and benefits of the surgery, risk of nodal metastasis, and individual patient preference.

Surgery was performed by 32 different surgeons from the University of Michigan Departments/Divisions of Dermatology, Surgical Oncology, Plastic Surgery, Otolaryngology-Head and Neck Surgery, Gynecology Oncology (one case), and Pediatric Surgery (one case). Those treated with WLE plus SLNB were treated by one of 14 surgeons who routinely perform SLNB, according to our standard practices.[6,8] Patients treated with WLE only usually had procedures performed with local anesthesia in a treatment room with a 1 cm margin.[8] All WLE specimens were processed using formalin-fixed permanent sections. SLNs were formalin fixed, serially sectioned and evaluated with hematoxylin and eosin, S100, and Melan A immunostains, as previously described.[28] All specimens were interpreted by dermatopathologists with expertise in melanoma and SLN evaluation.

Patients with a positive SLN(s) were counseled regarding completion lymph node dissection (CLND) as the standard of care following identification of a positive SLN. Adjuvant therapy was considered following consultation with attending physicians from Medical Oncology with expertise in melanoma. Adjuvant and systemic therapy options did change during the study time frame due to the development of new therapies.[29]

Statistical Method:

The outcomes evaluated were: SLNB positivity rate, local recurrence, in-transit recurrence, regional nodal recurrence, distant recurrence, and death from melanoma. Descriptive statistics were calculated for each clinical and pathological variable (frequency/percentage for a categorical variable, mean/standard deviation for a continuous variable). The events of interest were performance of SLNB (yes/no) and presence of nodal disease (defined as either a positive SLNB or nodal recurrence in the follow up period, regardless of SLNB status). To determine an

association between any factor and the event of interest, a logistic regression model was used. To appropriately control for potential confounding clinical and pathologic variables when explaining nodal disease, a multivariate logistic regression model was used. All variables were considered in the model, including the two-way interactions (age × mitotic rate, age × Breslow depth, and age × ulceration). A stepwise variable selection procedure was used to select important variables to be included in the final logistic regression model (a significance level of 0.3 was used to allow a variable into the model, and a significance level of 0.35 was used for a variable to stay in the model). The final model included age, Breslow depth, ulceration, and mitotic rate (no interaction was found to be statistically significant). The parameter estimates from the model, the p value from the Wald chi-square test for the significance of the parameter, the odds ratio (OR), and a 95% Wald-based confidence interval (95% CI) for the OR were reported. Significance was determined if $p<0.05$. For the univariate and multivariate analyses of features associated with the presence of nodal disease, age and Breslow depth were analyzed as categorical variables for consideration as potential patient selection criteria for SLNB in clinical practice guidelines. Consistent with current literature and our practice guidelines, categorical age was defined as ≤ 45 and > 45 years. Similarly, and with consideration of the new AJCC definition of T1a/b lesions based on a 0.8 mm cutpoint (to define tumor thickness measurements at the "tenth" rather than "hundredth" digit), categorical Breslow depth was defined as < 0.85 and ≥ 0.85 mm to allow for classifying as 0.8 mm or ≥ 0.9 mm, respectively. All analyses were conducted using SAS (version 9.4, SAS Institute, Cary, NC).

Results:

Based on initial biopsy, 552 thin melanomas with Breslow depth 0.75-0.99 mm were identified. Forty lesions were excluded after subsequent excisional biopsy or WLE demonstrated depth ≥

1.0 mm. In 24/40 (60%), residual tumor was noted at the consultation visit and deeper melanoma was suspected. The median final Breslow depth of these 40 lesions was 2.07 mm.

In the study cohort, there were 510 patients with 512 lesions Breslow depth 0.75-0.99 mm. The mean patient age was 56.7 years (range 16-92). Two hundred twenty-six (44.3%) were women, 284 (55.7%) were men. The majority of lesions were located on the extremities (238/512, 46.5%) and trunk (178/512, 34.8%) with a smaller number on the head or neck (96/512, 18.8%). The predominant histologic subtype was superficial spreading (405/512, 79.1%). The other main histologic subtypes included lentigo maligna melanoma (32/512, 6.3%), unclassified type (26/512, 5.1%), nodular (20/512, 3.9%), nevoid (12/512, 2.3%), and spitzoid (9/512, 1.8%).

Two hundred ninety-five (57.6%) tumors were treated with WLE plus SLNB. The remaining 217 (42.4%) tumors were treated with WLE alone. Comparison of patient and lesion characteristics for the WLE plus SLNB vs. WLE groups showed that younger age (continuous) ($p<0.001$), gender (F vs. M) ($p < 0.001$), Breslow depth (continuous) ($p<0.0001$), mitotic rate $\geq 1/mm^2$ ($p<0.001$), positive deep margin on biopsy ($p=0.019$), ulceration ($p=0.007$), and regression ($p=0.006$) were associated with performance of SLNB (Table 1).

The SLN identification rate was 98.3% (290/295). The median number of SLNs removed per patient was 2. Two hundred fifty-four patients (87.6%) had SLNs removed from only one nodal basin, 34 lesions (11.7%) mapped to two basins, and 2 lesions (0.7%) mapped to three unique nodal basins. The rate of SLNB positivity was 8.1% (24/295). Twenty-one patients (87.5%) had one positive SLN, 1 patient (4.2%) had two, and 2 patients (8.3%) had 3 positive SLNs. No extracapsular extension was identified. Nineteen (79.2%) of 24 patients with a positive SLNB underwent CLND. Three patients declined and two died prior to CLND from unrelated causes

(acute cerebrovascular accident and pyelonephritis). Of the 19 who had CLND, no additional positive nodes were identified.

Following CLND, 4 patients were treated with adjuvant high-dose interferon therapy. Two discontinued treatment due to side effects (after 2 months and 3 months, respectively). Another patient entered an adjuvant therapy clinical trial (Dabrafenib 150 mg p.o. twice daily + Trametinib 2 mg p.o. daily versus placebo).

Twenty-four patients (4.7%) were lost to follow up after the immediate post-operative period (12 WLE, 12 WLE plus SLNB). The median follow-up time for the remaining 486 patients (488 tumors: 205 WLE, 283 WLE plus SLNB) was 48 months. The treatment and outcomes of the cohort are represented in Figure 1.

Two tumors (0.4%) located on the head and neck (one lentigo maligna melanoma, one superficial spreading type) locally recurred after 15 and 28 months, respectively, after WLE only. Two patients (0.4%) developed in-transit recurrence. One patient (treated with WLE alone) was diagnosed concurrently with in-transit and nodal recurrence. The other patient (treated with WLE plus SLNB) developed in-transit recurrence at 52 months and nodal disease at 53 months.

Nine (1.8%) regional nodal basin recurrences developed; 4 in patients treated with WLE alone and 5 in patients treated with WLE plus negative SLNB. Thus, the false negative rate (FNR) was 17.2% (5 false negative SLNB/[5 false negative SLNB + 24 true positive SLNB]. All 5 patients with a negative SLNB who developed regional nodal recurrence failed in the same basin as the SLNB. For the two cases of false-negative SLNB on the head and neck, one patient was treated prior to routine use of single-photon emission computed tomography with CT (SPECT/CT) and, therefore, did not have SPECT/CT imaging as part of the SLNB procedure. Two patients

developed in-transit recurrence in addition to nodal recurrence (1 WLE alone [concurrent in-transit and nodal recurrence]), 1 WLE plus SLNB [in-transit recurrence one month before nodal recurrence]). The median time to nodal recurrence was 16 months (range: 6-53). No nodal recurrences occurred in patients who had a positive SLNB (median follow up time for this subset of patients was 32.5 months), including those who did not have CLND. The patient and lesion characteristics for cases of nodal recurrence are provided in Table 2.

In total, 33 (6.8%) patients ultimately developed nodal metastases from thin melanoma (24 found with positive SLNB and 9 nodal recurrences). Regional nodal disease was the most common first site of disease identified beyond the primary site (32 [1 with concurrent in-transit disease and 1 with concurrent distant disease] of 35 patients with stage III/IV disease). Univariate analysis showed that age ≤ 45 (p=0.027), Breslow depth ≥ 0.85 mm (p=0.04), mitotic rate >1/mm^2 (p=0.031), and ulceration (p=0.001) were significantly associated with nodal disease. Microsatellitosis was not present in any tumor. Multivariate analysis was performed as previously described. The final model considered age (> 45 vs. ≤ 45), Breslow depth (≥0.85 vs. <0.85 mm), mitotic rate (>1/mm^2 vs. ≤ 1/mm^2), and ulceration (present vs. absent); only age ≤ 45 (>45 vs. ≤ 45: p = 0.007, OR 0.336, 95% CI 0.152-0.74) and ulceration (present vs. absent: p = 0.003, OR 5.932, 95% CI 1.805 – 19.496) were statistically significant independent factors associated with nodal disease (Table 3).

Eight (1.6%) distant recurrences developed (the median time to distant recurrence was 28.5 months, range 10-74), resulting in 7 deaths. Four lesions were treated with WLE and 4 were treated with WLE plus negative SLNB. Nodal recurrence preceded distant metastasis in 5 cases (62.5%), by a median time of 12 months (range: 4-21). One patient developed nodal recurrence and distant metastasis concurrently after 10 months (WLE and false-negative SLNB). Two

patients developed distant metastatic disease without nodal recurrence (both were treated with WLE alone). One patient with distant metastasis remains alive (78 months from primary diagnosis, 23 months from initiation of systemic therapy). No distant recurrences developed in patients with a positive SLNB (median follow up time for this subset of patients was 32.5 months).

Discussion:

The intent of this study was to use SLNB data and recurrence outcomes to define the natural history of thin melanoma (0.75 – 0.99 mm) in terms of disease recurrence and risk of nodal metastases with and without SLNB, and to identify factors associated with nodal disease that could be useful as patient selection criteria for SLNB. This study was intentionally designed to include patients treated with WLE plus SLNB and patients treated with WLE alone and differs from the majority of outcome studies of thin melanoma that only evaluate patients undergoing WLE plus SLNB. As patients are frequently selected for SLNB because of higher risk features for nodal metastases, these prior studies are inherently biased and may overestimate the likelihood of nodal metastases from thin melanoma.

Outcomes from this study showed that regional nodal disease was the most common first site of disease identified beyond the primary site (24 patients with positive SLNB, 8 patients with delayed nodal recurrence [1 with concurrent in-transit recurrence, 1 with concurrent distant recurrence]). Five of the 8 patients with nodal recurrence subsequently died of distant disease. Only 2 patients developed distant disease as the first site of disease beyond the primary site and both patients died from melanoma.

In our cohort of all patients with thin melanoma, Breslow depth 0.75 – 0.99 mm, the overall nodal metastatic rate was 6.8% (33 nodal metastases/488 tumors). The nodal metastatic rate observed in patients treated with WLE plus SLNB (24 positive SLNB, 5 false-negative SLNB with nodal recurrence) was 10.2%. In patients treated with WLE alone, the rate of nodal disease was 2.0% (4 nodal recurrences). Compared to patients treated with WLE only, patients who underwent SLNB were more likely to be younger, female, have a deeper Breslow depth, mitotic rate ≥ 1 mm^2, positive deep margin, ulceration, and/or regression. Notably, all 4 of the patients treated with WLE alone that had nodal recurrence had primary lesions with Breslow depth ≥ 0.8 mm (0.91, 0.9, 0.9, and 0.8 mm) and two patients were < 45 years old (43 and 44) (Table 2).

The higher rate of nodal disease in the SLNB group may be, at least partly, attributable to lead-time bias and a relatively limited follow up time. Thin melanoma has been reported to recur long after initial treatment, in some cases > 10 years after diagnosis.[15] It is likely that additional recurrences will develop in all groups, including those patients with a negative SLNB and those treated with WLE alone. Continued follow-up of our cohort beyond the reported median 48 months will provide additional valuable information.

Interestingly, the largest meta-analysis (60 studies, 10,928 patients) to evaluate SLNB for thin melanoma was published in 2016 and included only those who had SLNB. Breslow depth ≥ 0.75 mm (adjusted odds ratio (AOR) 1.9; 95% CI 1.08-3.340), Clark level IV/V (AOR 2.24; 95% CI 1.23-4.08), mitotic rate $\geq 1/\text{mm}^2$ (AOR 6.64; 95% CI 2.77-15.88), and presence of microsatellites (unadjusted OR 6.94; 95% CI 2.13-22.60) were associated with a positive SLNB. The authors concluded that patients with melanoma ≥ 0.75 mm should be offered SLNB, based on a SLNB positivity likelihood of 8.8%. If other high-risk features are present, the rate of SLNB positivity may be even higher.[11]

Univariate analysis of our entire cohort, including patients treated with WLE alone, showed age ≤ 45, Breslow depth ≥ 0.85 mm, mitotic rate > 1/mm^2, and ulceration to be significantly associated with nodal disease (positive SLNB or nodal recurrence in the follow up period) supporting the use of these risk features as selection criteria for SLNB in patients with thin melanoma 0.75 – 0.99 mm. This analysis is more clinically relevant than prior reports because it uses the entire population of patient with thin melanoma rather than just the subset of those selected for SLNB. Our data would suggest that SLNB be considered for AJCC 8th Edition[30] T1b lesions 0.8 – 1.0 mm with any of the following high-risk features: age ≤ 45, Breslow depth ≥ 0.85 mm (rounded to 0.9 mm for the AJCC 8th Edition), mitotic rate > 1/mm^2, and/or ulceration.

In thin melanoma there is conflicting evidence regarding the prognostic significance of a positive SLN.[2,15,23,31] In our patients with a positive SLNB, no recurrences were noted in the follow up period. It is possible that the follow up time is insufficient to capture long-term events. However, this observation also raises the possibility that SLNB-directed early intervention may provide a therapeutic benefit with improved outcomes in thin melanoma similar to that demonstrated for intermediate depth melanoma in the Multicenter Selective Lymphadenectomy-I (MSLT-I) trial.[9] In our patients with a positive SLNB who underwent CLND (19/24 patients), no additional positive nodes were identified. Results from the Multicenter Selective Lymphadenectomy Trial-II and adjuvant therapy trials may lead to changes in the management of SLNB positive patients in the future.[32]

Our study population may be subject to potential selection bias based on patient referral to a tertiary cancer center. However, our Multidisciplinary Melanoma program evaluates and treats nearly 80% of all melanoma cases in our state. Additional limitations include the retrospective

design and relatively limited follow up time, though a median follow up of 48 months is equivalent to or longer than many comparable studies reported in contemporary literature.

Conclusions:

Patients with thin melanoma can and do develop regional lymph node and distant disease and may die from melanoma. The 8 distant recurrences and 7 deaths serve as a reminder that although thin melanoma has an excellent prognosis, some patients will have an adverse outcome. This study supports that regional nodal disease is the most common first site of spread detected beyond the primary site in the natural history of thin melanoma 0.75 – 0.99 mm. Furthermore, this study supports that a subset of these thin melanomas have a sufficient risk to consider nodal staging with SLNB. Specifically, SLNB should be strongly considered for thin melanoma 0.75 – 0.99 mm in the setting of patient age ≤ 45 years, Breslow depth ≥ 0.85 mm, mitotic rate > 1/mm^2, and/or ulceration of the primary lesion. Thin melanoma < 0.85 mm (to be defined as ≤ 0.8 mm in the 8th edition of the AJCC) without additional high-risk features likely has a low rate of nodal metastases and therefore may be treated with WLE alone.

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Figure 1 Title: Outcomes.

Figure 1 Legend: Outcome measures. This figure shows outcome measures including: local recurrence, in-transit recurrence, nodal metastasis, distant metastasis, and death from melanoma for 486 patients with 488 primary lesions 0.75-0.99 mm Breslow depth after a median follow up time of 48 months.

Table 1: Factors Associated with Performance of SLNB in Patients with Thin (0.75 to 0.99 mm) Melanoma

	SLNB Performed		Univariate Analysis			
Characteristics	Yes n=295	No n=217	p	OR	95% CI	
Age (continuous, +1 year)	Mean		<0.001	0.946	0.933	0.959
	52	63.2				
Gender (F vs. M)			<0.001	2.054	1.43	2.949
F	152	74				
M	143	143				
Breslow Depth (continuous, +0.1mm)	Mean		<0.0001	3.09	2.25	4.29
	0.88	0.84				
Mitotic rate (≥1/mm^2 vs. 0/mm^2)*			<0.001	3.91	2.673	5.719
≥1/mm2	226	98				
0/mm2	69	117				
Positive Deep Margin (yes vs. no)*			0.019	1.684	1.089	2.602
Yes	78	38				
No	217	178				
Ulceration (present vs. absent)*			0.007	15.667	2.089	117.493
Present	20	1				
Absent	274	215				
Regression (present vs. absent)			0.006	0.57	0.38	0.85
Present	61	68				
Absent	234	149				
Angiolymphatic Invasion (present vs. absent)*			0.12	3.37	0.72	15.7
Present	9	2				
Absent	286	214				
* Mitotic rate and ulceration unknown in 2 pts, Deep margin status and angiolymphatic invasion status unknown in 1 pt						

Table 2: Patient and Lesion Characteristics in Cases of Nodal Recurrence

Treatment	Age	Gender	Site	Melanoma Type	Breslow Depth (mm)	Mitotic Rate (#/mm^2)	Ulceration	Regression	ALI*	PNI*	Time to Recurrence (months)
WLE + FN SLNB*	59	M	Scalp	Superficial Spreading	0.80	2	No	Yes	No	No	11
WLE + FN SLNB	31	F	Foot	Superficial Spreading	0.86	2	No	No	No	No	53
WLE + FN SLNB	43	M	Leg	Superficial Spreading	0.90	3	No	Yes	No	No	17
WLE + FN SLNB	42	F	Neck	Superficial Spreading	0.78	1	Yes	No	Yes	No	7
WLE + FN SLNB	44	F	Foot	Superficial Spreading	0.90	1	No	No	No	No	10
WLE	70	M	Neck	Superficial Spreading	0.91	0	No	No	No	No	6
WLE	67	F	Arm	Nodular	0.90	0	No	No	No	No	16
WLE	44	M	Trunk	Superficial Spreading	0.80	0	No	No	No	No	40
WLE	43	M	Trunk	Spitzoid	0.90	0	No	No	No	No	39

*WLE: Wide Local Excision, FN SLNB: False-Negative Sentinel Lymph Node Biopsy, ALI: Angiolymphatic Invasion, PNI: Perineural Invasion

Table 3: Factors Associated with Nodal Disease in Patients with Thin (0.75 to 0.99 mm) Melanoma

	Nodal Disease		Univariate Analysis			
Characteristics	Yes	No	p	OR	95% CI	
Age (>45 vs. ≤ 45 years)			0.027	0.431	0.205	0.91
>45	21	365				
≤45	12	90				
Gender (F vs. M)			0.36	1.392	0.686	2.823
F	17	197				
M	16	258				
Breslow Depth (≥0.85 vs. <0.85 mm)			0.04	2.43	1.03	5.72
≥0.85 mm	26	275				
<0.85 mm	7	180				
Mitotic rate (≥1/mm^2 vs. 0/mm^2)			0.14	1.842	0.812	4.177
≥1/mm^2	25	285				

0/mm^2	8	168				
Mitotic rate (>1/mm^2 vs. ≤ 1/mm^2)			0.031	2.2	1.076	4.499
>1/mm^2	15	125				
≤1/mm^2	18	330				
Positive Deep Margin (yes vs. no)*			0.8	0.895	0.378	2.12
Yes	7	105				
No	26	349				
Ulceration (present vs. absent)*			0.001	6.282	2.087	18.91
Present	5	13				
Absent	27	441				
Regression (present vs. absent)			0.18	0.51	0.19	1.35
Present	5	118				
Absent	28	337				
Angiolymphatic Invasion (present vs. absent)*			0.68	1.55	0.19	12.58
Present	1	9				
Absent	32	445				
*Ulceration status unknown in 2 pts, Deep margin status and angiolymphatic invasion unknown in 1 pt						

Multivariate Analysis

Characteristic	p	Estimate	OR	95% CI	
Age (>45 vs. ≤45 years)	0.007	-0.5455	0.336	0.152	0.74
Breslow Depth (≥0.85 vs. <0.85 mm)	0.12	0.3532	2.027	0.838	4.899
Mitotic rate (>1/mm^2 vs. ≤ 1/mm^2)	0.14	0.2919	1.793	0.824	3.902
Ulceration (present vs. absent)	0.003	0.8902	5.932	1.805	19.496

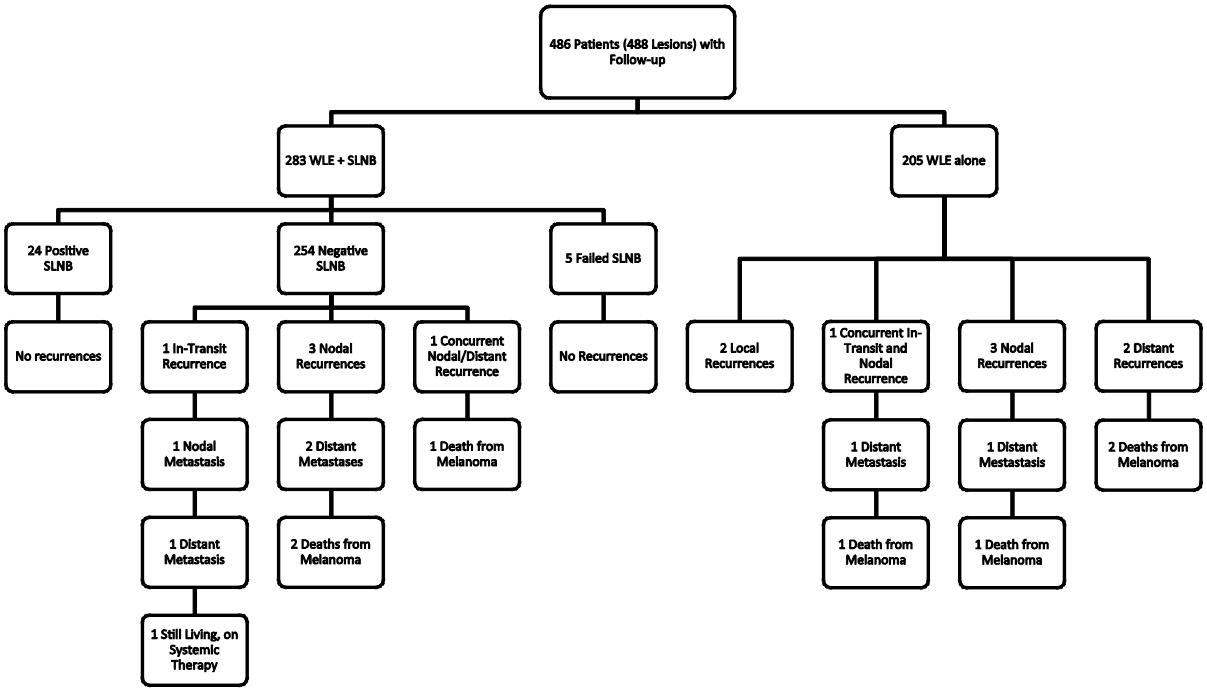

Figure 1