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Ana Eliza Souza Cunha
Yale Physician Associate Program, anaeliza.souzacunha@yale.edu

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DECISION MAKING IN PATIENTS WITH INITIAL POSITIVE DEEP MARGINS ON DIAGNOSTIC BIOPSY OF MELANOMA

A Thesis Presented to
The Faculty of the Yale University
School of Medicine

In Candidacy for the degree of Master of Medical Science

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Ana Eliza Souza Cunha, PA-SY3
Class of 2023
Yale Physician Associate Program

James Clune, MD
Associate Professor of Surgery (Plastic)
Yale University School of Medicine

ABSTRACT

Background: Current guidelines recommend SLN biopsy (SLNB) among patients with initial Breslow Thickness (BRES) ≥0.8mm at initial screening. However, there is limited guidance regarding SLNB among patients who have deeper final depth after initial biopsy.

Methods: We conducted a retrospective cohort study of 62 thin melanoma patients with primary lesions with initial Breslow Thickness (BRES) <0.8mm and final BRES ≥0.8mm at Yale New Haven Hospital between 2011 and 2022. Receipt of SLNB, tumor metastasis status, and recurrence (i.e., local, regional, and distal) were collected from Yale's Melanoma Database. Multivariable logistic regression was used to assess the adjusted association between receipt of SLNB and recurrence.

Results: Approximately 55% of patients (n = 34) included in our study underwent SLNB. After adjustment, there was no association between SLNB status and recurrence. Immunosuppressive drug use was associated with higher odds of local (OR= 28.56 CI 1.87- 435.53; p =0.016) and regional recurrence (OR= 28.55 CI 1.5–542.50; p =0.016). Smoking was also associated with higher odds of regional recurrence (OR= 18.48 CI 1.37-249.15; p =0.028). Lymphocytic infiltrate was associated with lower odds of regional (OR= 0.05 CI 0.004-0.70; p =0.03) and distant (OR= 0.97 CI 0.01–0.71; p =0.02) recurrence.

Conclusions: Among patients with initial Breslow Thickness (BRES) <0.8mm and final BRES ≥0.8mm, SLNB was not associated with recurrence. Further investigation in larger, prospective cohorts is warranted to provide clarity in the management of t1a melanoma.

Key words: *Melanoma—Metastases—Sentinel lymph node—Prognosis—Tumor thickness—Breslow level*

INTRODUCTION

The incidence of melanoma has been rising steadily for the past 50 years, with the American Cancer Society estimating approximately 100,000 new cases in U.S. alone for the year 2022. Thin-melanoma (T1), a melanoma of Breslow depth (BRES) equal to or less than 1.0mm, accounts for 70% of new cases and approximately 25% of melanoma deaths[1].

Recurrence of thin melanoma is separated into 3 subtypes: local, regional, and distant recurrence. Thin melanoma is thought to spread from its primary site (local) to regional lymph node and distant parts of the body such as lungs, liver, or bones[2]. Sentinel Lymph Node Biopsy (SLNB) is a surgical procedure that involves removing the sentinel lymph node – the first lymph node to which cancer cells are likely to spread – to determine if the cancer proliferated beyond the primary site. Sentinel lymph node status remains the most important independent prognostic factor in thin melanomas[1].

Criteria to best support which patients should undergo SLNB is continuously under active research and has driven changes in the National Comprehensive Cancer Network (NCCN) guidelines over the past decade[3]. In addition to BRES, which is directly associated with SLN positivity, other factors such as ulceration, mitotic rate, lympho-vascular invasion, and presence of microsatellites are being investigated as strong determinates of SLN positivity. In a recent meta-analysis of 38,844 patients with thin melanoma, it was found that the strongest predictors for SLN positivity were identification of microsatellites and ulceration, while BRES ≥0.8mm and mitotic rate >0/mm^2 significantly increase SLN positivity rate[4]. One study found that BRES >0.75 mm (Clark's Level ≥IV) and ulceration were independent predictors of SLN[5]. Tumor regression has not been as well established as a definitive indicator, as past studies have ranged from concluding it should not be used as an indicator for SLN positivity[5-7]. More recent studies, however, found regression increased the probability of SLN positivity by approximately 5.8 fold[8]. The American Joint Commission on Cancer and NCCN both recommend only including ulceration as an increased risk factor for T1 tumors, but active research such as Huang et al.'s meta-analysis[9] support the need for continued research in quantifiable measures of tumor growth that correlate with melanoma lymph node metastasis.

Current guidelines from the NCCN divided stage 1 (T1) thin melanoma into T1a and T1b. NCCN guidelines recommend that a melanoma of BRES <0.8mm thick with no ulceration should *not* be considered for SLN. On the contrary, T1b tumors <0.8mm with ulceration and T1b tumors between 0.8mm and 1.0mm +/- ulceration *should be considered* for SLNB. These guidelines lump stage 0 melanomas, or melanomas that remain primarily within the epidermis (in-situ), with the management of T1a melanomas. With the popularity of shave biopsies in clinic there is an increasing number of biopsies which may receive inadequate micro-staging on initial biopsy when compared to final staging, which is completed via wide local excision (WLE). Current guidelines have minimal guidance on patients screened for positive deep margins (+DM); there remains ambiguity within practice whether patients with +DM are at greater risk for metastasis. The question remains whether patients should return to clinic for SLNB if on final pathology a patient's deep margins are positive, and their final BRES is found to be ≥0.8mm on final pathology.

In our retrospective cohort study, we aimed to see whether, under the NCCN's 3.0 2022 guideline criteria, thin melanoma patients with +DM on initial biopsy who received SLNB have lower odds of metastasis than thin melanoma patients with +DM who did not receive SLNB. This is an important question to answer as sentinel lymph node biopsies are *not* curative; there are risks of pain, infection, and scaring in SLNB.

METHODS

Participants and Study Design

For this retrospective study, Institutional Review Board approval and a waiver of patient informed consent requirements were obtained prior to study initiation at Yale Cancer Center. Participants were identified from *Yale's Melanoma Database* which included patients in New Haven/Greater New Haven area and who underwent WLE biopsy for clinically localized melanoma at Yale New Haven Hospital between 2008-2022. All eligible participants had pre-consented to have their melanoma data monitored for up to 5 years after their excisional date, and some continued to be monitored through Yale Dermatology beyond the 5-year follow-up period. Study outcomes of local, regional, and distant reoccurrence was recorded through pathology reports of study participants during routine 6-month follow ups throughout the 5-year period.

This study included melanoma database patients from 2011–2022 whose medical records mentioned "thin melanoma" with initial lesions that were shallower than the final pathology report. For consistency in reporting of pathologic variables, subsequent to the American Joint Commission on Cancer staging system update in 2009[10] and digitalization of YNNH notes transferred to EPIC in 2011. Exclusion criteria included patients that underwent SLN biopsy with >1.0mm melanoma on initial pathology or those that had baseline metastasis from previous melanoma or other cancer.

Data Collection and Study Variables

Patients were categorized based on whether they received a sentinel lymph node biopsy (SLNB). Receipt of SLNB was determined based on timing of patient SLNB: patient's receiving a SLNB within 6 months of their WLE were assigned to the SLNB group and those who received SLNB after 6 months were assigned as No SLNB. SLNB "status," whether the SLNB was positive for metastasis or not, were also recorded and determined by H&E or immunohistochemical staining.

Electronic medical records were reviewed for pathology reports from the referring institutions and the treating institution to collect information on tumor characteristics. Lymphocytic infiltrate involvement was recorded as not present, (brisk, or non-brisk) but dichotomized for simplicity as present or non-present in this research. Lymph-vascular invasion and ulceration were dichotomous and recorded as either present or non-identified. Given the sample size of this study's population, the "hot spot" technique where mitotic rate is dichotomized as either 0 or $\geq 1/mm^2$ was forgone for mean (standard deviation) to investigate nuance amongst tumor characteristics across the two groups. Melanoma type and location of primary tumor site (head and neck, upper extremity, trunk, and lower extremity) were recorded categorically, as described by a pathologist on report. Follow-up data reflected the last time the patient was seen at the treating institution. Sociodemographic and clinical variables included age, sex, diabetes status, use of immunosuppressive drugs, transplant status, and family history limited to patients with first-degree relative with melanoma.

Statistical Methods

We generated descriptive statistics for the study sample, such that we reported frequencies for categorical variables and means with standard deviations for continuous variables. We compared baseline characteristics between participants who received SLNB and those who did not using $\chi 2$ tests, Fisher's exact tests, and t-tests as appropriate. Time to recurrence was reported as medians with

interquartile ranges (IQRs). We conducted univariate and multivariable logistic regression models to evaluate the association between SLNB status and recurrent melanoma. Multivariable models were minimally adjusted for covariates selected based on clinical judgement and their univariate associations with SLNB status. All statistical analyses were performed using SAS, version 9.4. Data analysis was conducted from October 5, 2022, to March 14, 2023.

RESULTS

There were 3,740 WLEs for cutaneous lesions where residual melanoma resided. A total of 1,900 patients were logged as primaries with both the original biopsy and the final depth and were excluded from the study sample. An additional 1,628 patients were excluded because they had melanoma in-situ. Of the 272 patients left, an in-depth chart review of EMR notes revealed that 210 were ineligible due to having equivocal diagnosis or because the Breslow depth on initial pathology was ≥0.8mm. After exclusion criteria were applied, our analysis consisted of 62 patients with identified primary lesions who had initial Breslow depth <0.8mm and final Breslow depth ≥0.8mm (**Figure 1**).

Sample Characteristics

Baseline characteristics of all 62 patients stratified by receipt of SLNB are presented in **Table 1**. The mean age in the total study sample was 71.16 ± 15.59 and most participants were AMAB (61.29%). A total of 4 participants (6.45%) were taking immunosuppressive drugs, 9 (14.51%) had diabetes, 3 (4.83%) were transplant patients, and 30 (48.38%) are current or past smokers. 53 patients (85.48%) experienced their first melanoma, and 7 (11.29%) had a family history of melanoma. In terms of tumor characteristics, 11 (17.74%) had ulceration, 3 (4.83%) had lymph-vascular invasion, 41 (66.13%) had lymphocytic involvement, and 3 (4.83%) had perineural invasion. Among all patients, the mean final Breslow thickness of the tumors was 1.89 ±1.44. The most common primary tumor site was Head/Neck (40.32%); the most common melanoma type was superficial spreading (48.39%).

There were no statistically significant differences in baseline characteristics between patients who received SLNB and those that did not, with the exception of initial Breslow depth. Patients who received SLNB had a deeper mean initial Breslow depth (0.61 mm ± 0.26) when compared to non SLNB comparison group (0.42 mm ± 0.30; p= 0.0085). The final Breslow thickness was slightly higher for those who underwent SLNB 1.99 ±1.53 compared to who did not undergo SLNB 1.78±1.34, but this difference was not statistically significant (p= 0.56). There was no statistical difference between SLNB and non SLNB comparison groups for ulceration (5 [17.86%] vs 6 [17.65]; p = 0.54), Lymphocytic invasion (8 [64.29%] vs 23 [67.79%]; p= 0.54), or Lymph-vascular invasion (1 [1.61%] vs 2 [3.23%]; p= 0.50). Perineural invasion was not consistently collected within EMR, with only 7/62 patients having perineural invasion as a criterion within their pathology reports. Data collection would suggest higher perineural invasion in SLNB vs non SLNB comparison groups (n = 2 [5.88%], vs n = 1 [3.57%]); however, this difference is not significant (p= 0.63). Lastly, pathology reports indicated mitotic rate >1mmsq in 57/62 (91.93%) of patients. The mean mitotic rate for patients with SLNB was 2.63±2.46 which is slightly higher but not significantly different (p= 0.54) to the mean mitotic rate of the non SLNB cohort (2.18±3.76).

There was no significant difference across comparison groups in melanoma type (p= 0.25), with the most common tumor type being superficial spreading, representing 17/34 (50%) of SLNB cohort and 13/28 (46.43%) of the non SLNB cohort. First time melanomas were similar in reporting across comparison groups (n = 25 [89.29%] vs n = 28 [82.35%]; p= 0.49). There was no significant difference in

tumor site, with head/neck most commonly represented in both comparison groups (n = 10 [35.71%] vs n = 15 [44.12%]).

SLNB and Recurrence

Compared to patients who did not receive SLNB, the number of local (4 [11.76%] vs 1 [3.57%]; p= 0.37) was higher among patients who received SLNB, although these differences were not statistically significant. The number of regional recurrence was lower for those who received SLNB (1 [17.65%] vs 2 [2.90%]; p= 0.58), but this finding was not significant. There was no difference in distant recurrence between SLNB and non SLNB groups (3 [8.82%] vs 3 [10.71%]; p= 1.0) **(Table 2).**

Median time (days) to recurrence by location for SLNB patients showed lower measured time to local (213.50 [44.50-559.0] vs 852 [852-852]) and regional recurrence (175 [12.00- 338.0] vs 2221.50 [1315-3128]) than patients who did not receive SLNB **(Table 3)**. There was minimal difference in median time to distant recurrence for SLNB group (784 days [234-1165]) vs the non SLNB comparison group (729 days [116-1329]) **(Table 3).**

Unadjusted bivariate logistic regression of local, regional, and distant recurrence status adjusted for sociodemographic and medical history held no significant associations between SLNB and odds of recurrence **(Table 4a)**. Similarly, there were no significant associations after adjusting for diabetes, smoking, age and immunosuppressive drug use. However, immunosuppressive drug use was associated with higher odds of local (OR= 28.56, CI 1.87- 435.53; p= 0.016) and regional recurrence (OR= 28.55, CI 1.5–542.50; p= 0.026). Being a past or current smoker was also associated with higher odds of regional recurrence (OR= 18.48, CI 1.37-249.15; p= 0.028).

Unadjusted bivariate logistic regression of local, regional, and distant recurrence status adjusted for tumor characteristics held no significant associations between SLNB and odds of recurrence **(Table 4b)**. Similarly, there were no significant associations after adjusting for tumor characteristics including mitotic rate, ulceration, lymphocytic involvement, lymph-vascular invasion, original and final BRES. In adjusted logistic regression model for tumor characteristics, lymphocytic involvement was significantly associated with lower odds of regional recurrence (OR= 0.05, CI 0.004-0.70; p= 0.03).

DISCUSSION

Central Discussion

This retrospective cohort study aimed to investigate the outcomes of 62 patients with thin melanoma that were upstaged from T1a melanoma who received sentinel lymph node biopsy (SLNB) vs those that did not. We identified 34 patients that underwent SLNB and 28 patients that did not undergo SLNB (**Table 1).** From these comparison groups the data did not reveal any significant associations with local, regional, and distant recurrence in unadjusted and adjusted models. Our study did not find a significant difference for regional recurrence in those who received SLNB vs those who did not receive SLNB in T1a melanoma with greater than expected BRES on pathology (**Table 2)**.

The first Multicenter Selective Lymphadenectomy Trial demonstrated that SLNB emerged as the most powerful prognostic factor for melanoma >1.2mm[11] and was recommended for melanomas from 0.8mm to 1.0mm with high-risk features (stage T1b). For thin melanomas <0.8mm, the utility of SLNB was less clear. The decision whether patients with thin melanoma <0.8mm should undergo SLNB is often considered clinically complex and individualized. Although there are some studies that believe early

intervention for thin melanomas could decrease overall morbidity[12], SLNB, like any surgical procedure, has risks of complications[13,14]. Despite the risk of infection being low, the benefit of undergoing this operation should be weighed carefully in melanoma types with historically low incidence of metastasis[15]. With this consideration, there are several studies that challenge the 8th edition American Joint Committee on Cancer melanoma recommendation of SLNB for thin melanoma[16] and recommend that wide local excision (WLE) is enough to stage and treat thin melanoma alone[17].

The rationale behind the implementation of SLNB in the management of cutaneous melanoma is rooted in the belief that regional lymph nodes serve as a breeding ground for the subsequent dissemination of cancer to distant sites, spreading from local to regional and then distant[18,19]. It is commonly hypothesized that spread of melanoma occurs via the lymphatic system.[20]. Thick melanomas have a higher inclination for simultaneous distant spread. This spreading pattern confers that for disease with greater risk of regional recurrence, SLNB could be a significant predictor of disease recurrence[21] and propose clinicians utilize it as a valuable prognostic tool[22]. Due to a limited sample size, we were unable to distinguish significant differences in metastatic events by location with and without SLNB (**Table 2**). This was specifically true for regional recurrence: our data demonstrated no significant difference for those with SLNB vs the observed group (1 [17.65%] vs 2 [2.90%]; p= 0.58). Furthermore, the difference was negligent as one of the two patients in the observed group had regional recurrence most likely because they were a kidney transplant patient under immunosuppression. The smaller number of regional metastases (n = 1) found in the SLNB group does not correlate with SLNB as a diagnostic tool for regional recurrence in these patient populations, and under this data set would therefore not be recommended.

Although no significant difference was found in number of recurrences between SLNB and observed group, the time to diagnosis, though limited, can be utilized as a prognostic indicator. This study found that patients in the observed group were more prone to delayed diagnosis of regional recurrence. This is most likely due to the observed group being initially surveyed through physical exam only. This finding is demonstrated in Table 3, where median days to recurrence in the observed group is much greater than the SLNB group (2221.50 [1,315-3,128] vs. 175 [12.0-338]).

Other trends within our data suggest that the overall odds of our patient population developing distant recurrence was protective in patients who received SLNB vs those who did not (**Table 4a and 4b**). There are some studies that have shown the link between SLNB as a prognostic tool leading to overall greater melanoma specific survival (MSS)[11,12]. However, this is controversial as most research has focused on T1b melanoma, whereas T1a melanoma without other risk factors lacks investigation. Our trends within **Table 4a and 4b** were not statically significant and need further validation with a larger sample size to justify that SLNB should be done in T1a melanoma patients without other risk factors with ambiguous initial Breslow depth on initial pathology.

8th edition American Joint Committee on Cancer (AJCC) guidelines marked that the decision to proceed with SLNB in patients with melanoma measuring ≤1.0mm should be based on an assessment of the probability of detecting SLN metastasis, with a minimum expected rate of at least 5%. In our study of 34 patients with SLNB, total percentage of regional recurrence was 2.9% and therefore did not exceed 5% (**Table 2**). For those in the observed group, there were 2 patients with regional recurrence out of 28 total patients. However, one of these patients should not be considered within this category due to their immunosuppressive drug use while receiving kidney transplant. After this consideration the number of regional recurrences in the observed group is 1 out of 28 patients (3.57%) and therefore does not exceed the 5% minimum metastasis threshold.

Within our study, sociodemographic characteristics such as immunosuppressive drug use and smoking history were found to be clinically associated with higher odds of recurrence for patients with thin melanoma (**Table 4a).** Immunosuppressive drug use was significantly associated with higher odds of local and regional recurrence (Table 4a). Distant recurrence also trended higher odds, however this was not statistically significant. Evidence to support that patients with immunosuppressive drug use are at higher risk for melanoma has been well analyzed within the literature[23-25], as immunosuppressed individuals have a less than robust immune defense to tumor processes. Unlike immunosuppression, there is no clear association between smoking and risk of melanoma. In fact, some studies suggest a potential *protective* effect, although these findings are subject to debate and conflicting data[26-30]. Within our study, we found that smoking was statically associated with worse odds of regional recurrence (OR= 18.48, p= 0.028) but that trends within our data showed a protective effect with local recurrence (OR= 0.55, p= 0.6). Future studies more closely investigating these individual associations and exploring their underlying physiology may indicate other driving factors at play.

Continued controversy in the use of SLNB for thin melanoma has led to an increased effort in investigating secondary tumor characteristics that may better support SLNB in high-risk patients[31,32]. Currently there is no consensus regarding which patients with thin melanoma are at risk for metastases. In the 8th edition AJCC melanoma recommendations, ulceration is the only current characteristic that, when present, indicates a need for SLNB. Most reports that analyzed risk of progression of thin melanoma and the utility to perform SLNB confirmed the importance of ulceration and mitotic rate as main predictors[5,31,33,34]. Within our study there were no significant associations for either of these risk factors (**Table 4b**). However, trends in our data suggested high odds of local recurrence (15.29 [0.67–349.34], p= 0.088] for those with ulceration. Final Breslow depth, a key characteristic of melanoma staging, did not show a significant association with local, regional, or distant recurrence in patients with and without SLNB. Tumor-infiltrating lymphocytic involvement was the only significant association of lower odds of regional recurrence. This is not surprising because it is well known that lymphocytic tumor burden is a healthy sign of a responding immune system to melanoma and thus indicates a better prognosis[35,36]. It is worth noting that lesions were found primarily within the head and neck (**Table 1**). In a recent study of 70,605 patients, melanomas of the head and neck were heterogenous when compared to other anatomical sites; the overall survival rate of these melanomas was notably lower[37]. These anatomic sites may be considered higher risk for recurrent T1a melanoma and may require further evaluation and thorough clinical assessment.

Challenges and Limitations

This study is strengthened by the prospective collection of data and standardized follow-up examinations of participating patients. However, there were several challenges that limited this study. The primary limitation for this study was the small sample size, which on analysis was underpowered, to demonstrate significant associations. Secondly, it is unclear what effect the significant difference in initial Breslow depth between comparison groups had on the overall study; the final Breslow depth, which is directly associated with melanoma risk, had no difference between comparison groups (Table 1). In addition, the nature of thin melanoma's long time to metastasis could have led to under-reporting of regional melanoma, which is not always identified by painful lymph nodes on physical exam. Lastly, this study was completed at a single intuition thus limiting generalizability.

CONCLUSION

Approximately 70% of new melanoma cases are thin lesions, with the incidence of thin melanomas rising. Recent major studies, like the Multicenter Selective Lymphadenectomy Trial and multi-center studies, have driven support for the use of SLNB within T1b melanoma. Our aim was to investigate outcomes of +DM patients that were upstaged from T1a melanoma and whether these patients should be treated as initially staged T1b melanoma. Our study was underpowered and unable to determine significant odds of recurrence for those that had SLNB vs those who did not. Trends within our data did not demonstrate a significant difference in regional recurrence between those who received SLNB and those who did not. Other trends within our data suggest that patients who received SLNB had lower odds of distant recurrence than those who did not. Special attention should be given to those who have smoking history or those with current immunosuppressive drug use. Further investigation is warranted to evaluate the validity of these trends with appropriate sample size to provide better clarity within the management of T1a melanoma with low risk factors and +DM.

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Disclosures and Conflicts of Interest

There are no disclosures and no conflicts of interest.

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Appendices

Figure 1: Consort Diagram

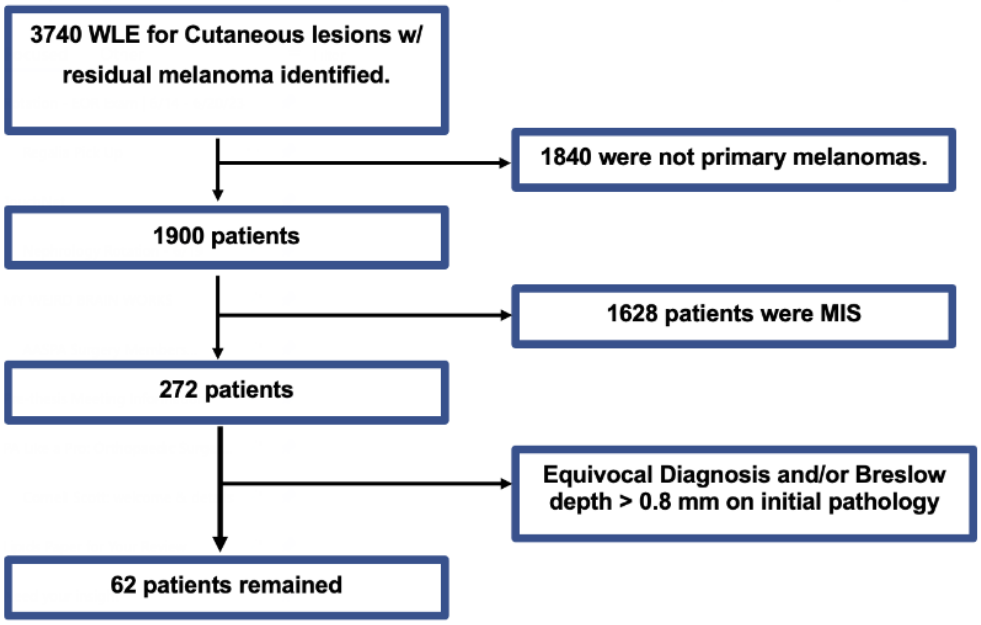

Figure 1: Consort Diagram outlining the inclusion and exclusion criteria of patients in this study. Population was derived from 3,740 patients identified from one institutional database who went for staging for thin melanoma.

Table 1: Clinical Features of Thin Melanoma in Patients with SLNB vs No SLNB

Clinical features	No SLNB n = 28	SLNB n = 34	p-Value	Totals, n (%)
Age (years), M±SD	67.70±16.44	75.35±13.34	0.52	71.16±15.49
Sex assigned at birth, n (%)			0.93	
Male	17 (60.71)	21 (61.76)		38 (61.29)
Female	11 (39.29)	13 (38.24)		24 (38.70)
Diabetes, n (%)	5 (17.86)	4 (11.76)	0.50	9 (14.51)
Smoking Status, n (%)			0.78	
Non-Smoker	15 (53.57)	17 (50.00)		32 (51.61)
Smoker (including past)	13 (46.43)	17 (50.00)		30 (48.39)
Immunosuppressive Drug Use, n (%)	2 (7.14)	2 (5.88)	0.84	4 (6.45)
Transplant patient, n (%)	1 (3.57)	2 (5.88)	0.67	3 (4.83)
Patient's First Melanoma, n (%)	25 (89.29)	28 (82.35)	0.49	53 (85.48)
Family History of Melanoma, n (%)	2 (7.14)	5 (14.71)	0.35	7 (11.29)
Tumor Characteristics				
Mitotic Rate (mitosis/mm^2), M±SD	2.18±3.76	2.63±2.46	0.54	2.43±3.09
Ulceration, n (%)	5 (17.86)	6 (17.65)	0.54	11 (17.74)
Lymphocytic Involvement, n (%)	18 (64.29)	23 (67.79)	0.54	41 (66.13)
Lymph-vascular Invasion, n (%)	1 (1.61)	2 (3.23)	0.50	3 (4.83)
Perineural Invasion, n (%)	1 (3.57)	2 (5.88)	0.63	3 (4.83)
Initial Breslow Depth (mm), M±SD	0.42±0.3	0.61±0.26	0.0085	0.53±0.29
Final Breslow Depth (mm), M±SD	1.78±1.34	1.99±1.53	0.56	1.89±1.44
Primary Tumor Site, n (%)			0.73	
Head Neck	10 (35.71)	15 (44.12)		25 (40.32)
Trunk	6 (21.43)	8 (23.53)		14 (22.60)
Lower Extremity	5 (17.86)	3 (8.82)		8 (12.90)
Upper Extremity	7 (25.00)	8 (23.53)		15 (24.19)
Melanoma Type, n (%)			0.25	
Superficial Spreading	13 (46.43)	17 (50.00)		30 (48.39)
Melanoma, NOS	7 (25.00)	6 (17.65)		13 (20.97)
Desmoplastic	4 (14.29)	1 (2.94)		5 (8.06)
Malignant Melanoma, Invasive	1 (3.57)	3 (8.82)		4 (6.45)
Spindle Cell	1 (3.57)	2 (5.88)		3 (4.83)
Nodular	0 (0)	4 (11.76)		4 (6.45)
Nevoid	1 (3.57)	0 (0)		1 (1.62)
Spitzoid Melanocytic	0 (0)	1 (2.94)		1 (1.62)
Lentigo	1 (3.57)	0 (0)		1 (1.62)

Table 1. Clinical Features in Thin Melanoma, n (%); age (years), M±SD: Socioeconomic factors, medical history, and tumor characteristics of all 62 patients represented in this study. Participants were identified from *Yale's Melanoma Database*. Patients were separated into sentinel lymph node biopsy (SLNB; n = 28) vs no SLNB (n = 34). We compared baseline characteristics using $\chi 2$ tests, Fisher's exact tests, and t-tests as appropriate.

Table 2: Number of Local, Regional, or Distant Recurrences in Patients with SLNB vs No SLNB

Metastatic Location, n (%)	No SLNB (n=28)	SLNB (n=34)	p-Value
Local Recurrence	1 (3.57)	4 (11.76)	0.37
Regional Recurrence	2[A] (7.14)	1 (0.029)	0.58
Distant Recurrence	3 (10.71)	3 (8.82)	1.00

Table 2. Number of Metastatic Events by location, n (%): Recurrence of local, regional, and distant thin melanoma for patients with SLNB compared to those without SLNB. We used fisher exact test to calculate p-values given the small sample size of metastasis in the study population. In patients with SLNB, a total of 8 patients developed metastasis with a total of 8 instances of recurrence. In patients without SLNB, a total of 5 patients developed metastasis with a total of 6 instances of recurrence.
[A]1 patient within this group was a kidney transplant patient utilizing consistent immunosuppressive medication.

Table 3: Median Days to Recurrence in Patients with SLNB vs No SLNB

Metastasis Location	No SLNB (n = 6; Median, [IQR])	SLNB (n = 13; Median, [IQR])
Local Recurrence	852 (852-852)	213.50 (44.50-559.0)
Regional Recurrence	2221.50 (1,315-3,128)	175 (12.0-338)
Distant Recurrence	729 (116-1,329)	784 (234-1,165)

Table 3. Time to Recurrence by Metastatic Location, Median (IQR): Median time (days) and interquartile range (IQR; Q1-Q3) to local, regional, and distant recurrence for patients with SLNB compared to those without SLNB.

Table 4a: Bivariate Logistic Regression Model of Sociodemographic Factors and Medical History

TABLE 4A	Local Recurrence				Regional Recurrence				Distant Recurrence			
Characteristics	Unadjusted (95% CI)	P-Value	Adjusted Odds (95% CI)	P-Value	Unadjusted (95% CI)	P-Value	Adjusted Odds (95% CI)	P-Value	Unadjusted (95% CI)	P-Value	Adjusted Odds (95% CI)	P-Value
SLNB	3.59 (0.37 - 34.20)	0.27	6.04 (0.38 – 95.10)	0.20	2.78 (0.51 - 15.05)	0.23	2.96 (0.40 - 21.99)	0.29	0.80 (0.15 - 4.34)	0.80	0.992 (0.17 – 5.97)	0.99
Diabetes	…		0.808 (0.03- 21.58)	0.90	…		…	…	…		1.28 (0.12- 13.58)	0.84
Smoking	…		0.55 (0.06 - 4.98)	0.60	…		18.48 (1.37 – 249.15)	0.028	…		2.11 (0.33 – 13.70)	0.43
Age	…		1.00 (0.93 - 1.08)	0.91	…		0.96 (0.91 – 1.02)	0.17	…		1.04 (0.96 - 1.12)	0.36
Immunosuppressive drug use	…		28.56 (1.87 – 435.53)	0.016	…		28.55 (1.5 – 542.50)	0.026	…		3.19 (0.26 – 38.93)	0.36

Table 4a. Sociodemographic Factors and Medical History, OR (95% CI): Bivariate logistic regression of local, regional, and distant recurrence status unadjusted and adjusted for sociodemographic and medical history. After adjusting for diabetes, smoking, age and immunosuppressive drug use there were no significant associations between SLNB and odds of recurrence. Immunosuppressive drug use was associated with higher odds of local (OR=28.56, CI 1.87- 435.53; p=0.016) and regional recurrence (OR=28.55, CI 1.5–542.50; p=0.016). Being a past or current smoker was associated with higher odds of regional recurrence (OR=18.48, CI 1.37-249.15; p=0.028).

Table 4b: Bivariate Logistic Regression Model of Tumor Characteristics

TABLE 4B	Local Recurrence				Regional Recurrence				Distant Recurrence			
Characteristics	Unadjusted (95% CI)	P-Value	Adjusted Odds (95% CI)	P-Value	Unadjusted (95% CI)	P-Value	Adjusted Odds (95% CI)	P- Value	Unadjusted (95% CI)	P-Value	Adjusted Odds (95% CI)	P-Value
SLNB	3.59 (0.37 - 34.20)	0.27	9.13 (0.41 – 202.96)	0.16	2.78 (0.51 - 15.05)	0.23	11.46 (0.81 – 161.64)	0.07	0.80 (0.15 - 4.34)	0.80	0.685 (0.08 – 5.67)	0.73
Mitotic Rate	…		0.90 (0.49 – 1.65)	0.73	…		1.24 (0.92 – 1.67)	0.16	…		1.11 (0.83 – 1.48)	0.50
Ulceration	…		15.29 (0.67 – 349.34)	0.088	…		0.47 (0.47 – 4.80)	0.53	…		10.86 (1.25 – 94.6)	0.99
Lymphocytic Involvement	…		1.31 (0.13 – 13.47)	0.82	…		0.05 (0.004-0.70)	0.03	…		0.21 (0.24 - 1.87)	0.16
Lymph-Vascular Invasion	…		…	…	…		1.60 (0.05 – 52.43)	0.79	…		2.32 (0.03 – 1.87)	0.71
Initial Breslow Depth	…		0.09 (0.003-2.81)	0.17	…		…	…	…		0.68 (0.014 – 32.95)	0.85
Final Breslow Depth	…		1.16 (0.54 – 2.48)	0.70	…		1.55 (0.92 – 2.63)	0.10	…		0.98 (0.47 - 2.05)	0.97

Table 4b. Tumor Characteristics, OR (95% CI): Bivariate logistic regression of local, regional, and distant recurrence status unadjusted and adjusted for tumor characteristics. After adjusting for mitotic rate, ulceration, lymphocytic involvement, lymph-vascular invasion, initial and final BRES, there were no significant associations between SLNB and odds of recurrence. Lymphocytic involvement was associated with lower odds of regional (OR=0.05, CI 0.004-0.70; p=0.03) and distant (OR=0.97, CI 0.01–0.71; p=0.02) recurrence.