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Meta-Analysis of Sentinel Lymph Node Positivity in Thin Melanoma (≤ 1 mm)

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Abstract

Background—Despite the lack of an established survival benefit of sentinel lymph node (SLN) biopsy, this technique has been increasingly applied in the staging of thin (≤ 1 mm) melanoma patients, without clear evidence to support this recommendation. We performed a meta-analysis to estimate the risk, potential predictors, and outcome of SLN positivity in this group of patients.

Methods—MEDLINE, EMBASE, and Cochrane databases were searched for rates of SLN positivity in patients with thin melanoma. The methodological quality of included studies was assessed using the MINORS criteria. Heterogeneity was assessed using Cochran's Q-statistic, and publication bias was examined through funnel plot and Begg and Mazumdar's method. Overall SLN positivity in thin melanoma patients was estimated using DerSimonian-Laird random effect method.

Results—34 studies comprising 3,651 patients met inclusion criteria. The pooled SLN positivity rate was 5.6%. Significant heterogeneity among studies was detected ($p=0.005$). There was no statistical evidence of publication bias ($p=0.21$). 18 studies reported select clinical and histopathologic data limited to SLN positive patients ($n=113$). Among the tumors from these patients, 6.1% were ulcerated, 31.5% showed regression, and 47.5% were Clark's level IV/V. Only 4 melanoma-related deaths were reported.

Conclusion—Relatively few patients with thin melanoma have a positive SLN. There are no clinical or histopathologic criteria which can reliably identify thin melanoma patients who might benefit from this intervention. Given the increasing diagnosis of thin melanoma, in addition to the cost and potential morbidity of this procedure, alternative strategies to identify patients at risk for nodal disease are needed.

Introduction

Patients with thin melanoma (≤ 1 mm) tend to have a favorable prognosis, with 10-year overall survival rates ranging from 83.1%–96.5%.^{1, 2} A subset of patients with thin melanoma, however, will develop metastatic disease, some after prolonged (>10 yrs) periods

of observation.³ Although various prognostic models for thin melanoma patients have been devised, the lack of independent and external validation among published studies underscores the challenge in identifying groups at risk for metastases.⁴ Based on survival analyses, the revised AJCC Staging System established ulceration and Clark's anatomic level > III as negative prognostic features of thin melanoma; but this classification scheme has been challenged.^{5, 6}

Sentinel lymph node biopsy (SLNB) is generally recommended for intermediate-thickness (1–4 mm) melanomas; however, the application of this technique has recently extended to thinner lesions.^{2, 7} Given the lack of evidence-based guidelines by which to stratify thin melanoma patients for this procedure, however, selection criteria vary widely among institutions. While it is common for physicians to perform SLNB in Stage T1b patients (thin melanoma with ulceration and/or Clark's level > III) or in the presence of regression, still others have proposed that age, gender, mitotic rate and vertical growth phase (VGP) are significant predictors of SLN positivity.^{8–11} The differing criteria by which patients are chosen for SLNB make meaningful comparisons among published studies difficult and may further explain the broad range of reported SLN positivity rates in thin melanoma patients, with current estimates between 0%–13.5%.^{8, 12} Given the low probability of nodal metastases in thin melanoma patients, one must also consider the associated costs and potential perioperative morbidity when selecting patients for this procedure.¹³ Further complicating this issue is the lack of data to support SLN status as a reliable predictor of outcome in this subgroup of patients.¹⁴

Considering that nearly 70% of melanomas today are diagnosed as thin lesions, establishing consensus guidelines for SLNB in this group of patients is of notable clinical relevance.¹⁵ In order to integrate previous findings on this topic, we performed a meta-analysis of published literature to provide a more objective estimate of the incidence and clinical outcome of SLN positivity in thin melanoma patients, as well as to examine potential predictors of nodal disease in this population. Although a systematic review of published studies on SLNB in melanoma has been previously conducted, the objective was focused solely on the correlation between tumor thickness and SLN positivity, with only 2 of the 12 studies reviewed reporting on thin melanoma patients.¹⁶ Lastly, we also chose to assess the incidence of SLN positivity in our own prospectively accrued melanoma database.

Methods

Search Strategy and Eligibility Criteria

A systematic review of original articles and abstracts analyzing the SLN status of patients with thin (< 1 mm) primary melanoma was performed by searching MEDLINE (January 1966 to July 2007), EMBASE (January 1980 to July 2007), Cochrane Library, Web of Science—Science Citation Index Database, and Biological Abstracts Database (1969–current). Studies were eligible if the SLN positivity rate in thin melanomas was reported. The search strategy included the following keywords in various combinations: “melanoma”, “lymph nodes”, “sentinel lymph node biopsy”, “sentinel node biopsy”, “lymphatic metastasis”, “ulceration”, “regression”, “size”, “thin”, “mitosis”, “mitotic index”, “neoplasm invasiveness”. The titles and abstracts of articles retrieved by this search were evaluated against inclusion criteria and the manuscripts of all studies deemed potentially eligible were obtained. There was no restriction criterion on the number of patients enrolled in the study. Given the volume of articles retrieved, articles were limited to English language only. When overlapping or duplicate data sets were detected on the same series of patients, only the most recent or most informative study was included in the analysis. Searches were supplemented by scanning bibliographies of included articles.

Data Extraction

Two investigators independently extracted data from selected articles, including year of publication, first author, patient selection criteria for SLNB, reported SLN positivity rate in thin melanoma patients, recurrence data, and summary statistics on SLN positive and negative cases, if available. To ensure the accuracy of this process and to minimize subjective judgment, data were verified between the two reviewers and discrepancies were settled through consensus discussion.

Assessment of Study Quality

The subject of judging research quality in studies to be combined for meta-analysis is of utmost importance since combining study results of poor quality may lead to biased and therefore misleading results. Although it is highly recommended that study quality be utilized for explaining the heterogeneity of the study outcomes, no consensus exists about the methods for incorporating quality at the analysis stage.¹⁷ We assessed the quality of each study using the Methodological Index for Non-Randomized Studies (MINORS) criteria as developed by Slim *et al* to evaluate the methodology of non-randomized studies.¹⁸ For each article, study quality was determined by blinded review by 2 independent reviewers (MW and JZ). They identified whether the authors had adequately reported on a total of 8 items, including whether 1) the study had a clearly stated aim, 2) consecutive patients were included, 3) data was collected prospectively, 4) endpoints were appropriate to study, 5) there was an unbiased assessment of endpoints, 6) follow-up period was adequate, 7) loss to follow-up was less than 5%, and 8) there was a prospective calculation of study size. This index allowed us to objectively assign a quality score to each study, the median of which was utilized to assess if the heterogeneity found in the outcome was due to study quality. To avoid selection bias, no study was excluded based on the quality score alone in the assessment of the overall effect.

NYU Study Population

396 thin melanoma patients were prospectively enrolled in the Interdisciplinary Melanoma Cooperative Group (IMCG) at the New York University (NYU) School of Medicine. Of these, 99 (25%) underwent SLNB. Clinicopathologic, demographic, and survival data were recorded prospectively for all patients. The NYU Institutional Review Board approved this study and informed consent was obtained from all patients at the time of enrollment.

Outcome Measures and Meta-Analysis

SLN positivity rate was the primary outcome. Inter-study heterogeneity was assessed by using Cochran's Q Statistic, which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method.¹⁹ Q is distributed as a chi-square statistic with k (number of studies) minus one degrees of freedom. Because studies were found to be heterogeneous, summary odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated using random-effects modeling. Publication bias (ie, negative trials are published less frequently and are therefore more likely to be missed in the search for relevant studies) was assessed through the construction of a funnel plot for the primary endpoint, as well as by Begg and Mazumdar's adjusted rank correlation method.²⁰ Sensitivity analyses were conducted by dichotomizing the included studies around the median quality score.

We also evaluated the proportion of SLN positive patients whose primary tumors had features of regression, ulceration, were Clark's level IV, or had mitoses present. Descriptive statistics were also generated for recurrence and survival data, including the number of recurrences and deaths in both the SLN negative and positive groups. Statistical

analyses were performed using StatsDirect version 2.5.2 (StatsDirect Ltd, Cheshire, England) for the meta-analysis portion and SAS Version 9.1 (SAS Institute, Inc., Cary, North Carolina) for the rest of the analyses.

Results

Characteristics of Included Studies

The initial search resulted in 1,768 citations. The title and abstract of each retrieved publication was reviewed to confirm that the article reported on the incidence of SLN positivity in thin melanoma patients. In the event that this approach was not informative, the full article was retrieved and further reviewed. This process resulted in the selection of 70 studies. Of these, 36 were further excluded from this analysis: 22 did not report on SLN positivity in $\geq$ or $<$ 1 mm thickness groups (i.e. reported SLN positivity using old AJCC T1 staging system), 12 presented overlapping data from other studies, 1 was a quantitative systematic review of published studies on SLNB in melanoma, and 1 was a review article summarizing a previous study on potential predictors of SLN positivity.

The 34 studies meeting inclusion criteria reported on 3,651 thin melanoma patients who had undergone a SLNB procedure (Table 1). The median number of thin melanoma patients enrolled per study was 63.5 (range, 4 to 465), with 11 (32.4%) studies enrolling $\geq$ 100 patients. Of studies which provided baseline demographic information on thin melanoma patients, 452 were female and 512 were male.^{10, 11, 14, 21–28} The mean age was reported in 4 studies and ranged between 47.6 years to 53 years^{23, 25, 26, 28}, and the reported median age ranged from 52.5 years to 54 years in 3 studies^{10, 14, 24}.

Selection criteria for performing SLNB in thin melanoma patients were reported in 20 of 34 (58.8%) studies, and included a primary tumor thickness $\leq$ 0.75 mm in 6 (30%) studies^{21, 24, 29–32}, presence of primary tumor ulceration in 13 (65%) studies^{9–14, 21, 23, 29, 32–35}, presence of primary tumor regression in 12 (60%) studies^{9–13, 21, 23, 29, 33–36}, and Clark's anatomic level $\leq$ IV in 12 (60%) studies^{10, 11, 13, 14, 21, 29, 32–37}. More uncommon inclusion criteria were primary tumor thickness $\leq$ 0.50 mm³⁸, $>$ 5 mitoses¹⁰, vascular invasion¹³, presence of vertical growth phase (VGP)^{11, 33}, Clark's anatomic level II–V³⁹, Clark's anatomic level III or IV²³, positive deep margin on primary tumor excision⁹, or subungual location³⁴. Inclusion criteria were commented on in an additional 2 studies, but were not specified.^{26, 28}

Thirty-one of 34 (91.2%) studies commented on the histopathologic examination of SLNs, which consisted of routine hematoxylin-eosin staining with additional sections evaluated by immunohistochemical staining for S-100 in 2 (6.5%) studies^{28, 40}, for MART1/Melan-A in 1 (3.2%) study²⁶, for S-100 and HMB-45 in 17 (54.8%) studies^{8, 10–12, 14, 24, 27, 29, 31, 32, 34, 38, 41–45}, for S-100 and MART1/Melan-A in 2 (6.5%) studies^{21, 39}, for HMB-45 and MART1/Melan-A in 2 (6.5%) studies^{25, 46}, and for S100, HMB-45, and MART1/Melan-A in 6 (19.4%) studies^{9, 22, 30, 33, 35, 37}. The specific immunostains were not reported in one study.¹³ Reverse transcriptase-polymerase chain reaction (RT-PCR) for the melanoma markers tyrosinase, MAGE-3, MART-1, and HMB-45 was also performed on a subset of immunohistochemistry negative SLNs in one study, although these results were not included in our analysis.²⁸

SLN Positivity in Thin Melanoma Patients – Outcome of Meta-Analysis

The random-effects model was applied to estimate the meta-analysis pooled SLN positivity rate, which we determined to be 5.6% (95% CI, 0.049 to 0.063, Figure 1). Significant heterogeneity among studies was detected (Cochran Q statistic 57.83, $p=0.0048$), prompting

us to examine the two subgroups of studies divided by the median quality score of six. Heterogeneity remained significant in both subgroups ($p = 0.0452$ for studies with a quality score above the median and $p = 0.017$ for studies with a quality score below the median), indicating there are other covariates or patient selection criteria that are responsible for this heterogeneity.

Examination of the funnel plot, shown in Figure 2, did not provide evidence of publication bias, as most studies fell within the expected funnel around the mean effect size ($p = 0.21$, Begg-Mazumdar test).

SLN positivity in melanomas ≤ 0.75 mm in thickness was reported in ten studies, with five studies^{10, 11, 21, 26, 39} noting SLN positivity in patients with melanomas ≤ 0.50 mm in thickness. The thinnest melanomas associated with SLN positivity were 0.40 mm in thickness.^{10, 21}

Histopathologic Features of SLN Positive Thin Melanoma Patients

Eighteen (52.9%) studies provided raw data on select clinical and histopathologic features of SLN positive patients ($n = 113$). The mean and median tumor thickness ($n = 71$) were 0.82 mm and 0.88 mm, respectively. Among the tumors from these patients, 6/98 (6.1%) were ulcerated, 17/54 (31.5%) showed regression, and 48/101 (47.5%) were invasive to Clark's level IV/V. Of 43 patients which had data on mitotic rate (MR) available, 33 (76.7%) had low MR (≤ 2 mitoses), 2 (4.7%) had moderate MR (3–5 mitoses), and 8 (18.6%) had high MR (> 5 mitoses).

Prognostic Significance and Predictors of SLN Positivity in Thin Melanoma Patients

Of the 34 studies analyzed, 14 studies reported on the results of completion lymph node dissection (CLND). These studies reported on a total of 1,135 patients with thin melanoma who underwent SLNB. Of these, only 1 of 1,135 had additional lymph nodes positive for melanoma on CLND.¹¹

Fourteen (41.2%) studies provided recurrence and/or survival data for either SLN positive patients, SLN negative patients, or both. In total, 4 melanoma-related deaths were reported in SLN positive patients and 4 deaths in SLN negative patients.^{14, 23, 29, 41} The primary tumor thickness was reported for 3 of the 4 SLN positive patients who died of disease and included one tumor 0.85 mm in thickness, another 0.90 mm in thickness, and the last 1.0 mm in thickness. Of SLN negative patients who died of melanoma, 3 of the 4 patients were reported to have had tumors ≤ 0.75 mm in thickness, although more specific data was not provided. In 8 of the 14 studies (57%) however, no recurrences and/or deaths occurred in either the SLN positive or negative groups.

A total of 10 (29.4%) studies evaluated the association between select demographic and histopathologic features of thin melanoma patients and SLN positivity. In 5 (50%) studies, none of the factors examined was significantly associated with SLN involvement. In the remaining 5 studies, tumor thickness⁴¹, Clark's level⁴¹, ulceration¹⁰, MR^{10, 11, 41}, VGP¹⁰, regression⁸, and lack of regression³⁶ were correlated with SLN positivity on univariate analysis. Of two studies which performed a multivariate analysis^{11, 21}, one study ($n = 146$) found no association between clinicopathologic factors and SLN tumor involvement.²¹ The remaining study, which reported on 181 VGP positive thin melanoma patients, found that MR > 0 was significantly associated with SLN positivity in a multivariate analysis controlling for age, sex, anatomic location, thickness, Clark's level, and ulceration.¹¹

NYU Experience - SLN Biopsy in Thin Melanoma Patients

Of the 880 primary and metastatic melanoma patients enrolled in the NYU IMCG between August 2002 and January 2008, 396 patients (45%) had melanomas ≤ 1 mm in thickness. Ninety-nine thin melanoma patients (25%) underwent 100 SLNB procedures during initial treatment. The mean tumor thickness for patients receiving SLNB was 0.82 mm (range 0.3–1.0 mm) and was 0.44 mm (range 0.12–1.0 mm) for those who were not selected for SLNB.

SLN metastases were identified in 2 (2%) of the 99 patients. This included one 38-year old male with a melanoma 0.82 mm in thickness located on the extremity. On histologic examination, the tumor was invasive to Clark's level III, was without evidence of ulceration, but did have features of regression, and had few (≤ 2) mitoses per high powered field (HPF). The second patient was a 48-year old male with an axial melanoma 0.5 mm in thickness, Clark's level III, without evidence of ulceration or regression, and few mitoses per HPF. Since their initial treatment, neither of the two patients developed recurrences and both remain disease free at last follow-up (9 and 50 months, respectively).

Of the 97 patients with negative SLNB, 7 (7%) had ulcerated tumors and 37 (38%) had evidence of tumor regression. Thirty melanomas (31%) were invasive to Clark's level III, 51 (52%) to Clark's level IV, and one case invaded to Clark's level V (1%). In terms of MR, 57 (58%) tumors had few mitoses per HPF, 12 cases (12%) had a moderate number of mitoses, and 6 (6%) had a high MR. Seven patients (7%) developed recurrences or metastases during a mean follow-up period of 17.4 months (range 1 to 100 months). Two of these patients (2%), one with a primary melanoma 0.66 mm in thickness and the other with a melanoma 0.95 mm in thickness, died of their disease at a follow-up time of 27 months and 57 months, respectively.

Discussion

There is no consensus regarding the application or clinical implications of SLNB in patients whose melanomas are ≤ 1 mm in thickness. To our knowledge, our study represents the first meta-analysis to focus on SLNB in this subset of patients. Our analysis reveals that the available data on this subject are inconsistent and are not adequate to establish criteria for patient selection.

According to the National Comprehensive Cancer Network Practice Guidelines in Melanoma (version 2.2008), "discussion of SLNB should be considered for patients with stage IA thin melanomas (1.0 mm or less) with adverse prognostic features such as thickness over 0.75 mm, high mitotic rate, and young patient age." For patients with stage IB (1.0 mm thick or less with ulceration or Clark level IV or V), the guidelines "encourage the use of SLNB." The current level for this recommendation is 2A, defined as "based on lower-level evidence including clinical experience and uniform consensus."⁴⁷ However, it is unclear what lower-level evidence this recommendation is based on. In fact, the guidelines further state that "since patients with thin melanoma have a generally favorable prognosis, the role of SLNB in this cohort is unclear." Given that patients with thin melanoma have not yet been addressed specifically by the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1), it has been difficult to assess the value of SLNB in this patient subset. It is this limitation of available data which prompted our current study.

Findings of the AJCC have demonstrated the independent prognostic value of ulceration and Clark's level in melanomas ≤ 1 mm.⁵ Since its incorporation in the melanoma staging system, many studies have further confirmed that ulceration and Clark's level $> III$ confer a poorer prognosis on patients with thin melanomas. However, large-scale studies have also presented contradictory results.^{6, 48} Our analysis suggests that even if these histopathologic

factors are predictive of overall survival in patients with thin melanoma, they do not necessarily predict the presence of micrometastatic nodal disease as detected by SLNB. While ulceration and Clark's level were the most frequently reported selection criteria among published studies, we found no consistent evidence supporting their correlation with SLN positivity in thin melanoma patients. Furthermore, only 6% of SLN positive patients for which we had data had ulcerated tumors, and less than half (48%) were invasive to Clark's level IV/V. In our own prospective melanoma database, ulceration was a feature of only 7 of 100 thin melanomas, none of which were associated with a positive SLN finding. Furthermore, both of our SLN positive patients had primary tumors invasive to Clark's level III.

The presence of regression was also a commonly cited selection criteria for SLNB; however, evidence to support this decision is limited at best. The clinical significance of regression in primary melanoma continues to be disputed, with several studies reporting a higher rate of metastasis in thin, regressed melanomas^{49, 50} and an equal number finding no association with recurrence or overall survival.^{51, 52} This inconsistency could be explained in part by the lack of uniform criteria to define regression, making the reproducibility of this diagnosis difficult.⁵³ In terms of its association with SLN status, only one study of thin melanoma patients to date has found evidence to suggest that regression is a significant predictor of SLN positivity.⁸ In our analysis of published data, approximately 1/3 of SLN positive patients had evidence of regression, although data on SLN negative patients was largely unavailable. In our NYU database, regression was present in 38 (43.2%) of thin melanomas, only one of which was associated with a SLN positive finding. Thus there is sparse evidence to support regression as a predictive factor for SLN positivity in thin melanoma patients at this time.

While varied clinical and histopathologic features were found to be predictive of SLN positivity among published studies, the majority failed to confirm these associations on multivariate analysis. One study focusing on thin melanoma patients, however, did identify MR > 0 as being significantly associated with SLN positivity (12.3% vs 0%) after controlling for other histopathologic features.¹¹ One additional study by Sondak *et al* found that MR was predictive of SLN positivity on multivariate analysis; however only 42 of 419 patients included in their study had melanoma ≤ 1 mm, and of those, only 4 had a positive SLN.⁹ Still yet, several large, prospective studies have validated MR as a prognostic indicator in thin melanoma patients.^{1, 3, 54} However, this cannot be taken as evidence to support MR as a predictor of nodal metastasis. In our analysis of SLN positive patients, of which 43 had data available on MR, only 10 (23.4%) patients had moderate MR (3–5 mitoses) or high MR (>5 mitoses). Given the absence of data on SLN negative patients in these studies, however, we could not estimate the predictive potential of a high MR. Upon reviewing our NYU data, none of the thin melanoma patients with either moderate (n=12, 15.6%) or high (n=6, 7.8%) MR were found to have a positive SLN. Thus, while MR may impact survival, with some having recommended the addition of this feature to the next version of the AJCC staging system, the clinical implications of MR on SLN positivity in thin melanoma patients remains controversial.⁵⁵

At this time, there is limited available evidence to support SLN status as a reliable predictor of disease recurrence or survival in thin melanoma patients, with most studies providing an inadequate follow-up time. In fact, only half of the studies we analyzed provided any follow-up information. Of the 14 studies which did, the total number of deaths in SLN positive patients was equivalent to that in SLN negative patients. Thus, based on published literature, the overall survival benefit of SLNB among patients with melanomas ≤ 1 mm in thickness appears marginal at most. Furthermore, since only one SLN positive patient had

evidence of disease in non-sentinel lymph nodes upon CLND, there does not seem to be an indication for CLND in these patients.¹¹

Although analysis of data from the MSLT-1 trial is still ongoing, interim published results have supported SLN status as an independent predictor of survival. Furthermore, there is general agreement that SLNB is an accurate means of melanoma staging and treatment planning, allowing for the selection and stratification of patients for adjuvant therapies. The impact of SLNB on survival, however, remains a matter of contention, with a 3% non-significant survival advantage having been found for patients in the SLNB group.⁵⁶ We would like to emphasize, however, that MSLT-1 data have been based on patients with intermediate thickness melanoma only, with the exclusion of thin and thick melanomas. Thus conclusions regarding survival advantage and treatment recommendations cannot simply be extrapolated to different subsets of melanoma patients at this time.

Our pooled meta-analysis SLN positivity rate was 5.6%. This must be interpreted in the context of a reported false-negative rate, the majority of which range from 0.6% to 7%, and are defined as a lymph node recurrence in the same nodal basin as that of the sentinel node and which occurs as the first site of recurrence.^{57–60} Based on such a limited number of SLN positive patients, meaningful correlative comparisons are difficult to perform. Given the increasing diagnosis of thin melanomas as well as the cost and morbidity associated with this procedure, alternative strategies to identify patients at risk for nodal disease, including molecular characterization of the primary tumor, should be considered. To this end, primary tumor expression of osteopontin, an integrin binding protein, was recently shown to be predictive of SLN metastasis and SLN burden in melanoma patients.⁶¹ Melanoma cell adhesion molecule (MCAM) expression has also been correlated with regional nodal disease independent of other clinicopathologic features, such as Breslow thickness and Clark's level.⁶² Thus expression of novel molecular prognostic markers may prove to be a more accurate and low-cost approach to the selection of patients for SLNB and should continue to be investigated.

We recognize the limitations of meta-analysis. The reliability of summary estimates is contingent upon the quality of the studies pooled. Although included studies met many of the *a priori* quality metrics, important deficiencies remained. Because the indication for SLNB and the ultimate outcome of those with a positive result is very hard to study in a randomized fashion, methodological shortcomings are inevitable. However, future research should adhere, in so far as possible, to the standardized definitions of thin melanoma, as well as the quality metrics specified herein in order to facilitate comparison.

Significant heterogeneity existed among studies with respect to both patient and study quality characteristics, as confirmed by the Q-statistic. Although random effect modeling incorporates this heterogeneity, the possibility remains that the SLN positivity rate in each study is mediated by one or more unmeasured factors, and the pooled SLN positivity rate is misleading as a result. We could not adjust our pooled estimate for the effects of confounding through a formal meta-regression due to the fact that covariate information was not consistently reported in the published studies. This limitation underscores the need for standardized reporting of relevant covariates in future observational studies within this literature.

In summary, there are insufficient data in the literature at this time to draw conclusions regarding SLNB in thin melanoma patients. While many clinicopathologic features of the primary tumor, including ulceration and MR, may be powerful independent prognostic factors in thin melanoma, they may not necessarily predict SLN positivity. Lastly, evidence

supporting SLN status as a reliable predictor of outcome in thin melanoma patients has not yet been demonstrated.

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Figure 1.
Meta-analysis of sentinel lymph node positivity in thin (< 1 mm) melanoma patients
(random-effects model)

Figure 2.
Funnel plot to assess publication bias

Table 1

Characteristics of 34 Included Studies

Reference	Year	No. of Patients	SLN (+) %	Average Quality Score
Cecchi et al ²²	2007	50	4.0	6.5
Starz et al ²⁴	2007	87	11.5	8.5
Kaur et al ³⁶	2007	62	3.2	7.5
Minutilli et al ⁴⁶	2007	23	4.3	1.5
Wong et al ¹⁴	2006	223	3.6	9
Hershko et al ²⁸	2006	64	7.8	5.5
Vaquerano et al ²⁹	2006	91	6.6	7
Nowecki et al ³²	2006	260	6.5	8
Cascinelli et al ³⁷	2006	145	4.1	9
Ranieri et al ⁴¹	2006	184	6.5	10.5
Kesmodel et al ¹¹	2005	181	5.0	7
MacNeill et al ³⁰	2005	4	75.0	6
Roka et al ³⁴	2005	24	4.2	6
Berk et al ³⁵	2005	45	0	7
Koskivuo et al ³⁹	2005	56	5.4	8
Puleo et al ⁴⁰	2005	409	4.9	4.5
Carlson et al ⁴²	2005	11	0	6.5
Sondak et al ⁹	2004	42	9.5	7.5
Chakera et al ¹²	2004	18	0	8
Stitzenberg et al ²¹	2004	146	4.1	6
Gipponi et al ³¹	2004	14	14.3	3.5
Cuellar et al ⁴⁴	2004	27	0	5
Borgognoni et al ⁴⁵	2004	114	1.8	8
Morton et al ⁶³	2003	465	7.3	6.5
Olah et al ⁸	2003	89	13.5	5
Filho et al ¹⁰	2003	77	7.8	3
Agnese et al ¹³	2003	91	1.1	8.5
Nahabedian et al ²³	2003	24	8.3	6.5
Jacobs et al ²⁵	2003	63	3.2	6
Lowe et al ²⁶	2003	46	6.5	5.5
Rousseau et al ³³	2003	388	4.1	7
Status Muller et al ³⁸	2001	104	6.7	6
Nguyen et al ⁴³	2001	21	0	4.5
Mazzuca et al ²⁷	2000	3	0	2

Abbreviations: SLN, sentinel lymph node