Impact of the time interval between primary melanoma excision and sentinel node biopsy: A systematic review and meta-analysis

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Background: Obtaining a sentinel lymph node biopsy (SLNB) specimen is a standard staging procedure in the management of cutaneous melanoma. However, there is no consensus on the safe time interval between the primary melanoma biopsy procedure and the SLNB procedure.

Objective: We evaluated the association between time from biopsy to SLNB and patients' outcomes for melanoma.

Methods: We performed this systematic review and meta-analysis based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results: Six retrospective studies were included. Nine thousand seven hundred five patients were identified, of which 4383 underwent a SNLB procedure at a time interval defined as early and 4574 at an interval defined as late. A combined hazard ratio of 1.25 (95% confidence interval [CI] 0.92-1.68) was determined, and there was high heterogeneity (I^2 = 83%; P = .002) of the SLNB time interval on melanoma-specific survival. The combined HR for disease-free survival was 1.05 (95% CI 0.95-1.15), with low heterogeneity (I^2 = 9%; P = .36). Regarding overall survival, a combined HR of 1.25 (95% CI 0.92-1.70) was found, with low heterogeneity (I^2 = 37%; P = .2).

Limitations: There is heterogeneity between some studies.

Conclusion: There are no significant differences in patient outcome between a short interval versus a long interval between the primary biopsy procedure and obtaining a SNLB specimen. (J Am Acad Dermatol 2021;85:128-34.)

Key words: disease-free survival; melanoma; melanoma-specific survival; overall survival; sentinel lymph node biopsy; timing of surgery.

The most important prognostic factor in melanomas with a Breslow depth of ≥1 mm is the status of the sentinel lymph node, and its selective biopsy is a standard staging procedure in its management.[1,2] However, in recent years its role has been considerably questioned, since a direct impact on overall survival (OS) or melanoma-specific survival (MSS) has not been demonstrated.[3,4] Moreover, in addition to the risk of local complications, it is usually a particularly stressful procedure for patients,

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given the implications in their management.[2,5] This might be worsened by the time interval between obtaining the primary melanoma biopsy specimen and the wide local excision (WLE) together with sentinel lymph node biopsy (SLNB). This interval may be determined by waiting times, institutional protocols, and morbidities, among other factors. Clinical guidelines for the management of cutaneous melanoma do not specify a maximum time interval between the primary biopsy and the WLE combined with SLNB, understanding that it should be performed as soon as possible.[6-8] Only the Dutch guide specifies a maximum time interval of 6 weeks.[9]

Furthermore, it is not clear if the time interval has an impact on patient outcome. Some studies have shown a better MSS when SLNB is performed before 30 days[10]; conversely, other authors suggest that the prognosis is worse if SLNB is performed early.[11]

Considering these controversial findings, the objective of this study was to evaluate the association between time interval from obtaining the primary biopsy specimen to SLNB and patients' outcomes for melanoma (OS, MSS, and disease-free survival [DFS]). To achieve this, we carried out a systematic review and meta-analysis with the data published in this regard.

CAPSULE SUMMARY

- Time interval between the diagnosis and management of patients with melanoma is a relevant issue with unknown effect in outcomes.
- This meta-analysis showed no association between patients' outcomes and the time interval between obtaining the primary melanoma biopsy specimen and the sentinel lymph node biopsy procedure.
- These results provide relevant information for the management of patients with melanoma

METHODS

This systematic review was developed based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12]

Eligibility criteria

We included all the research articles that aimed to evaluate the impact on OS, MSS, and DFS, expressed in hazard ratio (HR), of the delay time between obtaining the primary biopsy specimen of cutaneous melanoma and the SLNB. The exclusion criteria were: 1) articles in a language other than English; 2) duplicates of previous articles; 3) studies with cohorts included in other investigations; and 4) lack of information on HR.

Data sources and search strategy

We conducted a systematic review of all research articles in English, published up to May 31, 2020, in Medline, Embase, Cochrane, and Web of Science databases. The following search terms were used: "melanoma," "survival" and "lymph node biopsy" or "sentinel node biopsy," associated with "delay," "interval," "timing," or "waiting list."

The initial search yielded 292 articles, whose titles and abstracts were analyzed independently by 2 reviewers (PV and LP), excluding 266 articles. The same authors then independently reviewed the full text of the remaining 26 articles, selecting 8 that met the inclusion criteria. Two of them were excluded[11,13] because a significant part of these cohorts was included in cohorts with a larger number of patients.[14,15] Therefore, 6 studies were finally selected (Fig 1).[10,14-18] A third author (RG) defined disagreements between the 2 reviewers and approved the final list of included studies.

Data extraction

Two reviewers (PV and RG) extracted the information from the 6 selected articles, and discrepancies were resolved by a third reviewer (LP). The following data were obtained: name of the first author, year of publication, country, study design, number of patients, median follow-up, mean Breslow index, presence of ulceration, number and percentage of positive sentinel node, outcome (OS, MSS, or DFS), and HR with its corresponding 95% confidence interval (CI; Table I). In case the HR could not be obtained directly from each article, it was extracted from the Kaplan–Meier curves to extrapolate HR with a 95% CI, using previously described methods.[19] This was necessary to obtain the DFS in 2 studies.[14,15]

Quality assessment of individual studies

The Newcastle-Ottawa Scale for cohort studies was applied to evaluate the methodologic quality assessment of eligible studies by 2 reviewers (PV and LP) independently, classifying them as high quality if the final score was >6 points, among 3 quality parameters (selection, comparability, and outcome)

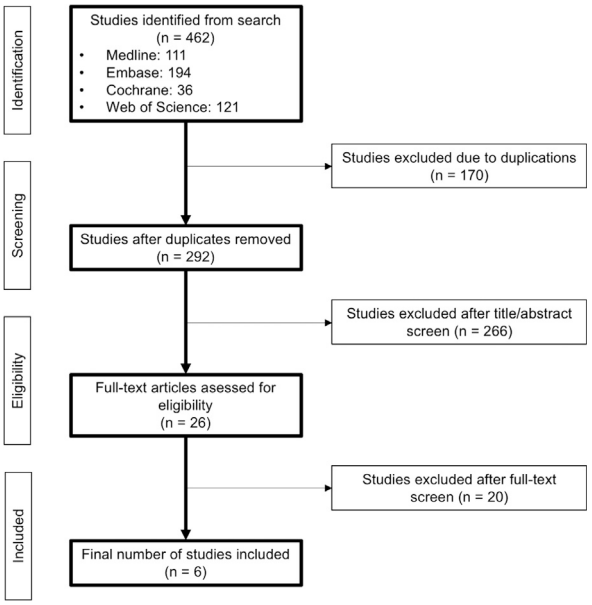

Fig 1. Selection process for the inclusion of studies in the systematic review.

divided across 8 specific items.[20] The final score of each study is shown in Table I.

Statistical analysis

A random-effects meta-analysis (DerSimonian–Laird method) was carried out, assessing the association between early/late SLNB and survival outcomes (OS, MSS, or DFS) through pooled HRs with 95% CIs. The articles were separated into subgroups according to the cutoff points (days) of time interval established in each case, and specific and global analyses were performed. A z test for overall effect was carried out for both subgroups and globally. The χ^2 and I^2 tests were used to assess heterogeneity, the latter ranging from 0% to 100%, considering 25% as low, 50% as moderate, and 75% as high heterogeneity, for each subgroup and for the global data.[21] The results were summarized in forest plots. The analyses were performed using Review Manager software version 5.3 (Cochrane Collaboration).

RESULTS

Selected studies

The 6 selected studies were retrospective studies. Nine thousand seven hundred five patients were identified, of which 4383 underwent a SLNB procedure in a time interval defined as early and 4574 in a time interval defined as late. In 1 study, the number of patients according to the time interval was not specified.[10] Regarding the cutoff values to define early SLNB and late SLNB, 43 days were used in 1 study,[15] 40 days in 2 studies,[14,17] 30 days in 2 studies,[10,18] and 28 days in the remaining study[16] (Table I). The median of the time intervals between obtaining the primary biopsy specimen and SLNB of the patients was used as cutoff point in 3 of the 6 selected studies.[15-17] In the remaining studies, the cutoff point was estimated based on the median contrasted and adjusted by the authors with previous studies,[18] cutoff value of the first quartile,[10] and analyzing intervals of 10 days, based on the minimum P value obtained and contrasted with a recursive partitioning method for categorical variables.[14]

Impact on the MSS

Three of the selected studies analyzed the effect of the SLNB time interval on MSS. A combined HR of 1.25 (95% CI 0.92-1.68) was determined, finding high heterogeneity (I^2 = 83%; P = .002; Fig 2).

Impact on the DFS

DFS was assessed in the 5 selected studies. The combined HR was 1.05 (95% CI 0.95-1.15), with low heterogeneity (I^2 = 9%; P = .36; Fig 3).

Impact on the OS

Regarding OS, a combined HR of 1.25 (95% CI 0.92-1.70) was found, with low heterogeneity in the 3 studies that evaluated this outcome (I^2 = 37%; P = .2; Fig 4).

DISCUSSION

This systematic review evaluated all the published articles assessing the effect of the time interval between the primary cutaneous melanoma excision and the date of WLE and SLNB on patient outcome, including a total of 1300 to nearly 9000 patients depending on the subanalysis performed. The results of our meta-analysis showed that time interval of SLNB after the diagnosis of cutaneous melanoma does not affect OS, MSS, or DFS for any of the cutoff points included.

First assumptions on this theme might suggest that a longer delay before the definitive management of melanoma could lead to greater tumor growth and the possibility of regional and systemic metastases. This would lead to worse outcomes, as has been evaluated and shown in other types of tumors.[22] In this systematic review, only the study by Carpenter et al,[16] which included 473 patients, suggested a slight tendency to a worse OS (HR 0.67 [95% CI 0.32-1.40]; P = .29) and DFS (HR 0.68 [95% CI 0.37-1.28]; P = .23) in the group of patients where the time interval was >56 days. This was later ruled out by the multivariate analysis, which attributed the effect solely to the Breslow and SLN status.

Table I. Studies included on the systematic review

Study/year	Country	Patients (n)	Median follow-up (mo)	Main BI (mm)	Ulceration, n (%)	Positive sentinel node, n (%)	Outcome	Newcastle-Ottawa scale final score (points)*
Carpenter et al, 2008[16]	USA	473	33.6	2.1	112 (28)	61 (13)	OS and DFS	7
Parrett et al, 2012[17]	USA	492	140.4	2.3	115 (23.5)	78 (15.9)	OS and DFS	8
Tejera-Vaquerizo et al, 2015[14]	Spain	1963	46	2.8	530 (34)	464 (23.6)	OS, MSS, and DFS	8
Oude Ophuis et al, 2016[15]	International	3546	50	N/I	2420 (68.2)	705 (19.9)	MSS and DFS	9
Fortes et al, 2016[10]	Italy	748	120	2.8	130 (17.4)	141 (18.9)	MSS†	8
Nelson et al, 2017[18]	International	2483	96	1.8	427 (17.2)	432 (17.4)	MSS and DFS	9

BI, Breslow index; *DFS*, disease-free survival; *MSS*, melanoma-specific survival; *N/I*, not informed; *OS*, overall survival.
*The Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of included studies. The scale consists of assessment of 3 quality parameters (selection, comparability, and outcome) divided across 8 specific items. Studies scoring 0-3, 4-6, and 7-9 points were identified as low, moderate, and high quality, respectively.[20]
†Hazard ratio described only in the subgroup with positive sentinel node.

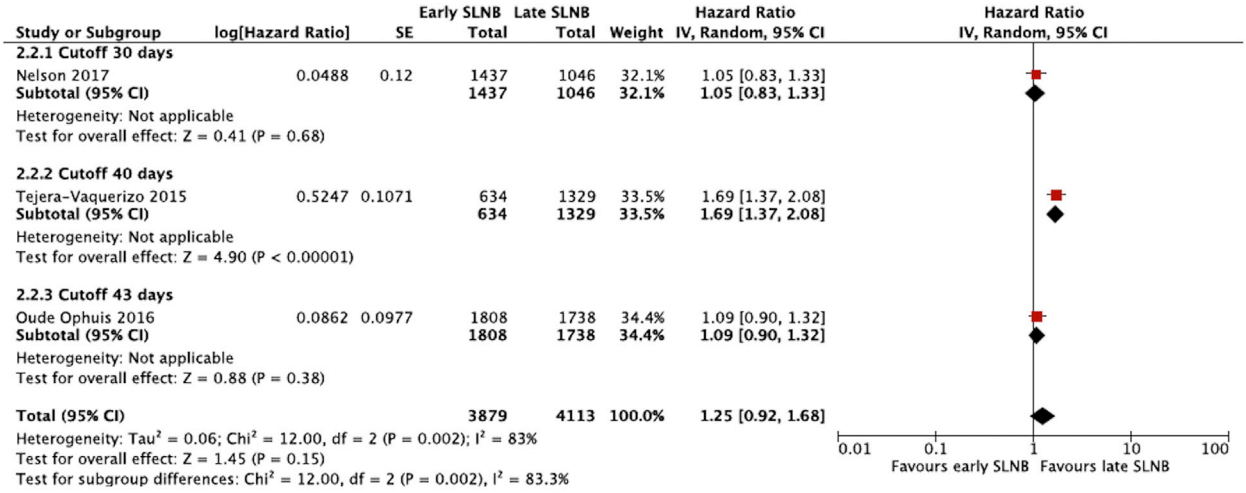

Fig 2. Forest plot of the impact of the time interval between primary melanoma excision and sentinel lymph node biopsy (SLNB) procedure on melanoma-specific survival. Squares indicate the 95% confidence intervals (CIs) and diamonds indicate the pooled proportions. *SE*, Standard error.

The results of our work confirm that reported in many studies included in the meta-analysis, which showed no effect of the time interval on patient outcome. Parret et al,[17] in a study of 492 patients, set a cutoff interval of 40 days and found no effect on MSS (P = .07), OS (P = .53), or DFS (P = .58) at 5 years' follow-up. Oude Ophuis et al[15] included a cohort of 3546 patients from 4 tertiary referral centers from the European Organization for Research and Treatment of Cancer Melanoma Group. It set a cutoff point for the time interval at the median of 43 days and found no differences in DFS (P = .729) or MSS (P = .617) at 5 years' follow-up. Nelson et al,[18] in a cohort of 2483 patients with 8 years of follow-up, set cutoff points for the time interval of 30 and 40 days. They found no effects on DFS (P = .85) or MSS (P = .67); controlling their results with the data from the cohort of the Multicenter Selective Lymphadenectomy Trial 1 (MSLT-1), they also did not find that a time interval >30 or <30 days affected DFS or MSS in those patients.

The studies carried out by Tejera-Vaquerizo et al[11,14] merit particular attention. The first of these set a cutoff point of 40 days and found that those patients where the SLNB was carried out early had a worse MSS (P = .0002) at the 5-year follow-up. In the stratified analysis by sentinel node status, this association was only maintained for patients with a negative lymph node status for both MSS (P = .001) and DFS (P = .0005).[14] To rule out possible bias in selection that might explain those apparently counterintuitive results, Tejera-Vaquerizo et al[11] conducted a second study in 2017, where through the

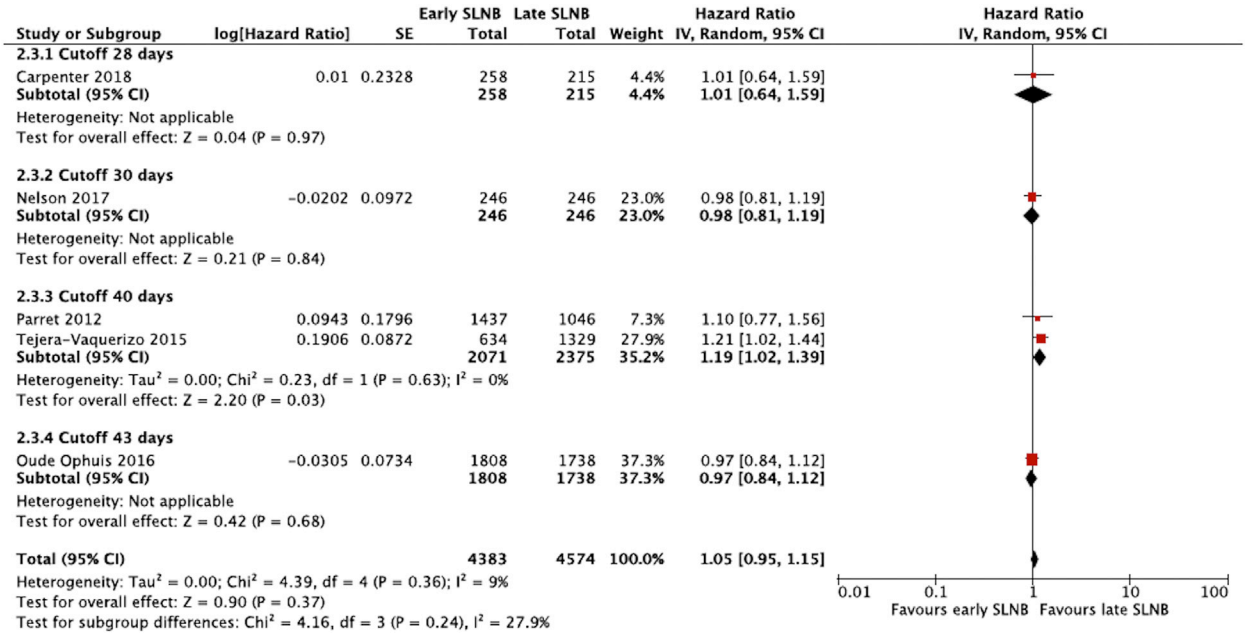

Fig 3. Forest plot of the impact of the time interval between primary melanoma excision and sentinel lymph node biopsy (SLNB) procedure on disease-free survival. Squares indicate the 95% confidence intervals (CIs) and diamonds indicate the pooled proportions. *SE*, Standard error.

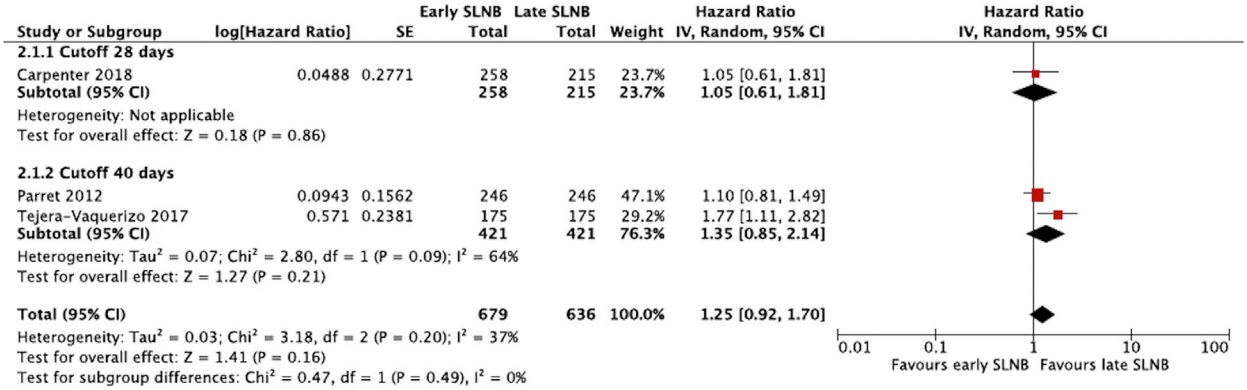

Fig 4. Forest plot of the impact of the time interval between primary melanoma excision and sentinel lymph node biopsy (SLNB) procedure on overall survival. Squares indicate the 95% confidence intervals (CIs) and diamonds indicate the pooled proportions. *SE*, Standard error.

"propensity score" model they matched pairs of patients with similar characteristics, and came to the same conclusions as the 2015 study. The authors suggested that early extirpation of the sentinel lymph node prevents the formation of a mature antitumoral immune response, and this results in worse outcomes for the patients.[11]

On the other hand, Fortes et al[10] studied 748 patients with 10 years' follow-up and concluded that patients where a SLNB procedure was carried out before 30 days and showed a positive SLN status had a 3 times better MSS compared with patients whose SLNB specimen was obtained after 30 days ($P < .0001$). When the analysis was done for an interval of 42 days, the effect disappeared. This suggests that the benefit only occurs if the SLNB specimen is obtained within the first month after the diagnosis of melanoma.

To elucidate the significance of these apparently contradictory results that suggest different effects of time interval on patient outcome depending on sentinel lymph node status, we carried out 2 new forest plots. One included only patients with negative SLN status and the other only patients with positive SLN status (data not shown). The negative SLN status group included 4947 patients from 3

studies[10,14,15]; the forest plot showed no effect of time interval on DFS (HR 1.1 [95% CI 0.65-1.88]; $P = .72$) or MSS (HR 1.47 [95% CI 0.92-2.34]; $P = .11$). The analysis of the group of patients with positive SLN status included 1726 patients from 4 studies[10,14,15,18]; the forest plot showed no effect of time interval on DFS (HR 1.14 [95% CI 0.88-1.48]; Z test for overall effect = 1.0; $P = .32$) or MSS (HR 0.98 [95% CI 0.67-1.43]; Z test for overall effect = 0.11; $P = .92$). These findings are concordant with that reported in the first study by Oude Ophuis et al,[13] which evaluated the effect of time interval in a study that included 1015 SLNB—positive patients only. It ruled out an effect on DFS ($P = .729$) or MSS ($P = .617$).

In addition to the SLN status, the included studies did not show a significant effect in the time interval—related outcome of other known prognostic variables, such as age, sex, ulceration, Breslow index, and mitotic index. Regarding age, Carpenter et al[16] found a slight increase in mean time interval in patients >75 years of age, probably attributable to the fact that elderly patients require additional appointments to facilitate a proper preoperative evaluation.

The MSLT-1[23] and MSLT-2[24] studies showed a lack of therapeutic effect of carrying out a WLE followed by SLNB together with a completion lymph node dissection compared with carrying out a WLE alone and node status follow-up. Taking this into consideration, it would seem reasonable to question the plausibility of the results of this meta-analysis, which suggest that the time interval between diagnosis of melanoma and the WLE together with SLNB would not affect the prognosis for patients. However, in subsets of patients where SLN status might determine the use of other therapies, the time interval might be important. Although this was not evaluated in the present study, it does not seem likely that a delay of a few weeks or months would have a decisive effect in this subgroup of patients. Moreover, most of the studies that evaluated SLN status included in this systematic review suggest that the effect of time interval is not related to patient SLN status, in the time ranges examined.[10,14-16]

Considering all of the above, there is broad consensus that SLNB is the most important prognostic factor in patients with 1- to 4-mm melanomas.[1,25] It is therefore necessary to make recommendations about the best time to carry it out. The cutoff points included in this meta-analysis give us a safe range of 28 to 43 days between when melanoma is diagnosed and WLE and SLNB is carried out, when patient outcome is not affected. Nevertheless, some of the studies included also evaluated the extreme quartiles of time interval for their respective cohorts, suggesting that cutoff points of 40,[18] 56,[16] 60,[15] and ≤63[13] days also had no effect on patient outcome. Even further, the MSLT-1[23] and SUNBELT[26] trials, although their main objective was not to evaluate the delay in carrying out SLNB, considered maximum time intervals of 84 and 90 days, respectively.

Although it is difficult and probably unnecessary to establish time limits based on the information mentioned, it seems probable that time intervals of 1 to 3 months present no risk in relation to patient prognosis. A reasonable, safe waiting time can be set that does not stress health care systems or increase the anxiety of doctors or patients.

Our study has some limitations. First, all the articles included were retrospective, nonrandomized clinical trials, which may have led to selection bias. Second, some of the included data were not available in the respective articles and had to be extrapolated from the provided curves or from direct questions to the authors. Third, there was a significant heterogeneity among some of the subgroups included. Yet despite these disadvantages, a robust statistical analysis was performed, and the results obtained reliably summarize the information available on this topic, allowing recommendations for clinical practice to be provided.

CONCLUSION

This systematic review and meta-analysis shows that there is no significant association between time interval from primary biopsy of cutaneous melanoma to SLNB and patient outcomes (OS, MSS, and DFS).

Conflicts of interest

None disclosed.

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