Article

Sentinel Lymph Node Biopsy vs. Observation in Thin Melanoma: A Multicenter Propensity Score Matching Study

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Abstract: The therapeutic value of sentinel lymph node biopsy (SLNB) in thin melanoma remains controversial. The aim of this study is to determine the role of SLNB in the survival of thin melanomas (≤1 mm). A multicenter retrospective observational study was designed. A propensity score matching was performed to compare patients who underwent SLNB vs. observation. A multivariate Cox regression was used. A total of 1438 patients were matched by propensity score. There were no significant differences in melanoma-specific survival (MSS) between the SLNB and observation groups. Predictors of MSS in the multivariate model were age, tumor thickness, ulceration, and interferon treatment. Results were similar for disease-free survival and overall survival. The 5- and 10-year MSS rates for SLN-negative and -positive patients were 98.5% vs. 77.3% (p < 0.001) and 97.3% vs. 68.7% (p < 0.001), respectively. SLNB does not improve MSS in patients with thin melanoma. It also had no impact on DFS or OS. However, a considerable difference in MSS, DFS, and OS between SLN-positive and -negative patients exists, confirming its value as a prognostic procedure and therefore we recommend discussing the option of SLNB with patients.

Keywords: melanoma; sentinel lymph node biopsy; survival

1. Introduction

Sentinel lymph node biopsy (SLNB) is a commonly used procedure in the management of cutaneous melanoma [1]. Although the Multicenter Selective Lymphadenectomy Trial I (MSTL-I) showed that SLNB does not improve disease-specific survival in melanoma (MSS) [2], it did not include tumors with a Breslow thickness < 1.2 mm in the analysis. The therapeutic effect of SLNB in thin melanoma thus remains to be determined. This is important, particularly in our setting, where tumors with a Breslow thickness < 1 mm are the most common diagnosed melanomas [3]. In addition, SLNB is recommended for patients with stage T1b melanoma and stage T1a melanoma if there are other high-risk factors, such as a mitotic rate > 2 mitoses/mm² [4], lymphovascular invasion, and young age [5].

The main aim of this study was to determine whether SLNB improves MSS in patients with thin tumors. Secondary objectives were to compare disease-free survival (DFS) and overall survival (OS) between patients who undergo SLNB and those who undergo observation and to examine the effect of SLN positivity on survival.

2. Materials and Methods

2.1. Study Population

We designed a multicenter observational study following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [6].

Patients were selected from the databases of nine hospitals that form part of the Sentinel Lymph Node Study Group in Melanoma (Sentimel). Seven of the hospitals are in Spain: Instituto Valenciano de Oncología in Valencia, Hospital Universitario de Salamanca in Salamanca, Hospital La Fe in Valencia, Hospital Universitario Virgen Macarena in Seville, Hospital de la Coruña in A Coruña, Hospital Germans Trias i Pujol in Badalona, and Hospital Clínic in Barcelona. The other two hospitals are in Portugal (Centro Hospitalar e Universitário de Coimbra) and Italy (University Hospital “Città della Salute e della Scienza di Torino”).

We included all patients aged ≥18 years who were registered in the hospital databases up to 31 December 2017 with a diagnosis of thin melanoma (Breslow thickness ≤ 1 mm) and no evidence of metastasis at diagnosis. 1 January 1998 was chosen as the start date for inclusion, as this is when most hospitals started to use SLNB in the management of melanoma [7]. SLNB is performed using a similar procedure at all the hospitals with any combination of vital blue dye, radioactive tracer, and preoperative lymphography (+/− preoperative PET-CT/CT) for SLN mapping. Thin primary melanomas are excised with a 1-cm margin, as recommended by clinical practice guidelines. The procedure for
pathologic SLN examination has been described previously [8]. Hospital Clinic in Barcelona has been using the Minitub protocol (EORTC 1208: Minitub registration study) since 2011. The study was approved by the lead ethics committee, located at Hospital Universitario Reina Sofia in Cordoba (reference 3569).

2.2. Study Groups and Outcome Variables

The patients were divided into two groups: an SLNB group and an observation-only group. Patients in the SLNB group were further classified as SLN-positive or SLN-negative. The outcome variables were DFS, MSS, and OS. Survival was defined as time in months from excision of the primary tumor to first recurrence (DFS), death due to melanoma (MSS), or death due to any cause (OS). Recurrence was classified as local recurrence or satellite, regional lymph node recurrence, or distant metastasis. In patients with multiple simultaneous recurrences, the most advanced type of recurrence was considered.

2.3. Propensity Score Matching

Propensity score matching is a relatively new statistical technique that controls for selection biases in non-randomized studies comparing two interventions or treatments [9]. It consists of matching patients according to their likelihood of being assigned to one group or another, in our case: SLNB or observation. The first step was to perform logistic regression with SLNB as the dependent variable and all the other variables as independent variables. The independent variables were chosen because of their potential prognostic value in melanoma [10] and comprised Breslow thickness [11], ulceration [11,12], regression [13,14], Clark level, microscopic satellitosis [15], mitotic rate [16], vascular invasion [16], tumor infiltrating lymphocytes [17], histologic subtype, age, sex, anatomic location [18], hospital, year, and treatment with interferon [19]. Histologic subtypes were “superficial spreading melanoma”, “nodular melanoma” and “other” histological subtypes. For the convergence of the models it was mandatory to reunify the rest of the histologic subgroups (lentigo maligna, acral lentiginous melanoma, . . . ) into a single simple group (other).

2.4. Statistical Analysis

Between-group comparisons were made using the Mann–Whitney U test and the t test for qualitative and quantitative variables respectively. Breslow thickness and age were log-transformed to avoid skewed distribution. Separate models were built for DFS, MSS, and OS. Survival times were calculated from excision of the primary tumor to the event in question. Cases with no events up to the date of the last follow-up were treated as censored data. Survival curves estimated using the Kaplan–Meier method were compared using the log-rank test to compare survival between patients in the SLNB and observation-only groups. The same method was used to compare SLN-positive and SLN-negative patients. Univariate Cox regression was used to assess the effect of each variable on survival according to the performance of SLNB or not. A multivariate model was built to analyze the impact on survival of all variables with a significance level of \( p < 0.2 \) in the univariate analysis.

2.5. Missing Data

Assuming that missing data were missing at random, we generated 20 complete datasets using multivariate imputation by chained equations (mi impute chained procedure in Stata). The procedure included all variables that were to be subsequently analyzed in addition to any variables that could help explain the missing data. Each of 20 imputed datasets was analyzed using Cox regression to fit the model of interest to the outcome variables (DFS, MSS, and OS). Finally, the results of the complete datasets were combined into a single set of estimates using Rubin rules [20]. All analyses were performed in STATA v.14.1 (Stata Corp. 2015. Stata Statistical Software: Release 14).
3. Results

3.1. Study Population Characteristics

We included 5049 patients with thin localized melanoma (≤1 mm) at diagnosis; 1083 had undergone SLNB and 3966 observation only (Figure 1). In total, 1438 patients were matched by propensity scores.

Before matching, patients in the observation group were more likely to be women (58% vs. 53%, \( p < 0.001 \)) and to have melanoma of the head and neck (14% vs. 7%, \( p < 0.001 \)) and less likely to have ulceration (1% vs. 10%, \( p < 0.001 \)), regression (26% vs. 45%, \( p < 0.001 \)), and a Clark level IV (6% vs. 26%, \( p < 0.001 \)). They also had lower mitotic rates. There were no significant differences between the groups after matching (Table 1).

![Figure 1. Flow chart of the study population. PSM denotes propensity score matching; SLNB, sentinel lymph node biopsy.](image-url)

Table 1. Characteristics of patients with thin cutaneous melanoma (<1 mm) according to study group (SLNB vs observation) before and after propensity score matching.

| Characteristics | Before Propensity Score Matching | After Propensity Score Matching |
|-----------------|---------------------------------|---------------------------------|
|                 | OBSERVATION  | SLNB    | p-Value | OBSERVATION | SLNB    | p-Value |
| Year            | n = 3966     | n = 1083|         | n = 719     | n = 719 |         |
| \( \leq 2000 \) | 1295 (33)    | 97 (9)  | <0.001  | 103 (14)    | 88 (12) | 0.675   |
| 2001–2006       | 827 (21)     | 294 (27)|         | 186 (26)    | 197 (27)|         |
| 2007–2011       | 986 (25)     | 334 (31)|         | 227 (32)    | 227 (32)|         |
| 2012–2017       | 858 (22)     | 358 (33)|         | 203 (28)    | 207 (29)|         |
| Hospital        |              |         |         |              |         |         |
| Salamanca       | 108 (3)      | 21 (2)  | <0.001  | 12 (2)      | 14 (2)  | 0.544   |
| Valencia IVO    | 440 (11)     | 218 (20)|         | 119 (17)    | 132 (18)|         |
| Turin           | 1494 (38)    | 296 (27)|         | 187 (26)    | 204 (28)|         |
| Barcelona       | 1017 (26)    | 202 (19)|         | 163 (23)    | 160 (22)|         |
| Badalona        | 361 (9)      | 194 (18)|         | 133 (18)    | 105 (15)|         |
| Coimbra         | 65 (2)       | 14 (1)  |         | 14 (2)      | 12 (2)  |         |
| A Coruña        | 202 (5)      | 74 (7)  |         | 51 (7)      | 43 (6)  |         |
| Sevilla         | 203 (5)      | 40 (4)  |         | 23 (3)      | 31 (4)  |         |
| Valencia La Fe  | 76 (2)       | 24 (2)  |         | 17 (2)      | 18 (3)  |         |
| Sex             |              |         | <0.001  |              |         | 0.459   |
| Male            | 1646 (42)    | 509 (47)|         | 324 (45)    | 338 (47)|         |
| Female          | 2320 (58)    | 573 (53)|         | 395 (55)    | 381 (53)|         |
| Mean age (sd), y| 52.4 (16.4) | 51.9 (14.7)| 0.3372  | 52.9 (16.7) | 52.5 (14.9)| 0.6422  |
| Tumor location  |              |         | <0.001  |              |         | 0.266   |
### Table 1. Cont.

| Characteristics                          | Before Propensity Score Matching | After Propensity Score Matching |
|------------------------------------------|----------------------------------|---------------------------------|
|                                          | OBSERVATION \( n = 3966 \) | SLNB \( n = 1083 \) | \( p \)-Value | OBSERVATION \( n = 719 \) | SLNB \( n = 719 \) | \( p \)-Value |
| Head/neck                               | 528 (14) | 80 (7) | 86 (12) | 67 (9) |                          | 0.001            | 0.063 |
| Trunk                                   | 1579 (41) | 473 (44) | 300 (42) | 307 (43) |                          | 0.001            | 0.623 |
| Extremities (upper and lower)           | 1725 (45) | 518 (48) | 333 (46) | 345 (48) |                          | 0.001            | 0.001 |
| Log tumor thickness. median (p25–p75)   | −0.7 (−0.9–−0.4) | −0.2 (−0.5–−0.1) | <0.001 | −0.4 (−0.6–−0.2) | −0.7 (−0.3–−0.1) | 0.623 |
| Histologic subtype                      |                             |                             |                     |                             |                      |
| Superficial spreading melanoma          | 3293 (84) | 871 (81) | 578 (80) | 592 (82) |                          | 0.368            | 0.368 |
| Nodular melanoma                        | 45 (1) | 54 (5) | 23 (3) | 22 (3) |                          | 0.872            | 0.872 |
| Other                                   | 588 (15) | 145 (14) | 118 (16) | 105 (15) |                          | 1.000            | 1.000 |
| Ulceration                              |                             |                             |                     |                             |                      |
| No                                      | 3467 (99) | 890 (90) | 673 (94) | 681 (95) |                          | 0.368            | 0.368 |
| Yes                                     | 50 (1) | 100 (10) | 46 (6) | 38 (5) |                          | 0.872            | 0.872 |
| Regression                              |                             |                             |                     |                             |                      |
| No                                      | 2422 (74) | 494 (55) | 425 (59) | 428 (60) |                          | 1.000            | 1.000 |
| Yes                                     | 845 (26) | 399 (45) | 294 (41) | 291 (40) |                          | 1.000            | 1.000 |
| Microscopic satellite                   |                             |                             |                     |                             |                      |
| No                                      | 1529 (100) | 584 (99) | 710 (99) | 711 (99) |                          | 0.5505           | 0.5505 |
| Yes                                     | 4 (0) | 5 (1) | 9 (1) | 8 (1) |                          | 0.473            | 0.473 |
| Tumor infiltrating lymphocytes           |                             |                             |                     |                             |                      |
| No                                      | 272 (27) | 67 (27) | 192 (27) | 175 (24) |                          | 0.803            | 0.803 |
| Non-brisk                               | 580 (57) | 134 (54) | 377 (52) | 399 (55) |                          | 0.358            | 0.358 |
| Brisk                                   | 169 (17) | 48 (19) | 150 (21) | 145 (20) |                          | 0.838            | 0.838 |
| Vascular invasion                       |                             |                             |                     |                             |                      |
| No                                      | 1655 (100) | 608 (99) | 712 (99) | 710 (99) |                          | 0.5505           | 0.5505 |
| Yes                                     | 8 (0) | 4 (1) | 7 (1) | 9 (1) |                          | 0.473            | 0.473 |
| Interferon treatment                    |                             |                             |                     |                             |                      |
| No                                      | 2361 (99) | 738 (95) | 700 (97) | 694 (97) |                          | 0.5505           | 0.5505 |
| Yes                                     | 20 (1) | 37 (5) | 19 (3) | 25 (3) |                          | 0.838            | 0.838 |
| Clark level                             |                             |                             |                     |                             |                      |
| I-III                                   | 2897 (94) | 755 (74) | 588 (82) | 585 (81) |                          | 0.991            | 0.991 |
| IV                                      | 184 (6) | 263 (26) | 131 (18) | 134 (19) |                          | 0.5505           | 0.5505 |
| Mitotic rate (mitoses/mm²)              |                             |                             |                     |                             |                      |
| 0                                       | 1491 (82) | 248 (34) | 341 (47) | 339 (47) |                          | 0.991            | 0.991 |
| 1                                        | 225 (12) | 282 (39) | 247 (34) | 252 (35) |                          | 0.5505           | 0.5505 |
| 2                                        | 55 (3) | 116 (16) | 84 (12) | 81 (11) |                          | 0.5505           | 0.5505 |
| ≥3                                      | 49 (3) | 82 (11) | 47 (7) | 47 (7) |                          | 0.5505           | 0.5505 |

Log, logarithm; SLNB, sentinel lymph node biopsy.

### 3.2. Survival Rates

Median follow-up was 61 months. During this time, there were 82 recurrences (5.7%), 46 melanoma-specific deaths (3.2%), and 74 deaths due to another cause (5.1%); 8.3% of patients in the SLNB group and 10.3% of those in the observation group were lost to follow-up.

There were no significant differences in MSS between the SLNB and observation groups. The respective 5- and 10-year survival rates were 97.4% vs. 97.1% and 95.3% vs. 95.6%. The corresponding 5- and 10-year rates for DFS were 95.3% vs. 94.3% and 90.8% vs. 91.8%. The differences for 5-year and 10-year OS were also non-significant (Figure 2).
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Interferon treatment <0.001  0.358
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Yes 20 (1) 37 (5)  19 (3) 25 (3)  
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I-III 2897 (94) 755 (74)  588 (82) 585 (81)
IV 184 (6) 263 (26)  131 (18) 134 (19)
Mitotic rate
<0.001  0.991
0 1491 (82) 248 (34)  341 (47) 339 (47)
1 225 (12) 282 (39)  247 (34) 252 (35)
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When all other variables were controlled for in the multivariate analysis, SLNB was not a significant predictor of either MSS or DFS. It was, however, an independent predictor of OS (adjusted hazard ratio, 0.61; 95% CI, 0.37–1; \( p = 0.05 \)).

3.2.1. Melanoma-Specific Survival
The predictors of MSS in the multivariate model were age, tumor thickness, ulceration, and interferon treatment (Table 2).

![Figure 2. Estimated disease-free survival (a), melanoma-specific survival (b), and overall survival (c) according to study group. Survival curves calculated using the Kaplan–Meier method according to study group in the propensity score-matched sample (n = 1438). SLNB denotes sentinel lymph node biopsy.](image)

Table 2. Univariate and multivariate analysis of predictors of melanoma-specific survival in patients included in the study (\( n = 1438 \)).

| Crude Univariate Analysis | Adjusted Multivariate Analysis |
|---------------------------|-------------------------------|
|                           | HR 95% CI LL | 95% CI UL | p-Value | HR 95% CI LL | 95% CI UL | p-Value |
| SLNB                      |               |           |        | SLNB       |           |        |
| No                        | Ref           | -         | -      | -         | -         | -      |
| Yes                       | 0.96          | 0.53      | 1.73   | 0.884     | Yes       | 0.84    | 0.45   | 1.56   | 0.575 |
| Year                      |               |           |        |           |           |        |
| ≤2000                     | Ref           | -         | -      | -         | -         | -      |
| 2001–2006                 | 0.73          | 0.35      | 1.54   | 0.410     |            |        |
| 2007–2011                 | 0.98          | 0.42      | 2.27   | 0.958     |            |        |
| 2012–2017                 | 0.67          | 0.18      | 2.54   | 0.558     |            |        |
| Hospital                  |               |           |        |           |           |        |
| Salamanca                 | Ref           | -         | -      | -         | -         | -      |
| Valencia IVO              | 0.54          | 0.07      | 4.29   | 0.562     |            |        |
| Turin                     | 0.48          | 0.06      | 3.74   | 0.487     |            |        |
| Barcelona                 | 0.74          | 0.10      | 5.71   | 0.772     |            |        |
| Badalona                  | 0.39          | 0.05      | 3.22   | 0.379     |            |        |
| Coimbra                   | NA            |           |        |           |            |        |
| A Coruña                  | 0.25          | 0.02      | 4.01   | 0.328     |            |        |
| Sevilla                   | NA            |           |        |           |            |        |
| Valencia La Fe           | NA            |           |        |           |            |        |
| Sex                       |               |           |        |           |           |        |
| Male                      | Ref           | -         | -      | -         | -         | -      |
| Female                    | 0.57          | 0.31      | 1.02   | 0.057     |            |        |
| Age                       | 1.02          | 1.00      | 1.04   | 0.076     | Age       | 1.03    | 1.01   | 1.05   | 0.011 |
| Log age                   | 1.98          | 0.73      | 5.34   | 0.18      |            |        |
| Tumor location            |               |           |        |           |           |        |
| Head/neck                 | Ref           | -         | -      | -         | -         | -      |
| Trunk                     | 1.39          | 0.48      | 4.02   | 0.541     |            |        |
| Extremities (upper and lower) | 0.85      | 0.29      | 2.53   | 0.771     |            |        |
| Tumor thickness           | 13.71         | 2.68      | 69.96  | 0.002     |            |        |
Table 2. **Cont.**

|                                | Crude Univariate Analysis | Adjusted Multivariate Analysis |
|--------------------------------|---------------------------|-------------------------------|
|                                | HR  | 95% CI LL | 95% CI UL | p-Value | HR  | 95% CI LL | 95% CI UL | p-Value |
| Log tumor thickness            | 4.76 | 1.56     | 14.51     | 0.006   | Log tumor thickness |
| Histologic subtype             |     |           |           |         |     |           |           |         |
| Superficial spreading melanoma | Ref | -        | -         | -       | Ref | -        | -         | -       |
| Nodular melanoma               | 4.10 | 1.59     | 10.62     | 0.004   |     |           |           |         |
| Other                          | 1.94 | 0.92     | 4.08      | 0.082   |     |           |           |         |
| Ulceration                     |     |           |           |         |     |           |           |         |
| No                             | 3.23 | 1.43     | 7.28      | 0.005   | Yes | 2.66     | 1.11      | 6.38    | 0.028  |
| Yes                            | 0.97 | 0.50     | 1.89      | 0.922   |     |           |           |         |
| Regression                     |     |           |           |         |     |           |           |         |
| No                             | 0.90 | 0.41     | 1.98      | 0.787   |     |           |           |         |
| Yes                            | 0.62 | 0.14     | 2.67      | 0.517   |     |           |           |         |
| Microscopic satellite          |     |           |           |         |     |           |           |         |
| No                             | 1.92 | 0.93     | 3.95      | 0.076   |     |           |           |         |
| Yes                            | 4.16 | 1.34     | 12.89     | 0.014   |     |           |           |         |

HR, hazard ratio; LL, lower limit; Log, logarithm; SLNB, sentinel lymph node biopsy; UL, upper limit.

3.2.2. **Disease-Free Survival**

The independent predictors of DFS were age, histologic subtype other than superficial spreading melanoma and nodular melanoma, ulceration, Clark level, mitotic rate, and interferon treatment (Table 3).
Table 3. Univariate and multivariate analysis of predictors of disease-free survival in patients included in the study (n = 1438).

|                      | Crude Univariate Analysis |                |                | p-Value | Adjusted Multivariate Analysis |                |                | p-Value |
|----------------------|---------------------------|----------------|----------------|---------|--------------------------------|----------------|----------------|---------|
|                      | HR 95% CI LL 95% CI UL    | p-Value        | HR 95% CI LL   | 95% CI UL | p-Value                        |                |                |         |
| SLNB                 |                           |                |                |         |                                |                |                |         |
| No                   | Ref                       | - - -          | No             | Ref - - - | Yes 0.84 0.49 1.43 0.509       |                |                |         |
| Yes                  | 1.11 0.72 1.73 0.634       |                | Yes            | 0.84 0.49 1.43 0.509             |                |                |         |
| Year                 |                           |                |                |         |                                |                |                |         |
| ≤2000                | Ref                       | - - -          | No             | Ref - - - | No Ref - - -                   |                |                |         |
| 2001–2006            | 0.67 0.39 1.15 0.142       |                | Yes            | 0.84 0.49 1.43 0.509             |                |                |         |
| 2007–2011            | 0.62 0.34 1.14 0.124       |                | No             | Ref - - - | No Ref - - -                   |                |                |         |
| 2012–2017            | 0.42 0.17 1.07 0.068       |                | Yes            | 0.84 0.49 1.43 0.509             |                |                |         |
| Hospital             |                           |                |                |         |                                |                |                |         |
| Salamanca            | Ref                       | - - -          | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Valencia IVO         | 1.34 0.18 10.01 0.776      |                | Yes            | 0.84 0.49 1.43 0.509             |                |                |         |
| Turin                | 1.25 0.17 9.21 0.829       |                | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Barcelona            | 1.32 0.18 9.89 0.785       |                | Yes            | 0.84 0.49 1.43 0.509             |                |                |         |
| Badalona             | 0.58 0.07 4.64 0.606       |                | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Coimbra              | NA                        |                | Yes            | 0.84 0.49 1.43 0.509             |                |                |         |
| A Coruña             | 0.50 0.05 5.53 0.573       |                | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Sevilla              | NA                        |                | Yes            | 0.84 0.49 1.43 0.509             |                |                |         |
| Valencia La Fe       | 0.95 0.06 15.16 0.970      |                | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Gender               |                           |                |                |         |                                |                |                |         |
| Male                 | Ref                       | - - -          | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Female               | 0.73 0.47 1.12 0.152       |                | Yes            | 0.84 0.49 1.43 0.509             |                |                |         |
| Age                  | 1.02 1.01 1.04 0.006       |                | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Log Age              | 2.47 1.17 5.23 0.018       |                | Yes            | 0.84 0.49 1.43 0.509             |                |                |         |
| Localization        |                           |                |                |         |                                |                |                |         |
| Head/Neck            | Ref                       | - - -          | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Trunk                | 0.95 0.44 2.07 0.907       |                | Yes            | 0.84 0.49 1.43 0.509             |                |                |         |
| Extremities (upper and lower) | 1.02 0.48 2.17 0.965 |                | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Tumor thickness      | 7.32 2.33 23.06 0.001      |                | Yes            | 0.84 0.49 1.43 0.509             |                |                |         |
| Log tumor thickness  | 3.03 1.43 6.40 0.004       |                | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Histologic subtype   |                           |                |                |         |                                |                |                |         |
| Superficial spreading melanoma | Ref - - - |                | Yes            | 0.84 0.49 1.43 0.509             |                |                |         |
| Nodular melanoma     | 5.40 2.73 10.67 0.000      |                | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Others               | 2.36 1.39 4.01 0.001       |                | Yes            | 0.84 0.49 1.43 0.509             |                |                |         |
| Ulceration           |                           |                |                |         |                                |                |                |         |
| No                   | Ref                       | - - -          | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Yes                  | 4.14 2.34 7.33 0.000       |                | Yes            | 3.06 1.40 6.70 0.005             |                |                |         |
| Regression           |                           |                |                |         |                                |                |                |         |
| No                   | Ref                       | - - -          | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Yes                  | 0.69 0.41 1.16 0.161       |                | Yes            | 3.06 1.40 6.70 0.005             |                |                |         |
| Microscopic satellite |                           |                |                |         |                                |                |                |         |
| No                   | Ref                       | - - -          | No             | Ref - - - | No Ref - - -                   |                |                |         |
| Yes                  | 5.54 1.15 26.58 0.033      |                | Yes            | 3.06 1.40 6.70 0.005             |                |                |         |
| Tumor infiltrating lymphocytes | Ref - - - |                | No             | Ref - - - | No Ref - - -                   |                |                |         |
| No                   |                           |                | Yes            | 3.06 1.40 6.70 0.005             |                |                |         |
| Non-brisk            | 1.02 0.53 1.94 0.960       |                | Yes            | 3.06 1.40 6.70 0.005             |                |                |         |
| Brisk                | 0.91 0.28 2.94 0.873       |                | No             | Ref - - - | No Ref - - -                   |                |                |         |
Table 3. Cont.

|                        | Crude Univariate Analysis | Adjusted Multivariate Analysis |
|------------------------|---------------------------|--------------------------------|
|                        | HR 95% CI LL 95% CI UL    | p-Value                        | HR 95% CI LL 95% CI UL    | p-Value                        |
| Vascular invasion      |                           |                                |                           |                                |
| No                     | Ref - - -                 |                                | No Ref - - -              |                                |
| Yes                    | NA                        |                                |                           |                                |
| Interferon             |                           |                                |                           |                                |
| No                     | Ref 10.80 5.97 19.52      | 0.000                          | No Ref 15.12 7.36 31.07   | 0.000                          |
| Yes                    | NA                        |                                |                           |                                |
| Clark level            |                           |                                |                           |                                |
| I-II-III               | Ref 2.17 1.30 3.61        | 0.003                          | IV Ref 2.38 1.35 4.18     | 0.003                          |
| IV                     |                           |                                |                           |                                |
| Mitotic rate           |                           |                                |                           |                                |
| 0                      | Ref 1.72 0.85 3.50        | 0.131                          | 1 Ref 2.03 0.93 4.42      | 0.074                          |
| 2                      | 3.06 1.26 7.44            | 0.014                          | 2 3.08 1.15 8.21          | 0.025                          |
| ≥3                     | 7.30 3.38 15.78           | 0.000                          | 3 or more 7.66 3.02 19.45 | 0.000                          |

Table 4. Univariate and multivariate analysis of predictors of overall survival in patients included in the study (n = 1438).

3.2.3. Overall Survival

The independent predictors of OS, in addition to SLNB, were sex, age, ulceration, Clark level, and interferon treatment (Table 4).
Table 4. Cont.

|                                | Crude Univariate Analysis |         |        |        |         | Adjusted Multivariate Analysis |
|--------------------------------|---------------------------|---------|---------|---------|---------|-------------------------------|
|                                | HR            | LL 95%CI | UL 95%CI | p-Value | HR      | LL 95%CI | UL 95%CI | p-Value |
| Tumor thickness                | 4.47          | 1.40     | 14.33    | 0.012   |          |         |         |         |
| Log tumor thickness            | 2.38          | 1.12     | 5.03     | 0.023   |          |         |         |         |
| Histologic subtype            |               |         |         |         |         |         |         |         |
| Superficial spreading melanoma|               |         |         |         |         |         |         |         |
| Ref                             | -             | -        | -        | -       | No Ref   | -        | -        | -       |
| Nodular melanoma               | 2.36          | 0.94     | 5.94     | 0.068   | Yes 2.58 | 1.25     | 5.34     | 0.011   |
| Other                           | 1.52          | 0.83     | 2.79     | 0.177   |          |         |         |         |
| Ulceration                      |               |         |         |         |         |         |         |         |
| No                              | Ref           | -        | -        | -       | No Ref   | -        | -        | -       |
| Yes                             | 2.75          | 1.41     | 5.38     | 0.003   | Yes 2.58 | 1.25     | 5.34     | 0.011   |
| Regression                      |               |         |         |         |         |         |         |         |
| No                              | Ref           | -        | -        | -       |          |         |         |         |
| Yes                             | 1.32          | 0.81     | 2.18     | 0.267   |          |         |         |         |
| Microscopic satellite          |               |         |         |         |         |         |         |         |
| No                              | Ref           | -        | -        | -       |          |         |         |         |
| Yes                             | 3.43          | 0.51     | 23.23    | 0.202   |          |         |         |         |
| Tumor infiltrating lymphocytes  |               |         |         |         |         |         |         |         |
| No                              | Ref           | -        | -        | -       |          |         |         |         |
| Non-Brisk                       | 0.73          | 0.38     | 1.41     | 0.343   |          |         |         |         |
| Brisk                           | 0.49          | 0.15     | 1.68     | 0.254   |          |         |         |         |
| Vascular invasion               |               |         |         |         |         |         |         |         |
| No                              | Ref           | -        | -        | -       |          |         |         |         |
| Yes                             | NA            |          |          |         |          |         |         |         |
| Interferon treatment            |               |         |         |         |         |         |         |         |
| No                              | Ref           | -        | -        | -       | No Ref   | -        | -        | -       |
| Yes                             | 4.28          | 2.02     | 9.05     | 0.000   | Yes 5.69 | 2.43     | 13.31    | 0.000   |
| Clark level                     |               |         |         |         |         |         |         |         |
| I-II-III                       | Ref           | -        | -        | -       | I-II-III Ref | -        | -        | -       |
| IV                              | 2.00          | 1.15     | 3.45     | 0.014   | IV 1.86  | 1.06     | 3.27     | 0.031   |
| Mitotic rate                    |               |         |         |         |         |         |         |         |
| 0                               | Ref           | -        | -        | -       |          |         |         |         |
| 1                               | 1.57          | 0.80     | 3.09     | 0.190   |          |         |         |         |
| 2                               | 1.91          | 0.75     | 4.89     | 0.176   |          |         |         |         |
| ≥3                              | 2.61          | 1.04     | 6.54     | 0.041   |          |         |         |         |

HR, hazard ratio; LL, lower limit; Log, logarithm; SLNB, sentinel lymph node biopsy; UL, upper limit.

3.3. Prognostic Significance of SLNB

Forty-two patients in the SLNB group (5.8%) were SLN-positive, but seven false negatives were detected during follow-up. The overall false negative rate was 14.3%, which was calculated by dividing the number of false negatives by the sum of positive cases and false negatives according to the method described by van Akkooi et al. [21].

The 5- and 10-year MSS rates for SLN-negative and -positive patients were 98.5% vs. 77.3% \((p < 0.001)\) and 97.3% vs. 68.7% \((p < 0.001)\), respectively. The corresponding rates for the other survival categories were 96.6% vs. 60.9% \((p < 0.001)\) and 94.6% vs 48.9% \((p < 0.001)\) for DFS and 97.3% vs. 78.9% \((p < 0.001)\) and 95.5% vs. 66.6% \((p < 0.001)\) for OS (Figure 3).
Non-Brisk 0.73 0.38 1.41 0.343
Brisk 0.49 0.15 1.68 0.254

Figure 3. Estimated disease-free survival (a), melanoma-specific survival (b), and overall survival (c) according to sentinel lymph node status.

4. Discussion

The main conclusion of this study is that SLNB does not improve MSS in patients with thin melanoma. It also had no impact on DSF or OS. The conclusion for MSS is the same as that reached in the MSLT-I [2] but for melanomas with a Breslow thickness < 1 mm.

The theoretical basis for the introduction of SLNB in the treatment of cutaneous melanoma in the 1990s was that the regional lymph nodes act as an incubator for subsequent distant spread [22]. Our focus on thin melanomas is justified as these tumors have a different pattern of spread. Compared with thicker melanomas, they have a greater propensity for locoregional metastasis and are less likely to spread to distant sites [21]. Our results, however, indicate the presence of synchronous regional and distant metastasis in thin melanoma, which would explain the absence of a significant survival benefit for SLNB in this setting [23–25].

Very few observational studies have analyzed the impact of SLNB on survival in patients with thin melanoma. Using data from the Surveillance, Epidemiology, and End Results (SEER) program, Sperry et al. [26] found no difference in MSS in 1104 propensity score-matched patients with thin melanoma who had undergone SLNB or nodal observation. More recently, Murtha et al. [27], using the same database, reported a significant difference in OS but not MSS over a median follow-up period of 16 months for a population of 3439 patients with melanoma with a thickness of 0.75 to <1 mm. Finally, in another propensity score matching study using data from the US National Cancer Data Base, Sinnammon et al. [28] found no differences in OS between 4262 pairs of melanoma patients with a Breslow thickness of 0.5 to 0.7 mm. They did, however, find a difference for OS among patients with tumors measuring 0.8 to 1.0 mm. One limitation of their study, however, was that the database does not contain information on MSS.

Our analysis of SLN-positive and -negative patients show worse survival rates than in similar studies [29,30], probably because of differences in patient selection criteria. These differences in survival could justify the use of new adjuvant therapies and should be discussed with patients [5].

The main limitation of this study is its retrospective design. The groups may not have been properly balanced as not all potential confounders were considered (e.g., comorbidities and performance status). Our study may also be underpowered, as it has been calculated that 6500 patients would be needed to detect a protective effect for SLNB using a similar design to the MSLT-I, based on a power of 90%, a follow-up period of 5 years, and an estimated hazard ratio of 0.8 for SLNB [26]. Furthermore, we did not specifically analyze time to recurrence at regional lymph nodes; the only expected benefit of the SLNB according to previous studies focused on thicker tumors.

Ulceration and thickness remain as independent prognostic factors associated with MSS survival in thin melanomas. Age also remains as an independent prognostic factor of MSS. It has been evidenced that patients at extreme age have a distinct natural history [31,32]. These data are congruent with the AJCC as ulceration is established as a variable that increases the staging according to a certain thickness while melanoma
thicknesses close to 1 mm are already considered another stage [7]. It remains to be seen whether advanced age may contribute in the future to defining these melanomas with a worse prognosis.

The fact that interferon treatment is associated to worse MSS (HR 7.29 $p < 0.001$) should be considered as subsidiary of positivity of the SLNB, because the result of the procedure was not included in the analysis and interferon treatment was only indicated in the cases of lymph node positivity in thin melanomas as indicated in the active guide lines during the period of the study.

5. Conclusions

SLNB is currently used for staging purposes in thin melanoma. Our study of a large cohort of patients with thin melanoma did not show that SLNB modifies survival in this setting. We did, however, observe a considerable difference in MSS, DFS, and OS between SLN-positive and -negative patients and therefore recommend discussing the option of SLNB with patients.

Author Contributions: A.T.-V., A.B. (Aram Boada) and E.N. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: A.T.-V. and E.N. Acquisition, analysis, and interpretation of data: S.O.-A., P.C., C.C., S.V.-S., R.P., A.T., S.P. (Sebastian Podlipnik), R.R., L.A., C.R., I.B., V.T., Á.P., A.F.-O., A.J., M.T.F.-F., N.A.R., R.B.-E., C.R.-C., L.F.-P., N.I.-P., C.F., J.M. and P.Q. Drafting of the manuscript: A.T.-V. Critical revision of the manuscript for important intellectual content: S.R., S.P. (Susana Puig), A.B. (Aram Boada), S.P. (Sabela Paradela), D.M.-R., J.C., B.d.U.-B., M.A.D.-G., A.B. (Ana Brinca), R.V. and E.N. Statistical analysis: M.A.D.-G. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the principles of the Declaration of Helsinki, and approved by the ethics committee at Hospital Reina Sofía in Córdoba (reference 3569).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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