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Impact of Time Between Diagnosis and SLNB on Outcomes in Cutaneous Melanoma

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Abstract

BACKGROUND—Hypothetically, delay between melanoma diagnosis and SLNB could affect outcomes, either adversely by allowing growth and dissemination of metastases, or beneficially by allowing development of an anti-melanoma immune response. Available data are conflicting about the effect of SLNB delay on patient survival. Our objective was to determine whether delay between initial diagnosis and SLNB affects outcomes in patients with cutaneous melanoma.

STUDY DESIGN—We performed query and analysis of a large prospectively maintained database of patients with primary cutaneous melanomas undergoing SLNB. An independent dataset from MSLT-1 (Multicenter Selective Lymphadenectomy Trial-1) was used for validation. Primary outcomes included disease-free survival and melanoma-specific survival.

RESULTS—Early and delayed SLNB were defined as less than 30 and 30 or more days from initial diagnosis, respectively. There were 2,483 patients that met inclusion criteria. Positive

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sentinel lymph nodes were identified in 17.4% (n = 432). Among all patients, 42% had SLNB 30 or more days after diagnosis and 37% of positive sentinel lymph nodes were at 30 or more days. No differences in sex, anatomic site, or histopathologic features were identified between the 2 groups. There was no difference in melanoma-specific survival or disease-free survival between those undergoing early or delayed SLNB. Examination of MSLT-1 trial data similarly demonstrated no difference in survival outcomes.

CONCLUSIONS—This, the largest study on this subject to date, found no adverse impact on long-term clinical outcomes of patients due to delay of SLNB beyond 30 days. The MSLT-1 data confirm this result. Patients can be reassured that if the operation is performed 30 or more days after diagnosis, it will not cause harm.

More than 25 years ago, Drs Morton and Cochran pioneered lymphatic mapping and SLNB in the management of cutaneous melanoma.[1] Since its introduction, a large body of research has been generated not only validating the use and accuracy of the technique,[2,3] but also demonstrating that early treatment of nodal metastases leads to substantial improvements in patient outcomes, including prolonged distant disease-free survival (DFS) and melanoma-specific survival (MSS).[4] In addition, extensive data have accumulated supporting the notion that the status of the sentinel node is the single most important prognostic factor for patients with early cutaneous melanoma.[4,5]

Based on the predictable and orderly manner in which melanoma spreads,[6] it would seem intuitive that expeditious definitive surgical management (wide local excision and SLNB) after initial diagnosis of a cutaneous melanoma would be advantageous. However, existing outcomes data on the effect of delaying initial surgical treatment are mixed and contradictory.[7–11]

Hypothetically, a delay between melanoma diagnosis and SLNB could affect outcomes, either adversely by allowing growth and dissemination of metastases, or beneficially by allowing development of an anti-melanoma immune response.[8,11] Currently, existing data on the effect of SLNB delay on patient survival are conflicting. Therefore, our objective was to determine whether modest delay between diagnosis and SLNB affects outcomes in patients with cutaneous melanoma.

METHODS

This study received IRB-exemption status after independent regulatory review. We queried our prospectively maintained database (July 1, 1991 through July 1, 2015) for all patients diagnosed with clinical stage I or II cutaneous melanoma and subsequently received wide local excision and SLNB.[12] Date of diagnosis was the date of cutaneous biopsy. To lessen any impact of referral bias, analysis was limited to patients definitively treated at our institution within 6 months of initial diagnosis. Patients with more than 1 primary melanoma were excluded, as were patients with early recurrence—within 90 days of wide local excision and SLNB—as this was considered concurrent disease, clinically inapparent at the time of initial treatment.

Patients were stratified into 2 groups: early and delayed SLNB. Previous series have examined delay times with cutoffs varying among 30, 40, 43, and 47 days, which reflected median "delay" before surgery for the respective study populations in those series.[7–11] Initial exploratory analysis of our cohort revealed a median delay from initial diagnosis to definitive wide local excision and SLNB of 27 days (mean 31.8 days; range 0 to 182 days). Stratified by 30-day intervals, 57.9% (n = 1,437) underwent SLNB less than 30 days from the time of initial diagnosis, 34.7% (n = 861) between 30 and 59 days, 4.8% (n = 120) between 60 and 89 days, and 2.6% (n = 65) at 90 days or more from the time of initial diagnosis. Based on these findings, as well as cutoffs examined in the literature previously, we defined early SLNB as occurring less than 30 days after initial cutaneous biopsy and delayed SLNB as occurring 30 or more days from initial diagnosis.

Treatment comprised wide local excision with excision margins determined by current recommendations, as well as SLNB, if indicated by the histopathology of the excision biopsy specimen. Technical details of performance of SLNB at the John Wayne Cancer Institute have been described previously.[13] Clinical follow-up consisted of complete dermatologic and physical examination every 3 months during the first 2 years and every 4 to 6 months for the next 3 years, then annually thereafter. Routine tests, including complete blood count, comprehensive metabolic panel, lactate dehydrogenase, and radiographic imaging, were obtained annually when indicated by pathologic stage.

Clinical factors, including age, sex, and anatomic site of the primary lesion, as well as histopathologic features, such as Breslow thickness; mitotic rate; presence of ulceration; and lymph node status, were compared between patients in the early and delayed treatment groups. Categorical variables were compared using chi-square test. For comparison of means, *t*-test or Wilcoxon rank-sum test were used where appropriate. Disease-free survival and MSS curves were generated using the Kaplan-Meier method and comparisons made using the log-rank test. Common prognostic variables and delay times were then included in multivariable analysis using Cox proportional hazards model to identify significant independent predictors of DFS and MSS.

To validate these findings, identical analyses were performed using an independent dataset from the SLNB arm of the first Multicenter Selective Lymphadenectomy Trial (MSLT-1), a multi-institutional prospective randomized trial.[4] The same cut point of 30 days was used in this analysis. Exploratory analysis of the MSLT-1 cohort revealed a median delay time from initial diagnosis to definitive wide local excision and SLNB of 29 days (mean 33.8 days; range 0 to 103 days). Stratified by 30-day intervals, 53.7% (n = 626) underwent SLNB less than 30 days from the time of initial diagnosis, 35.2% (n = 410) between 30 and 59 days, 10.6% (n = 123) between 60 and 89 days, and 0.5% (n = 6) more than 90 days from the time of initial diagnosis.

All statistical analyses were performed using SAS software, version 9.3 (SAS Institute) and p values < 0.05 were considered significant.

RESULTS

From July 1, 1991 to July 1, 2015, a total of 2,483 patients underwent wide local excision and SLNB for primary cutaneous melanoma. Median follow-up was 8 years (95.7 months). Median times to surgery for the early and delayed SLNB groups were 21 and 41 days, respectively. A majority of patients underwent early SLNB (58%).

Baseline demographics and histopathologic characteristics for the 2 groups are compared in Table 1. On univariate analysis, delayed SLNB patients were significantly older (56.3 vs 54.7 years; $p = 0.02$). There were no differences in sex, anatomic site of the primary lesion, or histopathologic features of the primary lesion between the 2 groups (all $p > 0.05$). However, patients with delayed SLNB had a lower frequency of sentinel lymph node positivity (15.1% vs 19.1%; $p = 0.01$). Despite differences in frequency of sentinel lymph node positivity between the 2 groups, there was no significant difference in DFS or MSS (Fig. 1A and B).

After adjusting for age, sex, Breslow thickness, presence of ulceration, and sentinel lymph node status, multivariable analysis indicated that early vs delayed SLNB was not an independent predictor of DFS (hazard ratio [HR] = 0.98; 95% CI 0.81 to 1.18; $p = 0.85$) or MSS (HR = 1.05; 95% CI 0.83 to 1.34; $p = 0.67$) (Table 2). Age, Breslow thickness, and presence of ulceration were independently associated with worse DFS and MSS (all $p < 0.001$). Positive sentinel lymph node status had the greatest prognostic significance of any independent variable for both disease recurrence (HR = 3.07; 95% CI 2.50 to 3.77; $p < 0.001$) and MSS (HR = 3.11; 95% CI 2.40 to 4.03; $p < 0.001$).

Because the status of the sentinel lymph node is of such profound prognostic significance, subgroup analysis was undertaken to determine whether delay times specifically impacted patients found to have positive sentinel nodes. Positive sentinel lymph nodes were identified in 17.4% of patients (n = 432). Median times to wide local excision and SLNB were 26 and 28 days for patients with positive and negative sentinel lymph nodes, respectively (mean 30.7 and 32.1 days, respectively; $p = 0.003$). Of those patients with positive sentinel nodes, 37% (n = 158) had undergone delayed SLNB. No differences in age, sex, anatomic site, or histopathologic characteristics were noted between the 2 groups (all $p > 0.05$) (Table 3). No differences in DFS or MSS were identified between these groups (Fig. 1C and D).

To validate these findings, a separate analysis was undertaken using prospective data collected from the MSLT-1 trial. The same cutoff point of 30 days defined early and delayed SLNB groups. This cohort included 1,165 patients, of which 46.3% underwent delayed SLNB. Baseline demographics and histopathologic characteristics for the 2 groups are compared in Table 1. Among MSLT-1 patients, those in the early SLNB group were more frequently male, and primary lesions more commonly arose in the head/neck or trunk regions relative to the delayed SLNB group (both $p < 0.05$). Positive sentinel lymph nodes were identified in 19% (n = 221) of patients. Of note, contrary to the John Wayne Cancer Institute database cohorts, patients undergoing delayed SLNB in MSLT-1 more frequently had positive sentinel nodes than patients undergoing early SLNB (22.8% vs 15.6%; p =

0.002). Again, however, despite the differences in sentinel lymph node positivity between the 2 groups, there was no difference in DFS or MSS (Fig. 2A and B).

Among sentinel lymph node-positive patients, a slight majority (55.7%) had undergone delayed SLNB (Table 3). This was not associated with any measurable difference in DFS or MSS between the groups (Fig. 2C and D).

Because delay in SLNB was associated with significant but opposite effects on SLN positivity in the 2 study cohorts, we elected to perform multivariable logistic regression analysis to determine whether delay time remained a significant prognostic indicator for sentinel lymph node positivity. Recognized prognostic clinical and histopathologic factors including age, sex, primary anatomic site, Breslow thickness, ulceration, and mitotic rate were included in the model. In addition, delay time was included as a dichotomized variable (Table 4). Commonalities between the 2 datasets included increasing Breslow thickness as an independent predictor for sentinel lymph node positivity and increasing age and head/neck and upper extremity locations compared with trunk primary location; all were significantly associated with a decreased likelihood of having a positive sentinel node. Interestingly, among patients in the John Wayne Cancer Institute dataset, delay time of less than 30 days was independently associated with a 33% increased risk of sentinel lymph node positivity (odds ratio = 1.33; 95% CI 1.05 to 1.67; p = 0.02). Conversely, among MSLT-1 patients, delay time of less than 30 days was independently associated with a 36% decreased risk of having a positive sentinel lymph node (odds ratio = 0.64; 95% CI 0.47 to 0.88; p = 0.006).

DISCUSSION

Timely diagnosis of many cancers is associated with improved outcomes by identifying lesions at their earliest and most treatable stages. This principle forms the foundation of many successful screening programs. Conversely, delay in presentation, diagnosis, and/or treatment of cancer has been linked to poor outcomes.[14] For melanoma in particular, it has been demonstrated that delayed initial presentation is associated with more advanced lesions at diagnosis, with negative prognostic implications.[15] The prognostic impact of subsequent delays, such as between initial diagnosis and definitive surgical management, remains unclear. Previous series examining delay between diagnostic biopsy and wide local excision of the primary showed no impact from delays ranging from less than 14 days to more than 92 days on long-term outcomes.[16] However, this series did not assess management of the sentinel node.

In cutaneous melanoma, the most important prognostic factor is sentinel lymph node status[17] and, therefore, definitive initial surgical management of intermediate thickness and high-risk thin melanomas is wide local excision and SLNB.[18] Modest delays can occur between initial biopsy-based diagnosis of melanoma, referral for definitive surgical management, and definitive wide local excision and SLNB. Such delays theoretically could affect outcomes, either adversely by allowing growth and dissemination of metastases or favorably by allowing development of an anti-melanoma immune responses.[8,11]

At least 4 smaller series have explored this question and produced varied findings. In the earliest series, Parrett and colleagues[7] performed a retrospective analysis of 492 patients diagnosed with cutaneous melanoma, with a median time to SLNB of 39.5 days. Based on this, they stratified and compared patients by delay times of less than 40 days vs at least 40 days and found that delay time was not associated with any detrimental effect on DFS (p = 0.13) or overall survival (p = 0.14).[7] Similarly, a series reported by the European Organization for Research and Treatment of Cancer Melanoma Group, which included 1,015 sentinel lymph node-positive patients with a median time of 47 days from diagnosis to definitive surgery, and demonstrated that "delay" time had no impact on 5-year MSS (p = 0.72) and was not an independent prognostic factor for MSS (p = .57).[10]

A few studies have noted differences in outcomes based on the interval between diagnosis and SLNB. In 2015, Tejera-Vaquerizo and colleagues[8] published a much larger series addressing this clinical question. The authors found that among 1,963 patients, early SLNB (less than 40 days) was associated with a worse MSS (HR = 1.7; 95% CI 1.2 to 2.5; p = 0.007).[8] On subgroup analysis, the impact of delay time on MSS remained significant only for those with negative sentinel lymph nodes and absence of regression in the primary tumor. The authors postulated that early excision and SLNB can negatively affect development of anti-melanoma immunity. Conversely, in a recent series by Fortes and colleagues,[11] in which 748 patients with cutaneous melanoma underwent wide local excision and SLNB, the authors found that for patients with positive sentinel lymph nodes, delay times of less than 30 days were associated with a 3-fold decreased risk of melanoma mortality compared with patients with positive sentinel nodes whose surgery had been delayed more than 30 days.[11]

In the current study of nearly 2,500 patients who had wide local excision and SLNB at the John Wayne Cancer Institute in recent decades, we found no impact on disease recurrence or MSS that could be attributed to early (less than 30 days) or delayed (30 days or more) SLNB. In addition, such delays did not produce any measurable effect on the DFS or MSS of even those patients found to have positive sentinel nodes at the time of surgery. These results are in keeping with those of Parrett and colleagues[7] and Oude Ophuis and colleagues.[10] Our findings are validated using data from the multinational, prospective MSLT-1 dataset, where delays of less than 30 vs 30 or more days between time of initial diagnosis and definitive surgery had no impact on DFS or MSS in all patients, with and without positive sentinel nodes.

Interestingly, we found that delay in SLNB was associated with significant, but opposite effects on SLN positivity in the 2 study cohorts. Among patients in the John Wayne Cancer Institute dataset, delay time of less than 30 days was independently associated with a 33% increased risk of sentinel lymph node positivity, and for MSLT-1 patients, delay time of less than 30 days was independently associated with a 36% decreased risk of having a positive sentinel lymph node. A clear explanation for this finding is not evident based on the data. The delayed cohort from the John Wayne Cancer Institute dataset was significantly older compared with the corresponding early SLNB group (56.3 vs 54.7 years; p = 0.02). Comparatively, the early and delayed SLNB groups from MSLT-1 were similar in age (p = 0.21). There is some evidence to suggest that lymphatic function declines with age and therefore could result in reduced nodal positivity rates in older individuals.[19] This represents

one possible explanation for the differences noted. Nodal positivity in both groups is associated with reduced DFS and MSS. However, the data are clear that timing of the SLNB, whether less than 30 or more than 30 days, does not independently impact outcomes.

Although this is the largest study to date that addresses this key clinical question, there are limitations that should be acknowledged. This was a retrospective study of prospectively collected data and is therefore subject to the limitations of any dataset review, including missing data and loss to follow-up. However, the results of this study were validated using data from the MSLT-1 trial, a prospective, randomized controlled trial with complete preoperative, perioperative, and long-term follow-up data. It is possible that a more clinically relevant cutoff point exists that would be better than the 30-day cutoff used in this series. Earlier series have explored delay times ranging between 30 and 47 days and, as in the current study, these earlier studies selected delay times based on median time to surgery to determine their respective cohorts. We also used a 40-day cutoff to stratify patients, and time as a continuous variable but in both cases found no difference in DFS or MSS (data not shown). In the current series, we focused on outcomes for all patients and sentinel node-positive patients separately because intuitively the latter would be most likely to be impacted by delay. However, because Tejera-Vaquerizo and colleagues[8] reported worse MSS in patients undergoing early SLNB (less than 30 days) who had a negative sentinel node, we also performed analysis on our negative sentinel node patients and again found no significant difference in DFS or MSS (data not shown). The John Wayne Cancer Institute is a high-volume melanoma referral center, which could result in a component of referral bias that selected for more advanced or challenging cases. We attempted to control for this by including only referral patients who underwent SLNB within 6 months of their initial biopsy and excluding patients with early (less than 90 days) disease recurrence. Patients with multiple primary cutaneous melanomas were also excluded.

Although the results of this study support the conclusion that a modest delay of 30 or more days to SLNB (median of 41 days in the delayed SLNB group) does not appear to impact prognosis negatively, we cannot determine a safe upper limit of delay time. In the current study, we included patients who underwent SLNB no more than 6 months from the time of initial diagnosis, however, few patients suffered such extreme delay. In MSLT-1, median time to development of clinically relevant nodal disease in the wide local excision alone arm was 19.2 months.[4] This delay was associated with worse outcomes for node-positive patients, indicating that there is a delay that would be excessive and allow preventable progression. However, the range of delays encountered in routine practice appear to be safe. Defining a fixed maximum time interval beyond the modest delay found to be safe in this study seems to be unnecessary at this time. What is important is to be able to offer reassurance and minimize the stress and anxiety that accompanies a new diagnosis of melanoma. Up to 30% of patients diagnosed with melanoma will report clinically relevant psychological distress[20] and issues related to prognosis and fear of death are often cited as sources for anxiety in these patients.[21] Delays between time of diagnosis and definitive surgical management are often inevitable. However, based on the results of this study, patients can be reassured that if the procedure must be delayed, there is a margin of time during which the efficacy of the operation is unlikely to be diminished.

CONCLUSIONS

This study demonstrated that a delay to SLNB beyond 30 days after initial biopsy does not adversely impact long-term clinical outcomes in cutaneous melanoma. Patients can be reassured that should the operation occur more than 30 days from diagnosis, it will not affect their overall prognosis. Expeditious definitive care should, however, always be the goal.

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Abbreviations and Acronyms

DFS	disease-free survival
HR	hazard ratio
MSLT-1	Multicenter Selective Lymphadenectomy Trial-1
MSS	melanoma-specific survival

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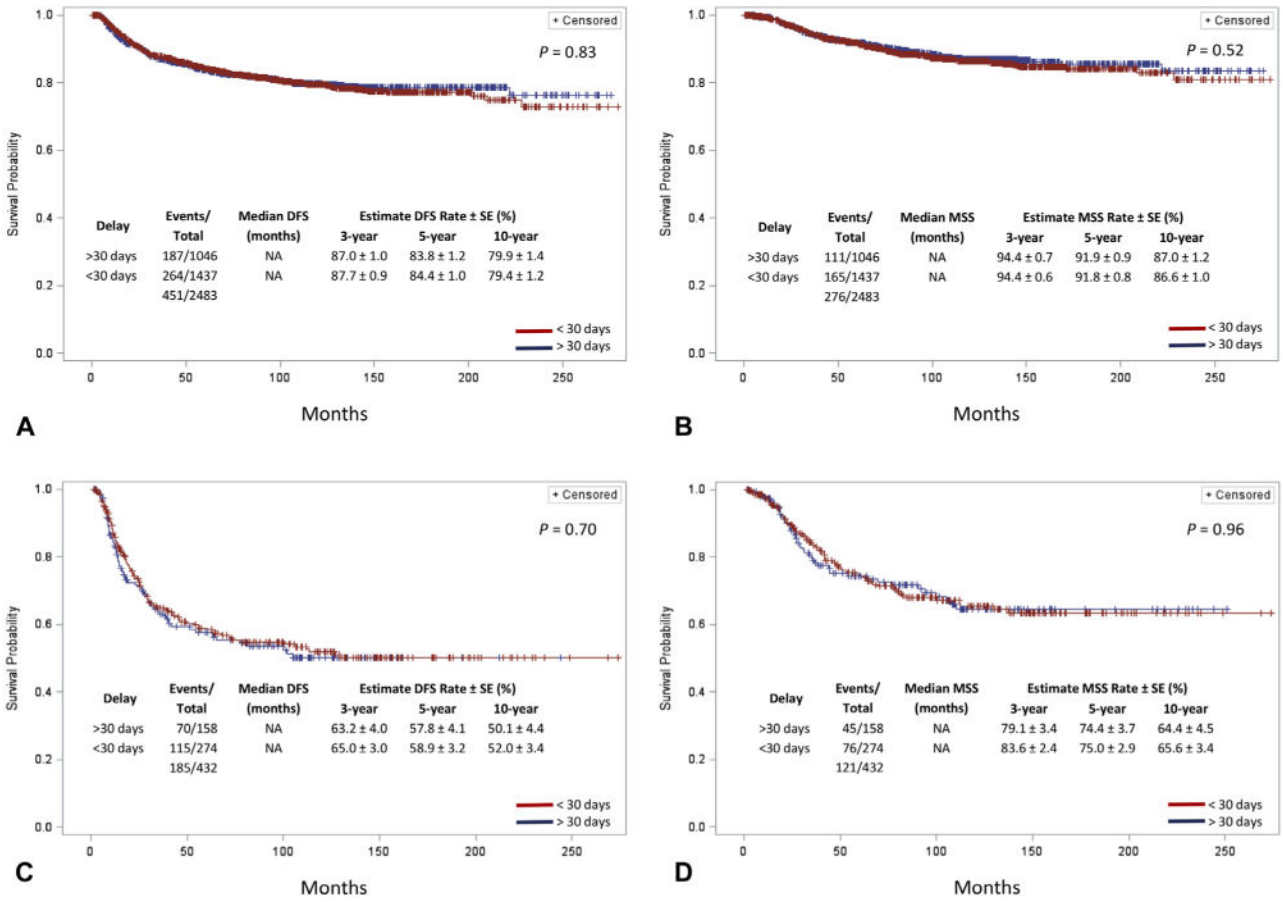

Figure 1.

(A) Disease-free survival (DFS) and (B) melanoma-specific survival (MSS) for all patients and (C) DFS and (D) MSS for sentinel lymph node-positive patients from John Wayne Cancer Institute, stratified by delay between initial diagnosis and time of wide local excision and SLNB. NA, not applicable.

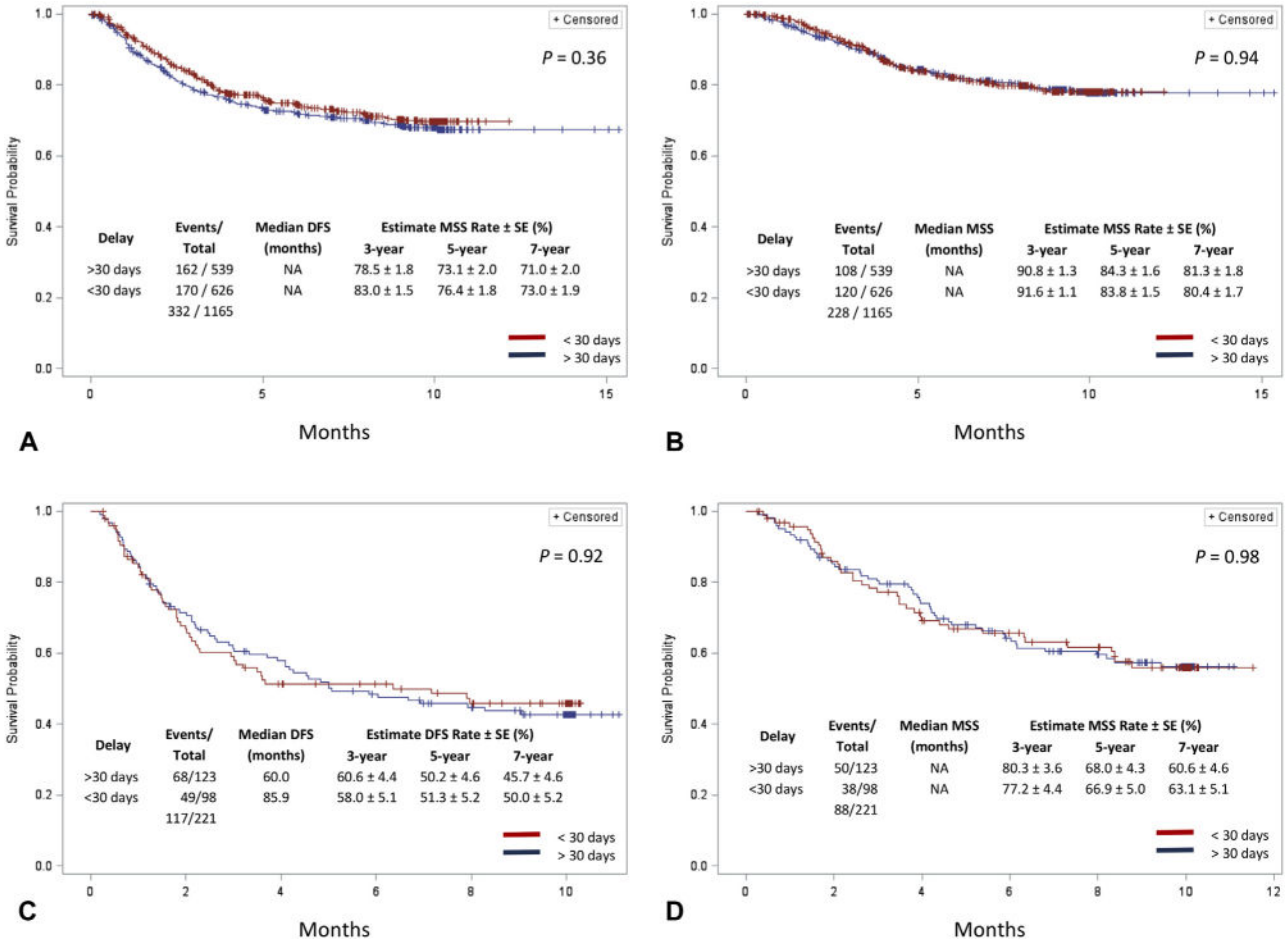

Figure 2.

(A) Disease-free survival (DFS) and (B) melanoma-specific survival (MSS) for all patients and (C) DFS and (D) MSS for sentinel lymph node-positive patients from the SLNB arm of Multicenter Selective Lymphadenectomy Trial-1, stratified by delay between initial diagnosis and time of wide local excision and SLNB. NA, not applicable.

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Table 1

Demographics and Histopathologic Characteristics of All Patients Undergoing Wide Local Excision and SLNB John Wayne Cancer Institute

	John Wayne Cancer institute				Multicenter Selective Lymphadenectomy Trial-1			
	Delay time				Delay time			
Characteristic	**<30 d (n = 1,437)**	**≥30 d (n = 1,046)**	**Total (n = 2,483)**	**p Value***	**<30 d (n = 626)**	**≥30 d (n = 539)**	**Total (n = 1,165)**	**p Value***
Age, y				0.02†				0.21†
Mean	54.7	56.3	55.3		52	51	51.5	
Range	8.0–95.6	3.9–95.9	3.9–95.9		19–75	18–75	18–75	
Sex, n (%)				0.17				0.03
Female	589 (41.0)	400 (38.2)	989 (39.8)		245 (39.1)	244 (45.3)	489 (42.0)	
Male	848 (59.0)	646 (61.8)	1,494 (60.2)		381 (60.9)	295 (54.7)	676 (58.0)	
Breslow thickness, mm				0.97‡				0.23‡
Mean	1.75	1.83	1.78		2.41	2.57	2.48	
Range	0.07–15.0	0.07–18.0	0.07–18.0		0.60–13.0	0.70–12.0	0.60–13.0	
Ulceration, n (%)				0.95				<0.0001§
Absent	1,150 (80.0)	835 (79.8)	1,985 (79.9)		426 (68.0)	312 (57.9)	738 (63.4)	
Present	245 (17.0)	182 (17.4)	427 (17.2)		181 (28.9)	160 (29.7)	341 (29.3)	
Unknown	42 (2.9)	29 (2.8)	71 (2.9)		19 (3.0)	67 (12.4)	86 (7.4)	
Primary site, n (%)				0.41				0.03
Head/neck	271 (18.9)	218 (20.8)	489 (19.7)		104 (16.6)	70 (13.0)	174 (14.9)	
Lower extremity	308 (21.4)	236 (22.6)	544 (21.9)		163 (26.0)	181 (33.6)	344 (29.5)	
Upper extremity	293 (20.4)	194 (18.6)	487 (19.6)		118 (18.8)	95 (17.6)	213 (18.3)	
Trunk	565 (39.2)	398 (38.0)	963 (38.8)		241 (38.5)	193 (35.8)	434 (37.2)	
Clark level, n (%)				0.41				0.78
I	1 (0.1)	2 (0.2)	3 (0.1)		0 (0)	0 (0)	0 (0)	
II	184 (12.8)	157 (15.0)	341 (13.7)		1 (0.1)	0 (0.0)	1 (0.1)	
III	444 (30.9)	312 (29.8)	756 (30.4)		372 (43.4)	228 (42.3)	500 (42.9)	
IV	698 (48.6)	486 (46.5)	1184 (47.7)		330 (52.7)	292 (54.2)	622 (53.4)	
V	76 (5.3)	56 (5.4)	132 (5.3)		23 (3.7)	19 (3.5)	42 (3.6)	

Characteristic	John Wayne Cancer institute				Multicenter Selective Lymphadenectomy Trial-1			
	Delay time				Delay time			
	<30 d (n = 1,437)	≥30 d (n = 1,046)	Total (n = 2,483)	p Value*	<30 d (n = 626)	≥30 d (n = 539)	Total (n = 1,165)	p Value*
Unknown	34 (2.4)	33 (3.2)	67 (2.7)		0 (0)	0 (0)	0 (0)	
Mitotic rate, n (%)				0.99				0.58
1+ mitoses/hpf	461 (32.1)	335 (32.0)	796 (32.1)		462 (32.1)	346 (31.2)	808 (31.7)	
<1 mitoses/hpf	485 (33.8)	352 (33.6)	837 (33.7)		487 (33.8)	363 (32.7)	850 (33.3)	
Unknown	491 (34.2)	359 (34.3)	850 (34.2)		492 (34.1)	401 (36.1)	893 (35.0)	
SLNB status, n (%)				0.01				0.002
Negative	1,163 (80.9)	888 (84.9)	2,051 (82.6)		528 (84.4)	416 (77.2)	944 (81.0)	
Positive	274 (19.1)	158 (15.1)	432 (17.4)		98 (15.6)	123 (22.8)	221 (19.0)	

*The p values for categorical variables are from chi-square test.

†The p value for age is from *t*-test.

‡The p value for Breslow is from the Wilcoxon rank-sum test (nonparametric).

§If the unknowns were excluded, this difference would not be significant. hpf, high-power field.

Table 2

Cox Proportional-Hazards Model for Disease-Free Survival and Melanoma-Specific Survival for John Wayne Cancer Institute Patients

	Disease-free survival			Melanoma-specific survival		
Characteristic	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Age, continuous	1.02	1.01–1.02	<0.001	1.02	1.01–1.03	<0.001
Sex						
Female (ref)	1	—	—	1	—	—
Male	1.03	0.83–1.28	0.77	1.02	0.77–1.35	0.89
Breslow thickness						
<1.00 mm	0.44	0.32–0.61	<0.001	0.43	0.28–0.67	<0.001
1.00 to 1.99 mm (ref)	1	—	—	1	—	—
2.00 to 4.00 mm	1.96	1.55–2.48	<0.001	2	1.47–2.72	<0.001
>4.00 mm	2.77	2.09–3.66	<0.001	3.14	2.22–4.45	<0.001
Ulceration						
Absent (ref)	1	—	—	1	—	—
Present	1.44	1.16–1.79	<0.001	1.72	1.31–2.26	<0.001
Unknown	2.21	1.47–3.34	<0.001	2.93	1.82–4.74	<0.001
Primary site						
Head/neck	1.64	1.29–2.08	<0.001	1.3	0.96–1.76	0.09
Lower extremity	1.22	0.94–1.59	0.13	0.89	0.63–1.25	0.51
Trunk (ref)	1	–	–	1	–	–
Upper extremity	0.71	0.53–0.96	0.03	0.56	0.37–0.82	0.004
SLNB status						
Positive	3.07	2.50–3.77	<0.001	3.11	2.40–4.03	<0.001
Negative (ref)	1	—	—	1	—	—
Time to SLNB		—	—		—	—
Less than 30 d	0.98	0.81–1.18	0.85	1.05	0.83–1.34	0.67
More than 30 d (ref)	1	–	–	1	–	–

HR, hazard ratio.

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Table 3

Demographics and Histopathologic Characteristics of Sentinel Lymph Node-Positive Patients

	John Wayne Cancer Institute				Multicenter Selective Lymphadenectomy Triai-1			
	Delay time				Delay time			
Characteristic	**<30 d (n = 274)**	**≥30 d (n = 158)**	**Total (n = 432)**	**p Value***	**<30 d (n = 98)**	**≥30 d (n = 123)**	**Total (n = 221)**	**p Value***
Age, y				0.46†				0.17†
Mean	53.3	54.7	53.3		50.4	47.9	49	
Range	11.5–94.9	3.9–94.5	3.9,94.9		25–75	23–74	23–75	
Sex, n (%)				0.75				0.63
Female	105 (38.3)	63 (39.9)	168 (38.9)		39 (39.8)	45 (36.6)	84 (38.0)	
Male	169 (61.7)	95 (60.1)	264 (61.1)		59 (60.2)	78 (63.4)	137 (62.0)	
Breslow thickness, mm				0.93‡				0.21‡
Mean	2.87	3.03	2.92		3.09	3.53	3.34	
Range	0.40–15.0	0.45–15.0	0.40–15.0		1.00–11.0	1.00–12.0	1.00–12.0	
Ulceration, n (%)				0.44				0.001§
Absent	186 (67.9)	110 (69.6)	296 (68.5)		63 (64.3)	57 (46.3)	120 (54.3)	
Present	85 (31.0)	44 (27.8)	129 (29.9)		34 (34.7)	48 (39.0)	82 (37.1)	
Unknown	3 (1.1)	4 (2.5)	7 (1.6)		1 (1.0)	18 (14.6)	19 (8.6)	
Primary site, n (%)				0.96				0.45
Head/neck	44 (16.1)	27 (17.1)	71 (16.4)		15 (15.3)	12 (9.8)	27 (12.2)	
Lower extremity	71 (25.9)	43 (27.2)	114 (26.4)		29 (29.6)	38 (30.9)	67 (30.3)	
Upper extremity	43 (15.7)	25 (15.8)	68 (15.7)		12 (12.2)	11 (8.9)	23 (10.4)	
Trunk	116 (42.3)	63 (39.9)	179 (41.4)		42 (42.9)	62 (50.4)	104 (47.1)	
Clark level, n (%)				0.29				0.89
I	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
II	6 (2.2)	2 (1.7)	8 (1.8)		0 (0)	0 (0)	0 (0)	
III	39 (14.2)	33 (20.9)	72 (16.7)		29 (29.6)	37 (30.1)	66 (29.9)	
IV	190 (69.3)	100 (63.3)	290 (67.1)		61 (62.2)	78 (63.4)	139 (62.9)	
V	32 (11.7)	16 (10.1)	48 (11.1)		8 (8.2)	8 (6.5)	16 (7.24)	

	John Wayne Cancer Institute				Multicenter Selective Lymphadenectomy Triai-1			
	Delay time				Delay time			
Characteristic	**<30 d (n = 274)**	**≥30 d (n = 158)**	**Total (n = 432)**	**p Value***	**<30 d (n = 98)**	**≥30 d (n = 123)**	**Total (n = 221)**	**p Value***
Unknown	7 (2.6)	7 (4.4)	14 (3.2)		0 (0)	0 (0)	0 (0)	
Mitotic rate, n (%)				0.16				0.002
1+ mitoses/hpf	114 (41.6)	52 (32.9)	166 (38.4)		97 (99.0)	105 (85.4)	202 (91.4)	
<1 mitoses/hpf	44 (16.1)	33 (20.9)	77 (17.8)		0 (0)	1 (0.8)	1 (0.4)	
Unknown	116 (42.3)	73 (46.2)	189 (43.8)		1 (1.0)	17 (13.8)	18 (8.1)	

*The p values for categorical variables are from chi-square test.

†The p value for age is from *t*-test.

‡The p value for Breslow is from the Wilcoxon rank-sum test (nonparametric).

§If the unknowns were excluded, this difference would not be significant. hpf, high-power field.

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Table 4

Multivariable Regression Analysis for Predictors of Sentinel Lymph Node Positivity

	John Wayne Cancer institute			Multicenter Selective Lymphadenectomy Triai-1		
Characteristic	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
Age, continuous	0.98	0.98–0.99	<0.001	0.98	0.97–0.99	<0.001
Sex						
Female (ref)	1	—	—	1	—	—
Male	1	0.78–1.28	0.98	1.25	0.89–1.74	0.19
Breslow thickness						
<1.00 mm	0.22	0.15–0.31	<0.001	0	0.00–999.9	0.98
1.00 to 1.99 mm (ref)	1	—	—	1	—	—
2.00 to 4.00 mm	2.65	2.01–3.49	<0.001	2.52	1.76–3.62	<0.001
>4.00 mm	3.41	2.39–4.87	<0.001	5.19	3.24–8.30	<0.001
Ulceration						
Absent (ref)	1	—	—	1	—	—
Present	1.15	0.88–1.52	0.31	1.06	0.75–1.50	0.74
Unknown	0.33	0.14–0.75	0.008	1.37	0.55–3.40	0.50
Primary site						
Head/neck	0.61	0.44–0.85	0.003	0.56	0.35–0.92	0.02
Lower extremity	1.16	0.86–1.57	0.34	0.81	0.56–1.19	0.29
Trunk (ref)	1	—	—	1	—	—
Upper extremity	0.7	0.50–0.97	0.03	0.43	0.26–0.71	0.001
Mitotic rate						
<1 mitoses/hpf	0.74	0.53–1.02	0.06	0.64	0.08–5.38	0.68
1+ mitoses/hpf (ref)	1			1		
Unknown	1.32	1.02–1.71	0.03	0.63	0.25–1.57	0.32
Time to SLNB						
<30 d	1.33	1.05–1.67	0.02	0.64	0.47–0.88	0.006
>30 d (ref)	1	—	—	1	—	—

hpf, high-power field; OR, odds ratio.