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Final Trial Report of Sentinel-Node Biopsy versus Nodal Observation in Melanoma

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ABSTRACT

BACKGROUND

Sentinel-node biopsy, a minimally invasive procedure for regional melanoma staging, was evaluated in a phase 3 trial.

METHODS

We evaluated outcomes in 2001 patients with primary cutaneous melanomas randomly assigned to undergo wide excision and nodal observation, with lymphadenectomy for nodal relapse (observation group), or wide excision and sentinel-node biopsy, with immediate lymphadenectomy for nodal metastases detected on biopsy (biopsy group).

RESULTS

No significant treatment-related difference in the 10-year melanoma-specific survival rate was seen in the overall study population (20.8% with and 79.2% without nodal metastases). Mean (±SE) 10-year disease-free survival rates were significantly improved in the biopsy group, as compared with the observation group, among patients with intermediate-thickness melanomas, defined as 1.20 to 3.50 mm (71.3±1.8% vs. 64.7±2.3%; hazard ratio for recurrence or metastasis, 0.76; P=0.01), and those with thick melanomas, defined as >3.50 mm (50.7±4.0% vs. 40.5±4.7%; hazard ratio, 0.70; P=0.03). Among patients with intermediate-thickness melanomas, the 10-year melanoma-specific survival rate was 62.1±4.8% among those with metastasis versus 85.1±1.5% for those without metastasis (hazard ratio for death from melanoma, 3.09; P<0.001); among patients with thick melanomas, the respective rates were 48.0±7.0% and 64.6±4.9% (hazard ratio, 1.75; P=0.03). Biopsy-based management improved the 10-year rate of distant disease–free survival (hazard ratio for distant metastasis, 0.62; P=0.02) and the 10-year rate of melanoma-specific survival (hazard ratio for death from melanoma, 0.56; P=0.006) for patients with intermediate-thickness melanomas and nodal metastases. Accelerated-failure-time latent-subgroup analysis was performed to account for the fact that nodal status was initially known only in the biopsy group, and a significant treatment benefit persisted.

CONCLUSIONS

Biopsy-based staging of intermediate-thickness or thick primary melanomas provides important prognostic information and identifies patients with nodal metastases who may benefit from immediate complete lymphadenectomy. Biopsy-based management prolongs disease-free survival for all patients and prolongs distant disease–free survival and melanoma-specific survival for patients with nodal metastases from intermediate-thickness melanomas. (Funded by the National Cancer Institute, National Institutes of Health, and the Australia and New Zealand Melanoma Trials Group; ClinicalTrials.gov number, NCT00275496.)

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*A complete list of investigators in the Multicenter Selective Lymphadenectomy Trial (MSLT) Group is provided in the Supplementary Appendix, available at NEJM.org.

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Regional node management in melanoma has remained controversial since Snow[1] recommended elective complete lymphadenectomy for all patients with melanoma, regardless of whether there was clinical evidence of regional nodal metastases. However, routine elective lymphadenectomy exposes all patients to procedure-related complications and cannot benefit the majority, who have no regional nodal metastases. Multiple randomized trials have suggested a benefit of routine lymphadenectomy in at least some groups of patients with melanoma.[2-6]

Because of dissatisfaction with both elective lymphadenectomy and nodal observation, lymphatic mapping and sentinel-node biopsy were introduced for individualized management of regional lymph nodes.[6-9] Sentinel-node biopsy is a minimally invasive, low-morbidity staging procedure performed with the use of blue dye and radiolabeled colloids. It identifies the first (i.e., sentinel) node or nodes in the regional basin that receive lymph from the primary melanoma site. Because the sentinel node is the initial site of regional metastasis,[10-14] its tumor status accurately predicts the tumor status of other nodes in the lymphatic basin. If focused pathological scrutiny of the sentinel node identifies no metastases, other regional nodes will probably also be negative.

The Multicenter Selective Lymphadenectomy Trial (MSLT-I) commenced in 1994 to determine whether sentinel-node biopsy could be used to identify patients with clinically occult nodal metastases and whether immediate-completion lymphadenectomy yielded better outcomes than complete lymphadenectomy performed only when nodal recurrence was revealed during observation. Enrollment closed in 2002, after 2001 patients had been registered. The 5-year results of the third interim analysis, published in 2006,[11] highlighted patients in the primary study group who had primary melanomas of intermediate thickness (defined as 1.20 to 3.50 mm). We now report 10-year follow-up data for that group as well as for patients with thick primary melanomas (defined as >3.50 mm thick). We also report the results of a new accelerated-failure-time latent-subgroup analysis of the treatment effect of sentinel-node biopsy.

Methods

Trial Design

Criteria for enrollment in the MSLT-I included both Breslow thickness and Clark level (a measure of the depth of tumor penetration within the anatomical layers of the skin). Candidates for inclusion were patients who had localized cutaneous melanomas of Clark level III with a Breslow thickness of 1.00 mm or more or melanomas of Clark level IV or V with any Breslow thickness. Patients with intermediate-thickness melanomas constituted the primary study group, because pretrial statistical modeling indicated that the timing of complete lymphadenectomy was most likely to affect survival in this group.[15] The results of a post hoc analysis of groups with melanomas of 1.00 to 4.00 mm in thickness were similar (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

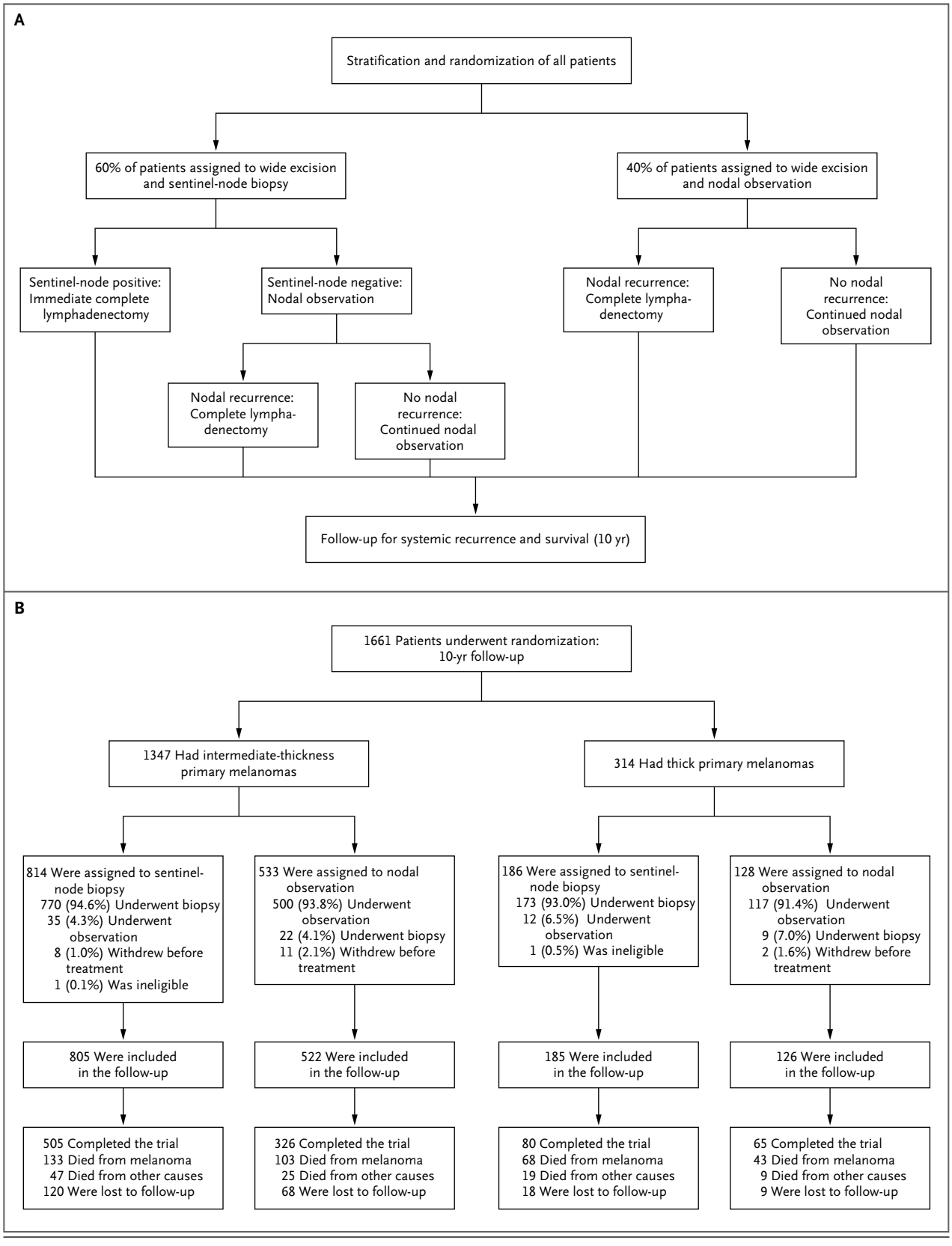
The study was conducted with the approval of the institutional review board or ethics committee at each of the participating institutions. All authors vouch for the accuracy and completeness of the data presented.

Figure 1 (facing page). Trial Design, Enrollment, and Outcomes.

Panel A shows the design of the trial. Panel B shows enrollment and outcomes at 10 years of follow-up for patients with intermediate-thickness primary melanomas (1.20 to 3.50 mm) and those with thick primary melanomas (>3.50 mm).

Patients

Eligible patients who provided written informed consent were randomly assigned to undergo wide excision of the primary melanoma plus sentinel-node biopsy (biopsy group, 60% of patients) or wide excision plus postoperative nodal observation (observation group, 40%) (Fig. 1A). For excision of intermediate-thickness and thick melanomas, margins of 2 to 3 cm were recommended, with adjustment permissible for anatomical or functional considerations. Patients in the observation group underwent delayed lymphadenectomy if nodal metastases developed during observation. Patients in the biopsy group underwent immediate lymphadenectomy if metastases were detected in sentinel nodes stained with hematoxylin and eosin or immunohistochemically stained for S-100, HMB-45, and melanoma antigen recognized by T cells (MART-1, also called MelanA [melanoma tumor antigen]).[9,16,17] The presence of immunopositive cells of appropriate cytologic type in nodal parenchyma or in afferent



lymphatic vessels was acceptable evidence of a nodal tumor, even if cells were identified by immunohistochemical analysis alone and even if only one such cell was identified. Nodal nevocytes were identified by their morphologic features, location, and characteristic immunophenotype (S-100 expression, MART-1 expression, and weak or no expression of HMB-45).

Patients in both groups were monitored postoperatively by means of clinical examination, blood testing, and chest radiography, performed every 3 months during the first 2 years, every 4 months during year 3, every 6 months during years 4 and 5, and then annually until year 10. Participating sites were permitted to use their routine follow-up procedure, which could include periodic positron-emission tomographic and computed tomographic scanning, nodal ultrasonography, and testing for melanoma markers such as S-100 and lactate dehydrogenase.

STATISTICAL ANALYSIS

For patients with intermediate-thickness or thick primary melanomas, randomization was stratified according to Breslow thickness (1.20 to 1.79, 1.80 to 3.50, or >3.50 mm) and primary tumor site (extremity or nonextremity) and was performed in random permuted blocks of four, six, and eight patients.[11] The primary end point was melanoma-specific survival (survival until death from melanoma). The secondary end points, described previously,[11,12] included disease-free survival, survival with tumor-positive or tumor-negative sentinel nodes, and the incidence of sentinel-node metastases, as compared with the incidence of clinically detected nodal metastases. Follow-up and survival were calculated from the date of randomization to the date of the last evaluation or death. Disease-free survival and distant disease–free survival were calculated from the date of randomization to the date of any melanoma recurrence within or beyond the primary tumor region, respectively. A false negative result of sentinel-node biopsy was defined as regional nodal recurrence in a patient whose sentinel nodes had been found to be tumor-free.

The initial sample size, 900 patients, for the group with intermediate-thickness melanomas was selected for 90% power with a 5% type I error rate. The underlying assumptions for the computation of sample size were based on historical data in the John Wayne Cancer Institute database.[11,15] After the second interim analysis, the sample size for the intermediate-thickness group was increased to 1200 patients, because the distribution of trial entrants was more skewed toward lower-risk patients than expected.[11,15] The final study sample included 2001 patients, with 1347 in the group with intermediate-thickness melanomas, 340 in the group with thin melanomas (defined as <1.20 mm), and 314 in the group with thick melanomas; these sample sizes provided power to detect differences in the 10-year survival rate of 10 to 16 percentage points, depending on the tumor-thickness category and primary tumor site.

The Kaplan–Meier method was used to estimate mean 5-year and 10-year rates of melanoma-specific and disease-free survival. P values for survival curves were derived from Wald tests for hazard ratios in the Cox proportional-hazards model. Baseline demographic, clinical, and pathologic characteristics were compared with the use of a t-test or chi-square test, and the Wilcoxon rank-sum test was used to compare numbers of tumor-involved nodes. We used SAS software, version 9.2 (SAS Institute), for all analyses. A two-sided P value of 0.05 or lower was considered to indicate statistical significance.

Comparisons of melanoma-specific and disease-free survival were based on data from patients who underwent their assigned treatment. Results of parallel analyses performed according to the intention-to-treat principle were consistent with those of the per-protocol analysis (see the Supplementary Appendix). Subgroup analyses included patients in the biopsy group for whom information on nodal status was available and patients in the observation group in whom clinically detectable nodal metastases developed. Because pathologic nodal status was initially known only in the biopsy group, there was concern about ascertainment bias relative to node-positive patients. In post hoc analyses, a latent-subgroup analytic method was developed to account for the possibility of such bias and to allow determination of treatment effect within the node-positive subgroups.[18] In this analysis, we used a semiparametric accelerated-failure-time mixture model with bootstrap methods to estimate variance. Performance of the analysis was corroborated in multiple simulations. The output of the analysis is a measure of treatment effect, which corresponds to an increase in survival time related to the experimental treatment.

RESULTS

TREATMENT GROUPS

Treatment groups were balanced with respect to primary tumor site, Clark level, Breslow thickness, ulceration, and age (Table S1 in the Supplementary Appendix). For the per-protocol analysis (Fig. 1B), 1270 patients with intermediate-thickness primary melanomas could be evaluated (770 in the biopsy group and 500 in the observation group), as could 290 patients with thick primary melanomas (173 in the biopsy group and 117 in the observation group), and 232 patients with thin primary melanomas (141 in the biopsy group and 91 in the observation group). Because of space constraints and event infrequency among patients with thin primary melanomas, data from this cohort are considered exploratory and are not reported on in this article.

SURVIVAL RATES

Among all patients with intermediate-thickness melanomas (with or without nodal metastases) there was no significant treatment-related difference in the 10-year melanoma-specific survival rates; the mean (±SE) rate was 81.4±1.5% in the biopsy group and 78.3±2.0% in the observation group (hazard ratio for death from melanoma in the biopsy group, 0.84; 95% confidence interval [CI], 0.64 to 1.09; P=0.18) (Fig. 2A). There was also no significant between-group difference in 10-year melanoma-specific survival rates among patients with thick melanomas (Fig. 2B).

Ten-year disease-free survival rates were significantly higher in the biopsy group than in the observation group. Among patients with intermediate-thickness melanomas (Fig. 2C), the rate was 71.3±1.8% in the biopsy group as compared with 64.7±2.3% in the observation group (hazard ratio for recurrence or metastasis, 0.76; 95% CI, 0.62 to 0.94; P=0.01); among patients with thick melanomas (Fig. 2D), the respective rates were 50.7±4.0% and 40.5±4.7 (hazard ratio, 0.70; 95% CI, 0.50 to 0.96; P=0.03).

PROGNOSTIC SIGNIFICANCE OF THE SENTINEL NODE

In the biopsy group, patients with sentinel-node metastases had poorer outcomes than did patients with tumor-free sentinel nodes. In the group of patients with intermediate-thickness melanomas, the 10-year melanoma-specific survival rate was 62.1±4.8% among those with sentinel-node metastases as compared with 85.1±1.5% among those with tumor-free sentinel nodes (hazard ratio for death from melanoma, 3.09; 95% CI, 2.12 to 4.49; P<0.001) (Fig. S1A in the Supplementary Appendix)[11]; in the group of patients with thick melanomas, the respective rates were 48.0±7.0% and 64.6±4.9% (hazard ratio, 1.75; 95% CI, 1.07 to 2.87; P=0.03) (Fig. S1B in the Supplementary Appendix). In a multivariate analysis (Table 1), sentinel-node status was the strongest predictor of disease recurrence or death from melanoma.

PRESENCE OF NODAL METASTASES

The frequency of nodal metastasis across all Breslow-thickness groups was 20.8%. Long-term follow-up confirmed the similar rates of nodal metastases in the two treatment groups (Fig. 3A and 3B, and Table S1 in the Supplementary Appendix). Of 500 patients in the observation group who had intermediate-thickness melanomas, 87 (17.4%) had nodal metastases at a median of 19.2 months (95% CI, 13.6 to 24.1) after randomization (Table S1A in the Supplementary Appendix); the estimated 10-year cumulative incidence of nodal metastasis was 19.5% (Fig. 3A). Of 117 patients observed after wide excision of thick melanomas, 44 (37.6%) had nodal relapse at a median of 9.2 months (95% CI, 6.4 to 12.2) after randomization (Table S1B in the Supplementary Appendix); the estimated cumulative incidence of nodal metastases at 10 years was 41.4% (Fig. 3B).

Among the 770 patients in the biopsy group who had intermediate-thickness melanomas, sentinel nodes were identified in 765 (99.4%); metastases were identified in 122 of these patients (16.0%) (Table S1A in the Supplementary Appendix). Nodal metastases were detected during observation in 31 of 643 patients (4.8%) with tumor-free sentinel nodes; thus, the proportion of patients with intermediate-thickness melanomas who had nodal metastases in the biopsy group was 20.0% (153 of 765 patients), and the estimated cumulative incidence of nodal metastases at 10 years was 21.9% (Fig. 3A).

All 173 patients with thick melanomas in the biopsy group had sentinel nodes identified, and 57 (32.9%) had sentinel-node metastases (Table S1B in the Supplementary Appendix). Nodal metastases were subsequently detected in 12 of 116 patients (10.3%) with sentinel nodes that were initially tumor-free; thus, the

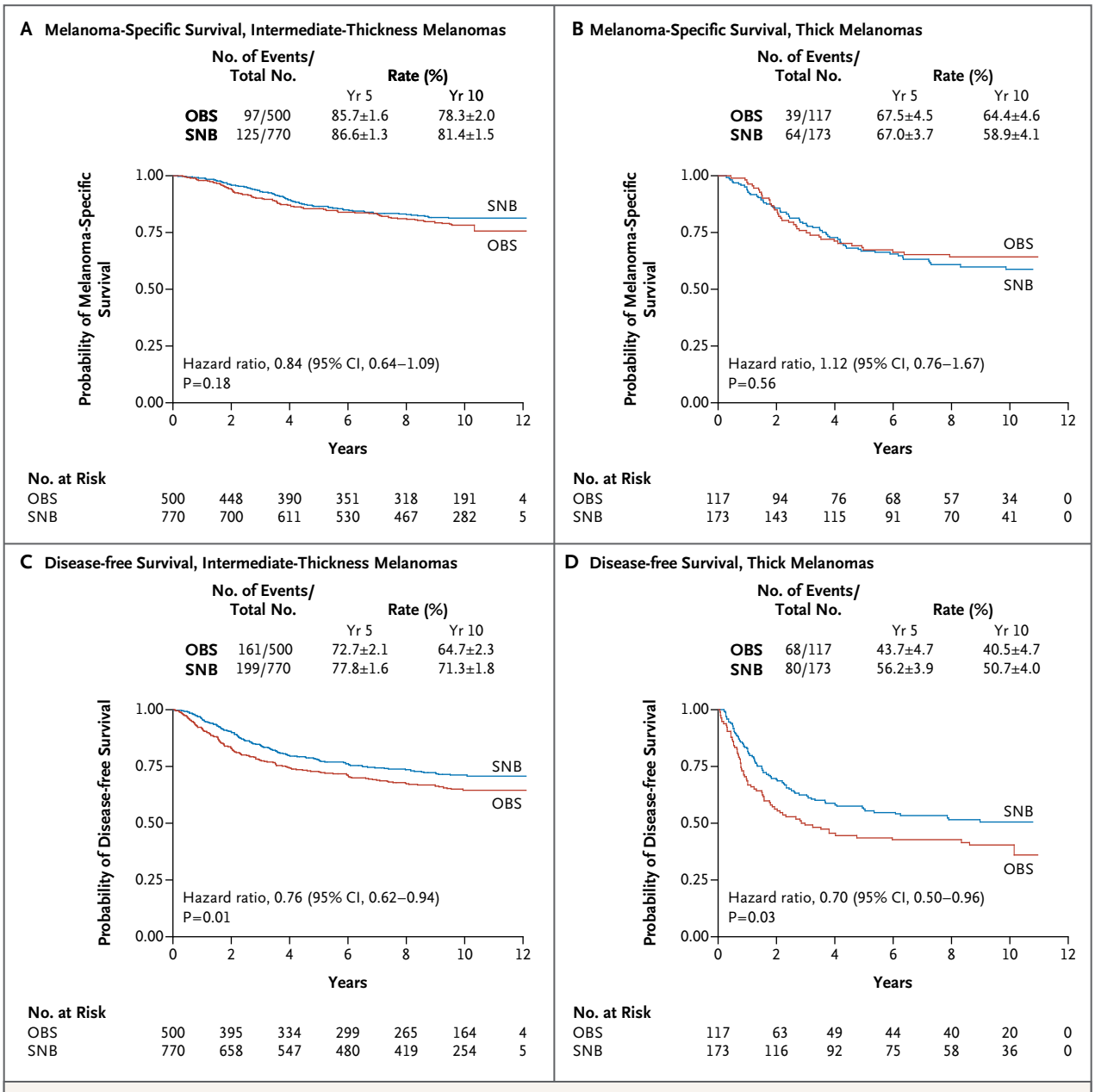


Figure 2. Melanoma-Specific and Disease-free Survival, According to Study Group and Melanoma Thickness.

Plus–minus values are means ±SE for the estimated rate of survival at specified time points. OBS denotes nodal observation, and SNB sentinel-node biopsy.

proportion of patients with thick melanomas who had nodal metastases in the biopsy group was 39.9% (69 of 173 patients), and the estimated cumulative incidence of nodal metastases at 10 years was 42.0% (Fig. 3B).

SURVIVAL IN GROUPS WITH NODAL METASTASES

The distribution of prognostic factors among patients with nodal metastases did not differ significantly between the two treatment groups, with the exception of age among patients with thick melanomas (Tables S1A and S1B in the Supplementary Appendix).

Among patients with nodal metastases from intermediate-thickness melanomas, the 10-year melanoma-specific survival rate was 62.1±4.8% in the biopsy group as compared with 41.5±5.6% in the observation group (hazard ratio for death

Table 1. Multivariate Hazard Ratios for Disease Recurrence and Death among Patients with Intermediate-Thickness Melanoma Who Underwent Sentinel-Node Biopsy, According to Prognostic Indicator.

Prognostic Indicator	Disease Recurrence		Death from Melanoma	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Sentinel-node status (positive vs. negative)	2.64 (1.92–3.64)	<0.001	2.40 (1.61–3.56)	<0.001
Breslow thickness (per 1-mm increase)	1.62 (1.31–2.01)	<0.001	1.59 (1.21–2.09)	<0.001
Ulceration (present vs. absent)	1.40 (1.04–1.89)	0.03	1.79 (1.24–2.58)	0.002
Site of melanoma				
Arm or leg*	1.00		1.00	
Trunk	1.42 (1.03–1.94)	0.03	1.91 (1.26–2.88)	0.002
Head or neck	1.20 (0.77–1.86)	0.42	1.19 (0.65–2.16)	0.58
Sex (male vs. female)	0.94 (0.70–1.26)	0.66	1.22 (0.82–1.79)	0.32
Age (per 1-yr increase)	1.01 (1.00–1.02)	0.07	1.01 (0.99–1.02)	0.33
Clark level (IV or V vs. III)	1.27 (0.94–1.71)	0.12	1.07 (0.74–1.54)	0.73

* This group served as the reference group.

from melanoma, 0.56; 95% CI, 0.37 to 0.84; P=0.006) (Fig. 3C). This treatment-related difference remained significant after patients with false negative sentinel nodes were included (10-year melanoma-specific survival rate, 56.0±4.3% in the biopsy group vs. 41.5±5.6% in the observation group; hazard ratio, 0.67; 95% CI, 0.46 to 0.97; P=0.04). A treatment-related difference was not seen for patients with thick melanomas (Fig. 3D): the 10-year melanoma-specific survival rate was 48.0±7.0% in the biopsy group and 45.8±7.8% in the observation group (hazard ratio, 0.92; 95% CI, 0.53 to 1.60; P=0.78). The melanoma-specific survival rate among patients in whom same-basin nodal metastases developed after a negative result of sentinel-node biopsy was similar to that among patients in whom nodal metastases developed during observation (Fig. 3C and 3D).

Among patients who did not have nodal metastases (those in whom no tumor was found by sentinel-node biopsy or during clinical observation), there was no treatment-related difference in the 10-year melanoma-specific survival rate for patients with intermediate-thickness melanomas (88.0±1.4% in the biopsy group and 86.6±1.8% in the observation group; hazard ratio for death from melanoma in the biopsy group, 0.89; P=0.54) (Fig. 3C) or those with thick melanomas (69.8±5.0% in the biopsy group and 76.1±5.2% in the observation group; hazard ratio, 1.18; P=0.61) (Fig. 3D).

Distant disease–free survival was significantly improved when patients with nodal metastases from intermediate-thickness melanomas received immediate rather than delayed lymphadenectomy (hazard ratio for distant metastasis, 0.62; 95% CI, 0.42 to 0.91, P=0.02) (Fig. S2A in the Supplementary Appendix). A similar benefit was not seen among patients with thick melanomas (hazard ratio, 0.96; 95% CI, 0.56 to 1.64, P=0.88) (Fig. S2B in the Supplementary Appendix).

LATENT-SUBGROUP ANALYSIS

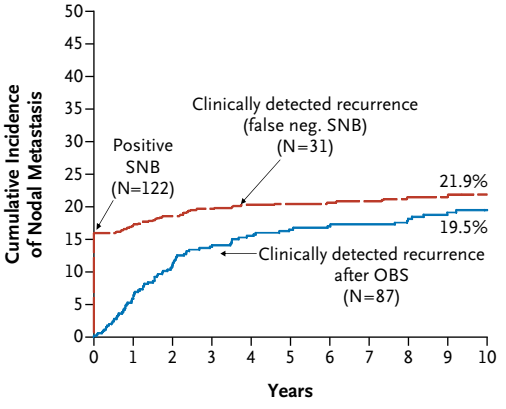
Latent-subgroup statistical methods were used to estimate the treatment effect of sentinel-node biopsy with immediate lymphadenectomy in the subgroup of patients with nodal metastases.[17] Among patients with intermediate-thickness melanomas, both disease-free and distant disease–free survival were improved in the biopsy group; the estimated treatment effect on disease-free survival was 1.17 (P<0.001), and the estimated effect on distant disease–free survival was 0.73 (P=0.04). For melanoma-specific survival, the estimated treatment effect was 0.68 (P=0.05). These treatment effects on disease-free survival, distant disease–free survival, and melanoma-specific survival indicate an increase in survival times by factors of 3.2, 2.1, and 2.0, respectively.

DISCUSSION

A joint committee of the Society of Surgical Oncology and the American Society of Clinical Oncology recently issued an evidence-based

A Cumulative 10-Yr Incidence of Nodal Metastasis, Intermediate-Thickness Melanomas

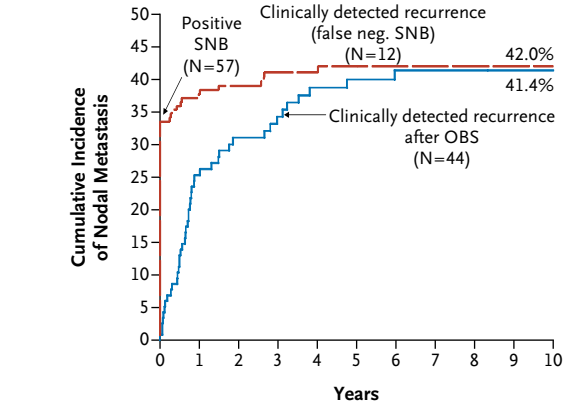
	Rate (%)				
	Yr 3	Yr 5	Yr 7	Yr 9	Yr 10
OBS	13.7±1.58	16.3±1.71	17.0±1.75	18.8±1.86	19.5±1.91
SNB	19.5±1.44	20.3±1.46	20.7±1.48	21.2±1.50	21.9±1.54



No. at Risk						
OBS	500	380	338	305	260	175
SNB	770	551	484	432	364	245

B Cumulative 10-Yr Incidence of Nodal Metastasis, Thick Melanomas

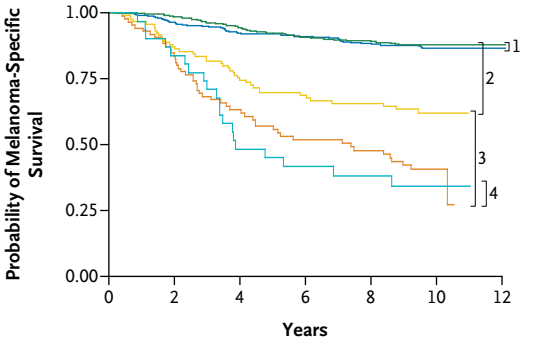
	Rate (%)				
	Yr 3	Yr 5	Yr 7	Yr 9	Yr 10
OBS	33.2±4.5	38.7±4.8	40.0±4.8	41.4±4.9	41.4±4.9
SNB	40.4±3.8	41.1±3.8	42.0±3.8	42.0±3.8	42.0±3.8



No. at Risk						
OBS	117	63	50	47	39	25
SNB	173	86	68	53	43	26

C Melanoma-Specific Survival, Intermediate-Thickness Melanomas

	No. of Events/ Total No.	Rate (%)	
		Yr 5	Yr 10
OBS, no nodal recurrence	48/413	92.0±1.4	86.6±1.8
OBS, nodal recurrence	49/87	57.5±5.4	41.5±5.6
SNB, true neg.	63/612	92.3±1.1	88.0±1.4
SNB, pos.	41/122	69.8±4.4	62.1±4.8
SNB, false neg.	20/31	45.2±8.9	34.4±8.7

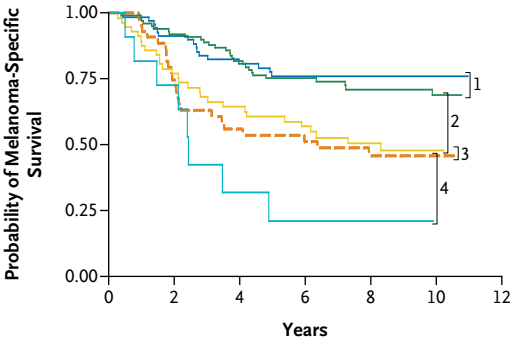


No. at Risk							
OBS, no nodal recurrence	413	375	339	311	282	175	4
OBS, nodal recurrence	87	73	51	40	36	16	0
SNB, true neg.	612	570	511	448	395	243	5
SNB, pos.	122	100	81	68	60	31	0
SNB, false neg.	31	26	15	12	10	6	0

1. SNB, neg. vs. OBS, no nodal recurrence: HR, 0.89 (95% CI, 0.61–1.29); P=0.54
2. SNB, pos. vs. SNB, neg.: HR, 3.93 (95% CI, 2.65–5.83); P<0.001
3. SNB, pos. vs. OBS, nodal recurrence: HR, 0.56 (95% CI, 0.37–0.84); P=0.006
4. SNB, false neg. vs. OBS, nodal recurrence: HR, 1.15 (95% CI, 0.68–1.94); P=0.60

D Melanoma-Specific Survival, Thick Melanomas

	No. of Events/ Total No.	Rate (%)	
		Yr 5	Yr 10
OBS, no nodal recurrence	16/73	76.1±5.2	76.1±5.2
OBS, nodal recurrence	23/44	53.8±7.6	45.8±7.8
SNB, true neg.	27/104	76.0±4.4	69.8±5.0
SNB, pos.	28/57	60.8±6.6	48.0±7.0
SNB, false neg.	9/12	19.4±12.2	—



No. at Risk							
OBS, no nodal recurrence	73	62	52	47	43	25	0
OBS, nodal recurrence	44	32	24	21	14	9	0
SNB, true neg.	104	92	78	61	46	26	0
SNB, pos.	57	43	34	28	22	15	0
SNB, false neg.	12	8	3	2	2	0	0

1. SNB, neg. vs. OBS, no nodal recurrence: HR, 1.18 (95% CI, 0.63–2.18); P=0.61
2. SNB, pos. vs. SNB, neg.: HR, 2.20 (95% CI, 1.29–3.73); P=0.004
3. SNB, pos. vs. OBS, nodal recurrence: HR, 0.92 (95% CI, 0.53–1.60); P=0.78
4. SNB, false neg. vs. OBS, nodal recurrence: HR, 1.96 (95% CI, 0.90–4.27); P=0.09

Figure 3 (facing page). Estimated 10-Year Incidence of Nodal Metastasis and Melanoma-Specific Survival, According to Study Group, Melanoma Thickness, and Presence or Absence of Nodal Recurrence.

Panels A and B show the cumulative incidence of nodal metastasis at 10 years among patients with intermediate-thickness melanomas and those with thick melanomas, respectively. Data are from the per-protocol analysis; patients who left the study or were lost to follow-up were excluded. In the biopsy group, nodal recurrence in patients whose sentinel nodes were negative for tumor (i.e., false negative biopsy results) was assessed. Plus–minus values are means ±SE for the estimated rate of nodal metastasis. The abbreviation neg. denotes negative, and pos. positive. Panels C and D show the probability of melanoma-specific survival (i.e., survival until death from melanoma) among patients with intermediate-thickness melanomas and those with thick melanomas, respectively. Numbers (1–4) to the right of the survival curves refer to the numbered comparisons below each graph. Plus–minus values are means ±SE for the estimated probability of melanoma-specific survival.

guideline that recommends sentinel-node biopsy for patients with intermediate-thickness melanomas and consideration of the procedure for patients with thick melanomas.[19] Our current report, which provides the final long-term follow-up data from a randomized, international clinical trial of sentinel-node biopsy versus observation, augments the evidence base for the use of sentinel-node biopsy in such patients.[20-22]

Previous MSLT-I reports showed the feasibility and accuracy of sentinel-node biopsy.[7,10,11] A sentinel node was identified in 99.4% of patients with intermediate-thickness melanomas. Our long-term results confirm that sentinel-node biopsy correctly determines the pathologic status of the nodal basin in 96% of cases and is the most powerful prognostic indicator. Such prognostic information is particularly important in view of recently approved adjuvant therapy regimens and the continued need to evaluate new approaches to adjuvant therapy.[23]

These current, long-term data also confirm that sentinel-node–guided management protects patients from melanoma recurrence, particularly nodal recurrence. Although nodal metastases can usually be removed at the time of clinical presentation, such recurrences are associated with substantially compromised quality of life and a significantly increased risk of long-term morbidity after complete lymph-node dissection.[24,25] For these reasons, disease-free survival has been accepted as a valid end point for surgical trials, drug studies, and Food and Drug Administration approval.[11,20,26,27]

We did not see a significant survival advantage for all patients with intermediate-thickness melanomas. This is unsurprising, because the overall event rates, and therefore the power of the study, were lower than anticipated. The rate of false negative biopsy results may have further obscured the therapeutic effect of the intervention.[13] Early in the trial, mapping was performed with the use of blue dye alone, and the study personnel had less technical experience than they did later in the study; these factors are linked to higher false negative rates than are expected currently. Prior analysis of data from this trial showed decreasing rates of false negative results with greater experience.[13] Also, as with all trials of early nodal intervention, most patients in our trial did not have nodal metastases. The trial confirms that in patients without nodal metastases, nodal intervention provides critical prognostic information but no therapeutic benefit.

These results confirm that for patients with intermediate-thickness melanomas who have clinically occult nodal metastases, early intervention decreases the risk of nodal recurrence, distant metastases, and death from melanoma. Increases in distant disease–free survival and melanoma-specific survival were not seen among patients with thick melanomas. Although some patients with nodal metastases from thick melanomas may benefit from lymphadenectomy, our findings suggest that the timing of that intervention is not as critical as it is for patients with intermediate-thickness melanomas; this observation is consistent with the findings in studies from the era of elective lymph-node dissection.[28] The number of patients with thin melanomas in this trial was too small to permit conclusions about the therapeutic effect of biopsy-based treatment in such patients; this is an issue that remains unresolved.

A separate analysis of patients with node-positive disease is justified by the obvious biologic rationale (i.e., only patients with nodal disease can benefit from nodal intervention) and by the close similarity between the node-positive subgroups in the two treatment groups, especially with respect to several robust prognostic indicators: Breslow thickness, ulceration status, sex, and primary tumor site. The cumulative rates of nodal involvement in the two groups were also

similar. This similarity refutes previous assertions regarding false positive sentinel nodes.[29,30] Early in the follow-up period, the cumulative rate of nodal involvement was higher in the biopsy group than in the observation group, a difference that dwindled with increasing follow-up. Any remaining differences in the frequency of nodal metastasis may be accounted for by chance or by late nodal recurrences still pending in the observation group.[31,32] These data indicate that essentially all metastases detected by sentinel-node biopsy eventually would have become clinically evident if not removed.

Despite the consistent strength of the data from the MSLT-I, there has been some reluctance to accept the results of comparisons between node-positive patients in the biopsy group and those in the observation group, because of concern about ascertainment bias. Latent-subgroup analysis methods were used to address this statistical consideration.

Latent-subgroup analysis is used when a characteristic is immediately observable in one study group but not in the other.[17,33] In the MSLT-I, sentinel-node status was known for the biopsy group but not for the observation group. Since a one-to-one relationship between sentinel-node metastases and eventual, clinically detected nodal recurrence cannot be guaranteed, standard survival analyses are potentially biased toward the biopsy group. In latent-subgroup analysis, a semiparametric accelerated-failure-time mixture model is used for the estimation of a biologic treatment effect. This recovers the ability to estimate a treatment effect despite the inability to randomize or stratify on the basis of nodal status at the trial start. In addition, the semiparametric method requires fewer assumptions than would a parametric method. When applied to this final data set, latent-subgroup analysis showed a clear, significant benefit of sentinel-node biopsy: a doubling of melanoma-specific and distant disease–free survival and a tripling of disease-free survival.

These long-term results clearly validate the use of sentinel-node biopsy in patients with intermediate-thickness or thick primary melanomas. The procedure provides accurate and important staging information, enhances regional disease control, and, among patients with nodal metastases, appears to improve melanoma-specific survival substantially.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This article is dedicated to the memory of Donald L. Morton, M.D., an exceptional leader and cancer researcher, who died very shortly before its publication.

APPENDIX

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REFERENCES

1. Snow H. Melanotic cancerous disease. Lancet 1892;2:872.
2. Veronesi U, Adamus J, Bandiera DC, et al. Inefficacy of immediate node dissection in stage 1 melanoma of the limbs. N Engl J Med 1977;297:627-30.
3. Cascinelli N, Morabito A, Santinami M, MacKie RM, Belli F. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. Lancet 1998;351:793-6.
4. Balch CM, Soong S, Ross MI, et al.

Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0 to 4.0 mm). Ann Surg Oncol 2000;7:87-97.
5. Sim FH, Taylor WF, Ivins JC, Pritchard DJ, Soule EH. A prospective randomized study of the efficacy of routine elective lymphadenectomy in management of malignant melanoma: preliminary results. Cancer 1978;41:948-56.
6. Morton DL, Cochran AJ. The case for lymphatic mapping and sentinel lymphadenectomy in the management of primary melanoma. Br J Dermatol 2004;151:308-19.
7. Morton DL, Cagle LA, Wong JH, et al. Intraoperative lymphatic mapping and selective lymphadenectomy: technical details of a new procedure for clinical stage I melanoma. Presented at the 42nd Annual Meeting of the Society of Surgical Oncology, Washington, DC, May 20–22, 1990. abstract.
8. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 1992;127:392-9.
9. Cochran AJ, Morton DL, Stern S, Lana AM, Essner R, Wen DR. Sentinel lymph nodes show profound downregulation of antigen-presenting cells of the paracortex: implications for tumor biology and treatment. Mod Pathol 2001;14:604-8.
10. Thompson JF, McCarthy WH, Bosch CM, et al. Sentinel lymph node status as an indicator of the presence of metastatic melanoma in regional lymph nodes. Melanoma Res 1995;5:255-60.
11. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med 2006;355:1307-17. [Erratum, N Engl J Med 2006;355:1944.]
12. Morton DL, Thompson JF, Essner R, et al. Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. Ann Surg 1999;230:453-63.
13. Morton DL, Cochran AJ, Thompson JF, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. Ann Surg 2005;242:302-11.
14. Morton DL, Hoon DS, Cochran AJ, et al. Lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: therapeutic utility and implications of nodal microanatomy and molecular staging for improving the accuracy of detection of nodal micrometastases. Ann Surg 2003;238:538-49.
15. Morton DL, Wanek L, Nizze JA, Elashoff RM, Wong JH. Improved long-term survival after lymphadenectomy of melanoma metastatic to regional nodes: analysis of prognostic factors in 1134 patients from the John Wayne Cancer Clinic. Ann Surg 1991;214:491-9.
16. Cochran AJ, Wen DR, Herschman HR, Gaynor RB. Detection of S-100 protein as an aid to the identification of melanocytic tumors. Int J Cancer 1982;30:295-7.
17. Chakera AH, Hesse B, Burak Z, et al EANM-EORTC general recommendations for sentinel node diagnostics in melanoma. Eur J Nucl Med Mol Imaging 2009;36:1713-42.
18. Altstein L, Li G. Latent subgroup analysis of a randomized clinical trial through a semiparametric accelerated failure time mixture model. Biometrics 2013;69:52-61.
19. Wong SL, Balch CM, Hurley P, et al. Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guideline. J Clin Oncol 2012;30:2912-8.
20. Morton DL, Cochran AJ, Thompson JF. The rationale for sentinel-node biopsy in primary melanoma. Nat Clin Pract Oncol 2008;5:510-1.
21. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199-206.
22. Balch CM, Gershenwald JE, Soong SJ, et al. Multivariate analysis of prognostic factors among 2,313 patients with stage III melanoma: comparison of nodal micrometastases versus macrometastases. J Clin Oncol 2010;28:2452-9.
23. Eggermont AM, Suciu S, Testori A, et al. Long-term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma. J Clin Oncol 2012;30:3810-8.
24. Garreau JR, Faries M, Ye X, Morton D. Mood state and melanoma outcome in the Multicenter Selective Lymphadenectomy Trial. J Clin Oncol 2009;27:Suppl:15S. abstract.
25. Faries MB, Thompson JF, Cochran A, et al. The impact on morbidity and length of stay of early versus delayed complete lymphadenectomy in melanoma: results of the Multicenter Selective Lymphadenectomy Trial (I). Ann Surg Oncol 2010;17:3324-9.
26. Thomas JM, Newton-Bishop J, A'Hern R, et al. Excision margins in high-risk malignant melanoma. N Engl J Med 2004;350:757-66.
27. Balch CM, Cascinelli N. Sentinel-node biopsy in melanoma. N Engl J Med 2007;356:420-1.
28. Balch CM, Murad TM, Soong SJ, Ingalls AL, Richards PC, Maddox WA. Tumor thickness as a guide to surgical management of clinical stage I melanoma patients. Cancer 1979;43:883-8.
29. Morton DL, Cochran AJ, Thompson JF. Sentinel-node biopsy in melanoma. N Engl J Med 2007;356:419-20.
30. Morton DL, Cochran AJ, Thompson JF. Authors' response to a letter to the editor re: Sentinel node biopsy for early-stage melanoma. Ann Surg 2007;245:828-9.
31. Shen P, Guenther JM, Wanek LA, Morton DL. Can elective lymph node dissection decrease the frequency and mortality rate of late melanoma recurrences? Ann Surg Oncol 2000;7:114-9.
32. Faries MB, Steen S, Ye X, Sim M, Morton DL. Late recurrence in melanoma: clinical implications of lost dormancy. J Am Coll Surg 2013;217:27-34.
33. Altstein LL, Li G, Elashoff RM. A method to estimate treatment efficacy among latent subgroups of a randomized clinical trial. Stat Med 2011;30:709-17.