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## Sentinel-Node Biopsy or Nodal Observation in Melanoma

Donald L. Morton, M.D., John F. Thompson, M.D., Alistair J. Cochran, M.D., Nicola Mozzillo, M.D., Robert Elashoff, Ph.D., Richard Essner, M.D., Omgo E. Nieweg, M.D., Ph.D., Daniel F. Roses, M.D., Harald J. Hoekstra, M.D., Ph.D., Constantine P. Karakousis, M.D., Ph.D., Douglas S. Reintgen, M.D., Brendon J. Coventry, M.D., Edwin C. Glass, M.D., and He-Jing Wang, M.D., for the MSLT Group\*

### ABSTRACT

#### BACKGROUND

We evaluated the contribution of sentinel-node biopsy to outcomes in patients with newly diagnosed melanoma.

#### METHODS

Patients with a primary cutaneous melanoma were randomly assigned to wide excision and postoperative observation of regional lymph nodes with lymphadenectomy if nodal relapse occurred, or to wide excision and sentinel-node biopsy with immediate lymphadenectomy if nodal micrometastases were detected on biopsy.

#### RESULTS

Among 1269 patients with an intermediate-thickness primary melanoma, the mean ( $\pm$ SE) estimated 5-year disease-free survival rate for the population was  $78.3\pm 1.6\%$  in the biopsy group and  $73.1\pm 2.1\%$  in the observation group (hazard ratio for death, 0.74; 95% confidence interval [CI], 0.59 to 0.93;  $P=0.009$ ). Five-year melanoma-specific survival rates were similar in the two groups ( $87.1\pm 1.3\%$  and  $86.6\pm 1.6\%$ , respectively). In the biopsy group, the presence of metastases in the sentinel node was the most important prognostic factor; the 5-year survival rate was  $72.3\pm 4.6\%$  among patients with tumor-positive sentinel nodes and  $90.2\pm 1.3\%$  among those with tumor-negative sentinel nodes (hazard ratio for death, 2.48; 95% CI, 1.54 to 3.98;  $P<0.001$ ). The incidence of sentinel-node micrometastases was 16.0% (122 of 764 patients), and the rate of nodal relapse in the observation group was 15.6% (78 of 500 patients). The corresponding mean number of tumor-involved nodes was 1.4 in the biopsy group and 3.3 in the observation group ( $P<0.001$ ), indicating disease progression during observation. Among patients with nodal metastases, the 5-year survival rate was higher among those who underwent immediate lymphadenectomy than among those in whom lymphadenectomy was delayed ( $72.3\pm 4.6\%$  vs.  $52.4\pm 5.9\%$ ; hazard ratio for death, 0.51; 95% CI, 0.32 to 0.81;  $P=0.004$ ).

#### CONCLUSIONS

The staging of intermediate-thickness (1.2 to 3.5 mm) primary melanomas according to the results of sentinel-node biopsy provides important prognostic information and identifies patients with nodal metastases whose survival can be prolonged by immediate lymphadenectomy. (ClinicalTrials.gov number, NCT00275496.)

From the Departments of Surgical Oncology (D.L.M., R. Essner) and Biostatistics (R. Elashoff, H.-J.W.), John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, CA; the Sydney Melanoma Unit, Royal Prince Alfred Hospital, Camperdown, NSW, Australia (J.F.T.); the Department of Pathology and Laboratory Medicine, University of California at Los Angeles, Los Angeles (A.J.C.); the Department of Surgical Oncology, National Cancer Institute, Naples, Italy (N.M.); the Department of Biostatistics, University of California at Los Angeles, Los Angeles (R. Elashoff, H.-J.W.); the Department of Surgery, Netherlands Cancer Institute, Amsterdam (O.E.N.); the Department of Surgery, New York University School of Medicine, New York (D.F.R.); the Department of Surgical Oncology, University Medical Center Groningen and Groningen University, Groningen, the Netherlands (H.J.H.); the Department of Surgery, Millard Fillmore Hospital, Buffalo, NY (C.P.K.); the Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL (D.S.R.); the Department of Surgery, Royal Adelaide Hospital, Adelaide, SA, Australia (B.J.C.); and the Department of Nuclear Medicine, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles (E.C.G.). Address reprint requests to Dr. Morton at the John Wayne Cancer Institute at Saint John's Health Center, 2200 Santa Monica Blvd., Santa Monica, CA 90404, or at [mortond@jwci.org](mailto:mortond@jwci.org).

\*Members of the Multicenter Selective Lymphadenectomy Trial (MSLT) Group are listed in the Appendix.

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**I**N MOST PATIENTS WITH CLINICALLY LOCALIZED melanoma of intermediate thickness, wide resection is curative, but metastasis to regional nodes develops in 15 to 20%. Since metastasis to a regional node is the most important prognostic factor in early-stage melanoma,<sup>1,2</sup> immediate (elective) lymphadenectomy has been advocated to improve tumor staging and possibly survival.<sup>3,4</sup> However, this approach exposes patients to complications resulting from the procedure and has not been shown to improve overall survival<sup>5</sup>; in a minority of patients with occult nodal metastases, however, it may have benefit.<sup>3,4</sup>

We developed a technique for lymphatic mapping and sentinel-node biopsy as a minimally invasive surgical alternative to elective lymph-node dissection for nodal staging to identify patients with occult nodal metastases who might benefit from total lymphadenectomy.<sup>6-9</sup> Vital blue dye and radiocolloid were used to map the lymphatic drainage from a primary cutaneous melanoma to a tumor-draining regional lymph node (or nodes). (A Video of the mapping and surgical procedures is in the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org).) Lymphatic mapping shows the anatomical path of metastatic melanoma cells from the primary melanoma and accurately identifies for pathological scrutiny the node, known as the sentinel node, that receives lymph directly from a primary melanoma. The sentinel node, as compared with other regional nodes, is most susceptible to the immunosuppressive influences of the tumor<sup>10</sup> and is the initial site of regional nodal metastases. If the sentinel node is free of melanoma, the remaining nodes in the regional basin will also be tumor-free.<sup>8,11-13</sup> If, however, the sentinel node contains metastases, other nodes in the basin may also contain metastatic melanoma. The American Joint Committee on Cancer (AJCC) has incorporated the tumor status of the sentinel node into its staging system for melanoma.<sup>14</sup> Moreover, the tumor status of the sentinel node accurately reflects the status of the regional nodes in breast, colon, and lung cancers.

The Multicenter Selective Lymphadenectomy Trial (MSLT) was initiated on January 4, 1994, to study the usefulness of sentinel-node biopsy in the identification of patients with clinically occult nodal metastases and to evaluate the clinical effect of immediate, complete lymphadenectomy in patients with tumor-positive sentinel nodes. Enrollment in the trial closed in March 2002.<sup>15,16</sup>

After the third planned interim analysis, the data and safety monitoring committee recommended publication of data with implications for the management of early-stage melanoma. The data on surgical complications and the accuracy of sentinel-node biopsy have been published elsewhere<sup>16</sup>; this report presents interim data on the efficacy end points of the trial.

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## METHODS

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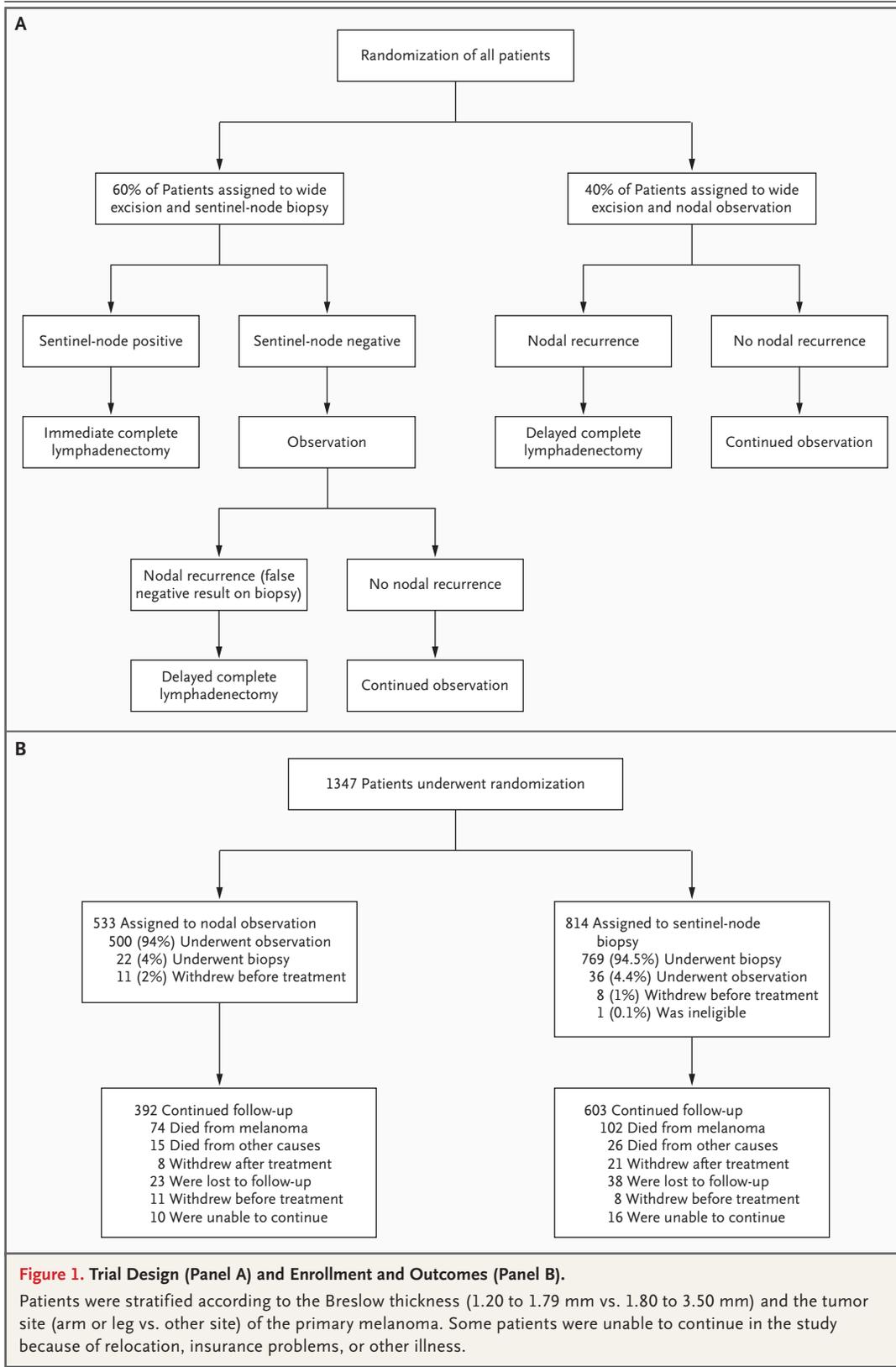
### TRIAL DESIGN

Patients with clinically localized primary cutaneous melanoma were randomly assigned to undergo either wide excision and sentinel-node biopsy (the biopsy group) or wide excision and postoperative observation of the regional nodal basin (the observation group). In the observation group, delayed lymphadenectomy was performed if nodal recurrences became clinically detectable; in the biopsy group, immediate lymphadenectomy was performed if micrometastases were detected in the sentinel-node biopsy. The sentinel nodes were examined in multiple permanent sections of tissue stained with hematoxylin and eosin and by immunohistochemical analysis with the use of antibodies to the melanoma-associated antigens S-100, HMB-45, and MART-1 or Melan-A.<sup>8,15,16</sup> If the node was found to contain metastases, a complete lymphadenectomy was performed shortly thereafter (Fig. 1A).

### PATIENTS

Eligible patients had invasive primary cutaneous melanomas that were classified as Clark level III with a Breslow thickness of 1 mm or more, or as Clark level IV or V with any Breslow thickness. The inclusion and exclusion criteria of the study have been described elsewhere.<sup>16</sup> Patients with melanomas 1.2 to 3.5 mm in thickness were selected as the primary study group, because pretrial statistical modeling on the basis of data from the prospective melanoma database of the John Wayne Cancer Institute<sup>1,17</sup> indicated that the timing of a complete lymphadenectomy (immediate elective surgery or delayed until nodal relapse) probably affects survival among patients with melanomas that are within this range.

Patients who gave written informed consent to participate were randomly assigned to biopsy or observation in a 60:40 ratio. All patients underwent wide excision of the primary melanoma<sup>16</sup> and were monitored postoperatively by means



of clinical examination, blood tests, and chest radiography at least 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.

#### STATISTICAL ANALYSIS

The primary end point was melanoma-specific survival (survival until death from melanoma). Other planned end points were disease-free survival before a first recurrence at any site (survival without evidence of recurrence or metastasis); melanoma-specific survival and disease-free survival with tumor-positive or tumor-negative sentinel nodes; the incidence of nodal metastasis as identified on pathological examination of a specimen of the sentinel node or on clinical examination during observation or after a sentinel-node biopsy with a false negative result; and survival with or without nodal metastases detected on biopsy or during observation. Follow-up and survival were calculated from the date of randomization to the date of the last examination or death.

Randomization was carried out centrally, in a stratified fashion, in random permuted blocks of four, six, and eight patients. The stratification factors were Breslow thickness (1.20 to 1.79 mm vs. 1.80 to 3.50 mm) and the primary site of the melanoma (arm or leg vs. other site). The initial planned sample size of 900 patients was calculated on the basis of a type I error rate of 5%, and a statistical power of 90% to detect melanoma-specific survival, and the sample size was derived by simulating stratification into four subgroups with negligible loss to follow-up (5%). The treatment effect was the Kaplan–Meier estimate of melanoma-specific survival among patients with the same prognostic factors who underwent early, as compared with delayed, lymphadenectomy (on the basis of data from the melanoma database of the John Wayne Cancer Institute).<sup>15,17</sup> At the second of four planned interim analyses, the sample size was increased to 1200 patients, because the distribution of those entering the trial was skewed toward patients at lower risk for recurrence or death, and therefore there were fewer events than expected. The final number of patients undergoing randomization was 1347, to balance the accrual among participating centers and to include patients who had given informed consent before enrollment was closed.

The planned statistical analysis for the primary and secondary end points was carried out by

the log-rank test. The censoring of deaths not due to melanoma and the treatment of such deaths as a competing risk yielded closely similar results for the primary end point. The Kaplan–Meier method was used to estimate mean ( $\pm$ SE) 5-year melanoma-specific survival and disease-free survival for the population, and the results were reported at particular times after randomization. A Cox proportional-hazards regression model was used that included sentinel-node status, Breslow thickness, Clark level, anatomic site of the primary melanoma, presence or absence of ulceration, age, and sex. The baseline demographic and clinical characteristics of the patients and the pathological factors were summarized with the use of descriptive statistics and were compared with the use of a t-test or the chi-square test. The numbers of tumor-involved nodes in the two study groups were compared by the Wilcoxon rank-sum test, and the distribution of nodal stage according to the AJCC classification system was compared by the chi-square test. All analyses were performed with the use of SAS software, version 9.1, and all reported P values are two-sided with a value of less than 0.05 considered to indicate statistical significance.

Comparisons of overall disease-free survival and melanoma-specific survival between the two study groups were based on 1269 patients who received the assigned treatment. The analysis of the subgroups of patients with nodal metastases was based on 764 patients in the biopsy group for whom complete information on nodal status was available and 500 patients in the observation group. Parallel analyses according to the intention-to-treat principle included 1327 patients; the results were consistent with those of the analysis involving 1269 patients.

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#### RESULTS

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Between January 20, 1994, and March 29, 2002, 1347 patients who underwent randomization (those with primary melanomas 1.2 to 3.5 mm in thickness) were enrolled. Nineteen patients dropped out after undergoing randomization and 1 patient was ineligible because of the presence of clinically palpable lymph nodes; the analysis includes the remaining 1327 patients (Fig. 1B): 221 from North America, 386 from Europe, and 720 from Australia. All patients had primary melanomas with closely similar characteristics (Table 1). During this period, 654 patients with lesions

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	All Patients†		Patients with Nodal Metastases‡		
	Observation (N=500)	Biopsy (N=769)	Observation (N=78)§	Biopsy, Positive Node (N=122)¶	Biopsy, False Negative Node (N=26)‖
<b>Patients</b>					
Male sex — %	55.0	58.0	60.3	60.7	65.4
Age — yr					
Mean ±SD	52.1±13.9	52.0±13.7	54.1±12.5	49.4±14.1	50.1±16.0
Median	53	53	54	50	51
<b>Primary melanoma</b>					
Location — %					
Arm or leg	42.6	46.6	43.6	36.1	34.5
Other site	57.4	53.4	56.4	63.9	65.5
Breslow thickness — mm					
Mean ±SD	2.01±0.65	1.98±0.63	2.31±0.65	2.19±0.63	2.26±0.67
Median	1.90	1.80	2.20	2.10	2.15
Clark level — %					
III	41.0	43.7	41.0	36.1	46.2
IV	57.4	55.3	56.4	63.9	53.8
V	1.6	1.0	2.6	0	0
Ulceration — %					
Present	29.0	26.3	30.8	30.3	38.5
Absent	62.8	63.8	57.7	56.6	53.8
Unknown	8.2	9.8	11.5	13.1	7.7
<b>Nodal metastasis — % (no./total no.)</b>	15.6 (78/500)	16.0 (122/764)**			
Breslow thickness — % (no./total no.)††					
1.20–1.79 mm	7.9 (17/214)	9.9 (33/334)	21.8	27.0	23.1
1.80–3.50 mm	21.3 (61/286)	20.7 (89/430)	78.2	73.0	76.9
Positive nodes‡‡					
1 — %			39.2	70.5	61.9
2 or 3 — %			35.1	27.9	9.5
4 or more — %			25.7	1.6	28.6
No. of positive nodes — mean ±SE			3.3±0.5	1.4±0.1	4.3±1.6
Site of first recurrence — no. (%)					
Nodal	65 (13.0)	32 (4.2)			
Distant	39 (7.8)	85 (11.0)			
Local or in-transit	30 (6.0)	42 (5.5)			
<b>No recurrence — no. (%)</b>	366 (73.2)	610 (79.3)			

\* According to the trial criteria, the primary melanoma had to be 1.2 to 3.5 mm in thickness in the prespecified primary study group. Because of rounding, percentages may not total 100.

† There was no significant difference between the two groups for all prognostic factors.

‡ There was no significant difference among the three subgroups regarding all prognostic factors except age: patients in the biopsy group with a positive sentinel node were, on average, 4 years younger than those in the observation group with nodal metastases ( $P=0.02$ , by the t-test).

§ These patients had nodal relapse and underwent delayed lymphadenectomy.

¶ These patients underwent immediate lymphadenectomy.

‖ These patients had nodal relapse after a false negative result on biopsy and underwent delayed lymphadenectomy.

\*\* Five patients in the biopsy group were not included in the analysis because the pathological report on the sentinel node was not available.

†† Among patients with nodal relapse, the total number is the number of patients in the observation group. Among those with positive sentinel nodes, the total number is the number of patients in the biopsy group.

‡‡ Data on the number of tumor-positive nodes in the specimen obtained on lymphadenectomy were missing for four patients in the observation group who underwent delayed lymphadenectomy and five patients who underwent lymphadenectomy for a recurrence after a false negative result on biopsy. One positive node is equivalent to AJCC nodal stage 1, two or three positive nodes are equivalent to AJCC nodal stage 2, and four or more positive nodes are equivalent to AJCC nodal stage 3. The number of positive nodes and the distribution according to AJCC nodal stage differed significantly in the two groups ( $P<0.001$  by the Wilcoxon rank-sum test and the chi-square test, respectively).

thinner than 1.2 mm and thicker than 3.5 mm entered the initial MSLT study; data on these patients were used to evaluate surgical morbidity and accuracy, as previously reported.<sup>16</sup>

#### SURVIVAL RATES

After a median follow-up of 59.8 months, the frequency of relapse at any site was 26.8% (134 of 500 patients) in the observation group and 20.7% (159 of 769) in the biopsy group (Table 1). The disease-free survival rate was significantly higher in the biopsy group than in the observation group at 5 years (78.3±1.6% vs. 73.1±2.1%; hazard ratio, 0.74; 95% confidence interval [CI], 0.59 to 0.93;  $P=0.009$ ) (Fig. 2A). Among the 1269 patients who received the assigned treatment, the rate of death from melanoma (melanoma-specific death) was similar in the two groups at 5 years: 13.8% (69 of 500 patients) in the observation group and 12.5% (96 of 769 patients) in the biopsy group. The melanoma-specific survival rate was also similar in the two groups: 90.1±1.4% and 93.2±0.9%, respectively, at 3 years, and 86.6±1.6% and 87.1±1.3%, respectively, at 5 years (hazard ratio, 0.92; 95% CI, 0.67 to 1.25;  $P=0.58$ ) (Fig. 2B).

#### PROGNOSIS AND SENTINEL-NODE STATUS

The melanoma-specific mortality rate in the biopsy group was 9.7% (62 of 642 patients) when the sentinel node was tumor-free and 26.2% (32 of 122) if the node contained metastases. At 5 years, the estimated disease-free survival rate was 53.4±4.9% if the sentinel node contained metastases and 83.2±1.6% if the node was free of metastases ( $P<0.001$ ) (Fig. 2C); the corresponding values for melanoma-specific survival were 72.3±4.6% and 90.2±1.3%, respectively ( $P<0.001$ ) (Fig. 2D). In the biopsy group, among patients with tumor-positive sentinel nodes, as compared with patients with tumor-free sentinel nodes, the hazard ratio for death was 2.48 (95% CI, 1.54 to 3.98;  $P<0.001$ ), and the hazard ratio for recurrence of melanoma was 3.04 (95% CI, 2.11 to 4.39;  $P<0.001$ ) in the multivariate Cox model that included the Clark level, Breslow thickness, presence or absence of ulceration, site of primary melanoma, age, and sex (Table 2).

#### PRESENCE OF NODAL METASTASES

After a median follow-up of 59.8 months, 78 of the 500 patients in the observation group (15.6%) had a clinical relapse detected in regional nodes (Table 1), with a cumulative predicted incidence

of 18.5±2.1% according to the Kaplan–Meier method after 8 years of follow-up (Fig. 3A). The median time to clinical detection of nodal relapse among the 78 patients was 1.33 years (95% CI, 1.02 to 1.76).

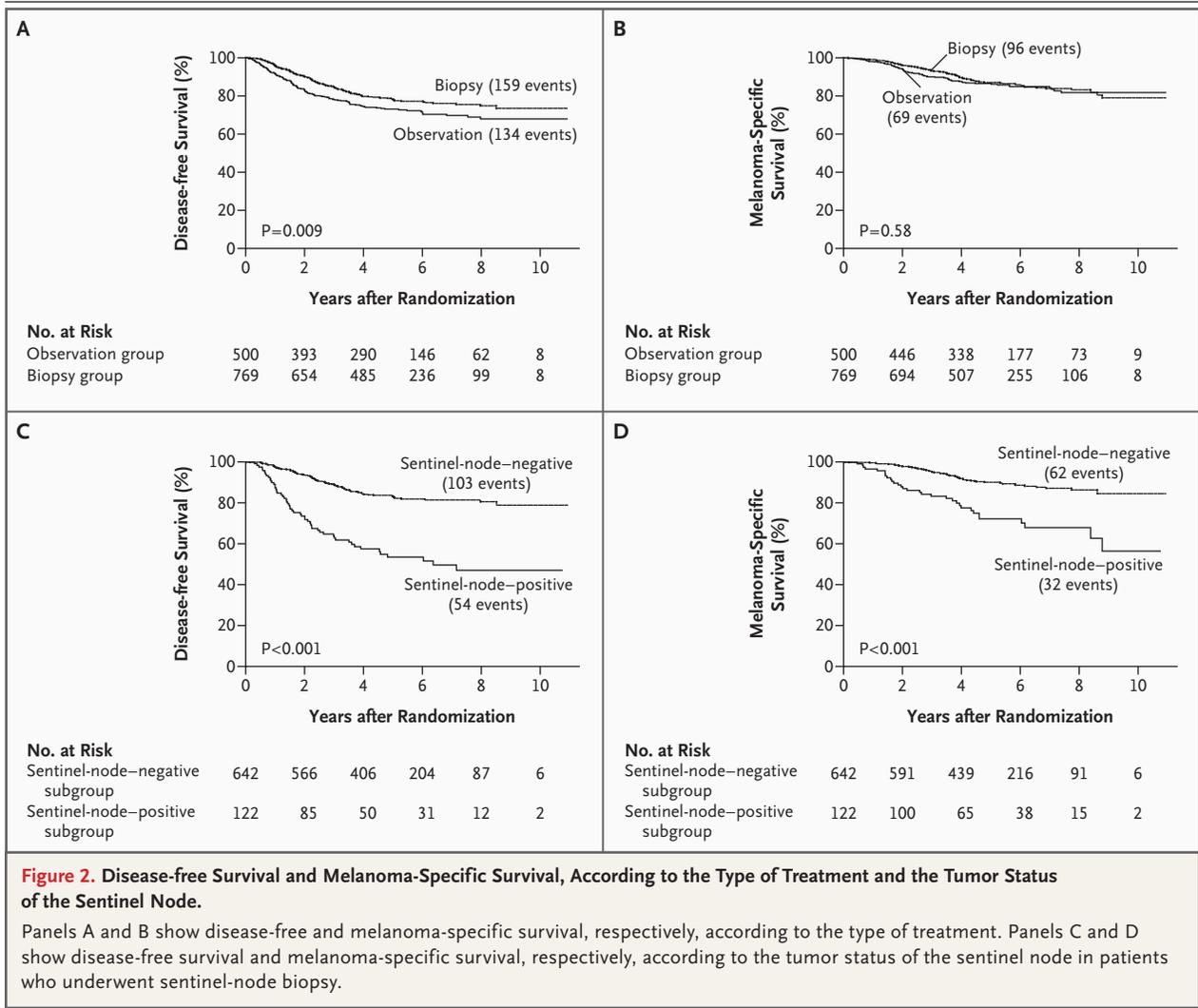
The histopathological status of the sentinel node was available for 764 of 769 patients in the biopsy group: in 122 (16.0%) of these patients, the specimens were tumor-positive. After a median follow-up of 59.8 months, a nodal recurrence was detected in 26 patients (3.4%) with a tumor-negative sentinel node on biopsy. Thus, the proportion of patients with nodal metastases in the biopsy group was 19.4% (148 of 764) (Fig. 3B). The rate of false negative results was 3.4%, which is within the range predicted on the basis of our experience (1.7%)<sup>18</sup> and reported in the literature (1.5%).<sup>19</sup>

#### NODAL METASTASES AND SURVIVAL

The distribution of prognostic factors between the two groups among patients with nodal metastases did not differ significantly except in relation to age (Table 1). After a median of 48.4 months, the rate of melanoma-specific deaths in the biopsy group was 26.2% (32 of 122 patients) among those who underwent immediate lymphadenectomy, as compared with 48.7% (38 of 78) in the observation group among those who underwent delayed lymphadenectomy. The corresponding rates of 5-year survival in these prespecified subgroups were 72.3±4.6% and 52.4±5.9%, respectively (hazard ratio for death, 0.51; 95% CI, 0.32 to 0.81;  $P=0.004$  by the log-rank test and  $P=0.007$  by the Cox model) (Fig. 3B).

Survival rates among patients with a nodal recurrence after a false negative result on biopsy were similar to those among patients with nodal relapse during observation (estimated 3-year survival, 68.4±9.3% and 64.9±5.4%, respectively;  $P=0.60$ ) (Fig. 3B); the 5-year survival rate was significantly higher in the biopsy group among patients with nodal metastases detected on biopsy or after a false negative biopsy than in the observation group among those with nodal recurrence (66.2±4.4% vs. 54.2±5.9%; hazard ratio for death, 0.62; 95% CI, 0.40 to 0.95;  $P=0.02$ ) (Fig. 3B).

Nodal metastases did not occur in 616 patients in the biopsy group and in 422 patients in the observation group. The 5-year survival rate in the two groups was similar (92.9±1.3% and 92.4±1.2%, respectively;  $P=0.98$ ) (Fig. 3C), indicating that survival among patients without regional



nodal metastases was unaffected by sentinel-node biopsy. The frequency of local or in-transit (regional endolymphatic) recurrence did not differ significantly at 5 years between the biopsy and observation groups ( $7.7\pm 1.0\%$  and  $8.4\pm 1.3\%$ , respectively;  $P=0.38$ ) (Fig. 3D).

#### TUMOR-INVOLVED REGIONAL NODES

AJCC nodal stage (defined according to the number of tumor-positive nodes), which is a surrogate for the risk of death from melanoma,<sup>2,14</sup> differed according to whether nodal metastases were identified during observation or on biopsy: 39.2% of patients with metastasis in the observation group were in nodal stage 1, as compared with 70.5% of such patients in the biopsy group ( $P<0.001$ ); the proportions in nodal stage 3 were 25.7% and 1.6%, respectively ( $P<0.001$ ) (Table 1). In the observa-

tion group, the mean ( $\pm$ SE) number of clinically detectable tumor-positive nodes in patients who underwent delayed lymphadenectomy was  $3.3\pm 0.5$ ; in the biopsy group, the mean number of clinically occult tumor-positive nodes among those who underwent immediate lymphadenectomy was  $1.4\pm 0.1$  ( $P<0.001$ ) (Table 1). Patients with nodal relapse after a false negative result on biopsy had more tumor-containing nodes than did those who underwent immediate lymphadenectomy after a positive result on biopsy ( $4.3\pm 1.6$  vs.  $1.4\pm 0.1$ ) (Table 1).

#### DISCUSSION

This third interim analysis of the results of the MSLT provides data of practical importance in the treatment of patients with melanoma. Our re-

**Table 2.** Cox Multivariate Analysis of the Prognostic Value of Various Factors for Patients Assigned to Sentinel-Node Biopsy.

Factor	Disease Recurrence		Death from Melanoma	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Sentinel-node status (positive vs. negative)	3.04 (2.11–4.39)	<0.001	2.48 (1.54–3.98)	<0.001
Breslow thickness (per mm)	1.74 (1.35–2.24)	<0.001	1.66 (1.20–2.30)	0.002
Ulceration (present vs. absent)	1.49 (1.06–2.08)	0.02	1.70 (1.11–2.62)	0.02
Site of melanoma				
Arm or leg	1.00*		1.00*	
Trunk	1.35 (0.94–1.94)	0.11	1.74 (1.08–2.81)	0.02
Head or neck	1.08 (0.65–1.81)	0.76	1.18 (0.59–2.35)	0.64
Sex (male vs. female)	1.00 (0.70–1.41)	0.99	1.34 (0.84–2.15)	0.22
Age (per yr of age)	1.02 (1.01–1.03)	0.005	1.01 (0.99–1.03)	0.22
Clark level				
III	1.00*		1.00*	
IV	1.14 (0.81–1.60)	0.46	0.93 (0.60–1.45)	0.75
V	1.06 (0.25–4.52)	0.94	1.48 (0.33–6.61)	0.61

\* This group served as the reference group.

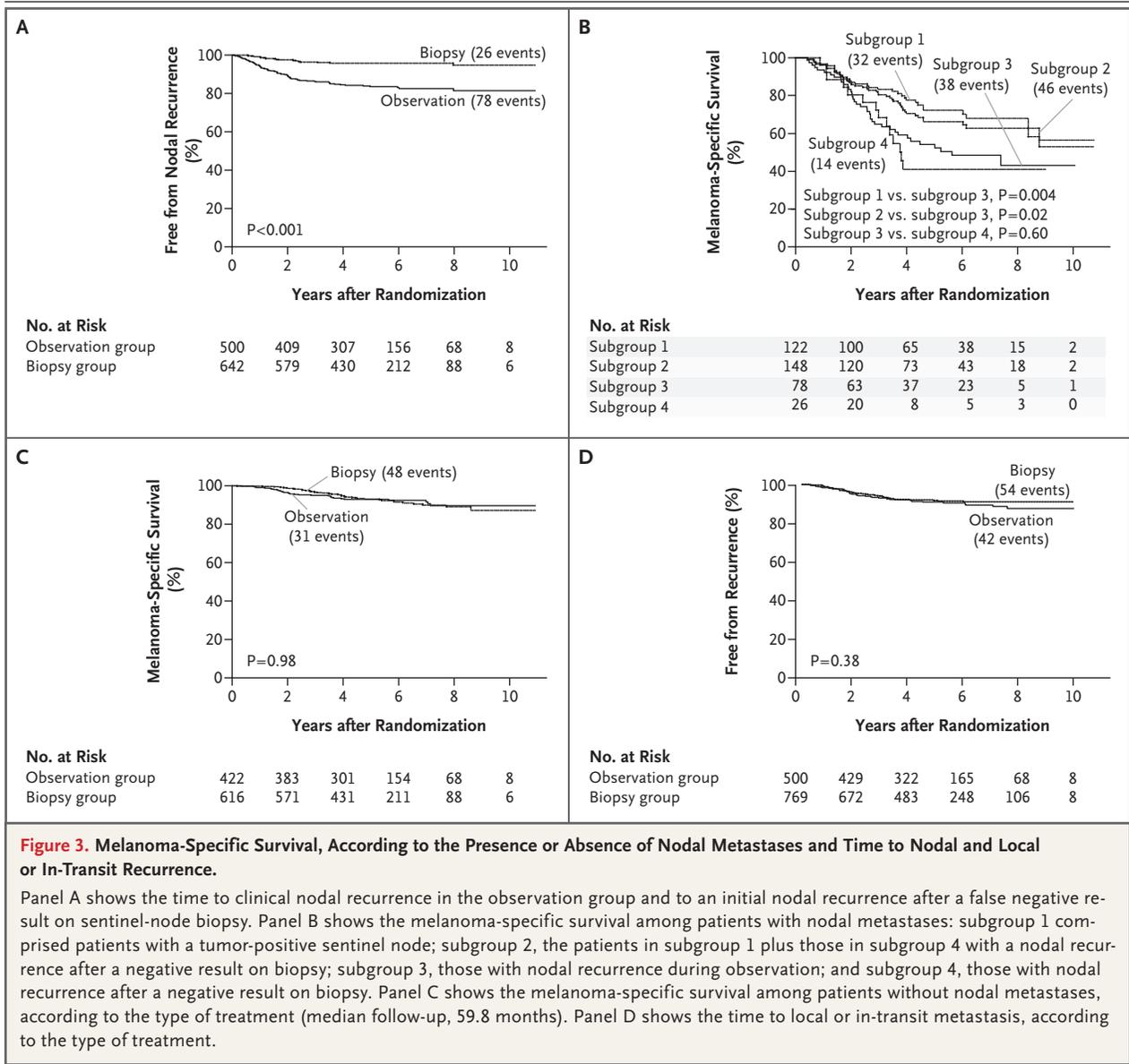
sults confirm that sentinel-node biopsy has a high value for staging clinically localized, intermediate-thickness melanoma and provides a more accurate basis for formulating a prognosis than do standard demographic and histopathological factors (Table 2). The presence or absence of tumor cells in the sentinel node is critical to both accurate AJCC staging<sup>14</sup> and decisions regarding lymphadenectomy and adjuvant therapy. Moreover, long-term follow-up of the patients in the MSLT indicates that experience gained from performing 55 or more sentinel-node biopsies<sup>16</sup> is required to carry out the procedure in a manner that reliably reduces nodal relapse.<sup>15-17</sup>

This interim analysis did not reveal a significant difference in melanoma-specific survival between the two study groups, but it did show that biopsy with immediate lymphadenectomy prolonged disease-free survival and diminished the trauma of recurrence (Fig. 2A).<sup>20,21</sup> Observation allows nodal micrometastases to enlarge<sup>22</sup> and spread to other nodes, thereby increasing the risk of distant metastases and decreasing the chance of long-term survival<sup>2,15,16,17,23</sup> (Table 1 and Fig. 3B). Immediate lymphadenectomy in patients with subclinical sentinel-node metastases increased the melanoma-specific 5-year survival rate, as compared with delayed lymphadenectomy for clinically detected nodal relapse (72.3%

vs. 52.4%; hazard ratio for death, 0.51; 95% CI, 0.32 to 0.81;  $P=0.004$ ) (Fig. 3B). We did not expect that the removal of tumor-free regional nodes would improve survival — indeed, biopsy did not improve survival among patients without nodal metastases (Fig. 3C).

Our findings are consistent with those of analyses of data of single-center<sup>1</sup> and international<sup>2</sup> studies and those of a smaller prospective, randomized trial conducted by the World Health Organization Melanoma Program<sup>3</sup>: all show improved long-term survival when lymphadenectomy is performed for microscopic rather than clinically detectable nodal disease. Our findings provide support for the matched-pair analyses by the John Wayne Cancer Institute, which showed a survival benefit from immediate lymphadenectomy, as compared with delayed lymphadenectomy, in patients with nodal metastases.<sup>17</sup> We also confirmed that the incidence of local or in-transit metastases was not increased among patients treated with sentinel-node biopsy.<sup>24-26</sup>

Because occult nodal metastases could not be identified before patients entered the trial, we relied on randomization to ensure a balance between the two study groups. As shown in Table 1, this balance was achieved with respect to Clark level, Breslow thickness, and the presence or absence of ulceration — features that correlate with



occult nodal metastases.<sup>8,11,13,16,23</sup> The striking similarity between the incidence of sentinel-node micrometastases and the frequency of nodal relapse during observation further suggests a balanced distribution: the projected frequency of palpable nodal relapse ( $\pm$ SE) at 8 years was  $18.5\pm 2.1\%$  in the observation group (Fig. 3A), whereas in the biopsy group the incidence of sentinel-node micrometastases or nodal relapse after a false negative result on biopsy was 19.4% (Table 1).

Our results provide evidence that occult micrometastases in the sentinel node usually progress to aggressive regional or distant disease. Were

this not the case, we would not have seen an overall improvement in disease-free survival among the patients assigned to biopsy (Fig. 2A), nor would there have been a significant difference in the rate of nodal relapse between patients with tumor-negative sentinel nodes and those assigned to observation (4.0% [26 of 642 patients] vs. 15.6% [78 of 500],  $P<0.001$ ) (Fig. 3A). The influence of the tumor status of the sentinel node on disease-free survival and melanoma-specific survival (Fig. 2C and 2D) ( $P<0.001$  for both comparisons) also indicates the aggressiveness of sentinel-node micrometastases.

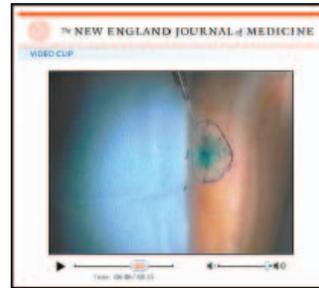
Our findings indicate that sentinel-node biopsy has staging and prognostic value in patients with intermediate-thickness melanoma and, coupled with immediate complete lymphadenectomy, improves survival among patients with a tumor-positive sentinel node. In patients with primary melanomas that are 1.2 to 3.5 mm in thickness, sentinel-node biopsy should be preferred to observation.

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A video showing sentinel-node biopsy is available with the full text of this article at [www.nejm.org](http://www.nejm.org).

#### APPENDIX

The MSLT participants were as follows: **Independent data and safety monitoring committee** — J. Kirkwood (chair), J. Daly, M. Kutner, M. Mihm, G. Smith, M. Urist, N. Beegun (patient advocate); **Trial sites and principal investigators** — Sydney Melanoma Unit, Sydney, Australia: J.F. Thompson; Istituto Nazionale dei Tumori de Napoli, Naples, Italy: N. Mozzillo; Netherlands Cancer Institute, Amsterdam: O.E. Nieweg; New York University, New York: D.F. Roses; University Medical Center Groningen and University of Groningen, Groningen, the Netherlands: H.J. Hoekstra; Millard Fillmore Hospital, Buffalo, NY: C.P. Karakousis; H. Lee Moffitt Cancer Center, Tampa, FL: D.S. Reintgen; University of California and Mt. Zion Medical Center, San Francisco: S.P.L. Leong; Royal Adelaide Hospital, Adelaide, Australia: B.J. Coventry; Roswell Park Cancer Institute, Buffalo, NY: W. Kraybill; Princess Alexandra Hospital, Brisbane, Australia: M. Smithers; Henry Ford Hospital, Detroit: S.D. Nathanson; University of Texas Southwestern Medical Center at Dallas, Dallas: J.F. Huth; University of Hawaii at Manoa, Honolulu: J.H. Wong; University of Pennsylvania, Philadelphia: D.L. Fraker; Tom Baker Cancer Centre, Calgary, AB, Canada: W. Temple; City Hospital of Nürnberg, Nürnberg, Germany: E. Paul; John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, CA: D.L. Morton.

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