Sentinel-Node Biopsy or Nodal Observation in Melanoma

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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 (±SE) estimated 5-year disease-free survival rate for the population was 78.3±1.6% in the biopsy group and 73.1±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±1.3% and 86.6±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±4.6% among patients with tumor-positive sentinel nodes and 90.2±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±4.6% vs. 52.4±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.)

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

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pat
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with
clinically
lo
calized
melanoma
of
intermediate
thick
ess,
wide
resec
tion
is
curative,
but
meta
tasis
to
regional
nodes
develops
in
15
to
20%.
Since
meta
tasis
to
a
regional
node
is
the
most
important
prognostic
factor
in
early
stage
melanoma,
immedi
ate
(elective)
lymphadenectomy
has
been
advocated
to
improve
tumor
staging
and
possibly
survival.
However,
this
approach
exposes
patients
to
complications
resulting
from
the
procedure
and
has
not
been
shown
to
improve
overall
survival
in
a
minority
of
patients
with
occult
nodal
metastases,
however,
it
may
have
benefit.

We
developed
a
technique
for
lymphatic
mapping
and
sentinel-node
biopsy
as
a
minimally
invasive
sur
gical
treatment
to
elective
lymph-node
dissection
for
nodal
staging
to
identify
patients
with
occult
nodal
metastases
who
might
benefit
from
total
lymphadenectomy.
Vital
dye
and
radio
collod
were
used
to
map
the
lymphatic
drainage
from
a
primary
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.nej
.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
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.
If,
however,
the
sentinel
node
contains
metastases,
other
nodes
in
the
basin
may
also
contain
metastatic
melanoma.

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.

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
sur
genical
complications
and
the
accuracy
of
sentinel-node
biopsy
have
been
published
elsewhere;
this
report
presents
interim
data
on
the
efficacy
end
points
of
the
trial.

METH
ODS

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
immuno
histochemical
analysis
with
the
use
of
antibodies
to
the
melanoma-associated
antigens
S-100,
HMB-45,
and
MART-1
or
Melan-A.
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
classic
level
III
with
a
Breslow
thickness
of
1
mm
or
more,
or
as
classic
level
IV
or
V
with
any
Breslow
thickness.
The
inclusion
and
exclusion
criteria
of
the
study
have
been
described
elsewhere.

Patients
with
melanomas
1.2
to
3.5
mm
in
thickness
were
selected
as
the
primary
study
group,
because
pretrial
 sta
tistical
modeling
on
the
basis
of
data
from
the
prospective
melanoma
database
of
the
John
Wayne
Cancer
Institute
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
and
were
monitored
postoperatively
by
means
of
the
new
england
journal
do
medicine

October
28,
2006

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WWW.NEJM.ORG
September
28, 2006

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Randomization of all patients

60% of Patients assigned to wide excision and sentinel-node biopsy

Sentinel-node positive

Immediate complete lymphadenectomy

Sentinel-node negative

Observation

Nodal recurrence

Delayed complete lymphadenectomy

No nodal recurrence

Continued observation

Nodal recurrence (false negative result on biopsy)

Delayed complete lymphadenectomy

No nodal recurrence

Continued observation

392 Continued follow-up
74 Died from melanoma
15 Died from other causes
8 Withdrew after treatment
23 Were lost to follow-up
11 Withdrew before treatment
10 Were unable to continue

814 Assigned to sentinel-node biopsy
769 (94.5%) Underwent biopsy
36 (4.4%) Underwent observation
8 (1%) Withdrew before treatment
1 (0.1%) Was ineligible

533 Assigned to nodal observation
500 (94%) Underwent observation
11 (2%) Withdrew before treatment

1347 Patients underwent randomization

 Patients were stratified according to the Breslow thickness (1.20 to 1.79 mm vs. 1.80 to 3.50 mm) and the tumor site (arm or leg vs. other site) of the primary melanoma. Some patients were unable to continue in the study because of relocation, insurance problems, or other illness.
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). 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 (±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.

**Results**

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

* 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.
‡‡‡ 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.16

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 mortality rate 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%)18 and reported in the literature (1.5%).19

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±1.0% and 8.4±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, 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 observation group, the mean (±SE) number of clinically detectable tumor-positive nodes in patients who underwent delayed lymphadenectomy was 3.3±0.5; in the biopsy group, the mean number of clinically occult tumor-positive nodes among those who underwent immediate lymphadenectomy was 1.4±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±1.6 vs. 1.4±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-
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 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 is required to carry out the procedure in a manner that reliably reduces nodal relapse.15-17 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).20,21 Observation allows nodal micrometastases to enlarge and spread to other nodes, thereby increasing the risk of distant metastases and decreasing the chance of long-term survival.12,15,16,17,23 (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-center1 and international2 studies and those of a smaller prospective, randomized trial conducted by the World Health Organization Melanoma Program3: 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.17 We also confirmed that the incidence of local or in-transit metastases was not increased among patients treated with sentinel-node biopsy.24-26 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

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<th>Table 2. Cox Multivariate Analysis of the Prognostic Value of Various Factors for Patients Assigned to Sentinel-Node Biopsy.</th>
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<tr>
<td><strong>Factor</strong></td>
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<tr>
<td>Sentinel-node status (positive vs. negative)</td>
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<td>Breslow thickness (per mm)</td>
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* This group served as the reference group.
occult nodal metastases.\textsuperscript{8,11,13,16,23} 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 (±SE) at 8 years was 18.5±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.

\textbf{Figure 3.} Melanoma-Specific Survival, According to the Presence or Absence of Nodal Metastases and Time to Nodal and Local or In-Transit Recurrence.

Panel A shows the time to clinical nodal recurrence in the observation group and to an initial nodal recurrence after a false negative result on sentinel-node biopsy. Panel B shows the melanoma-specific survival among patients with nodal metastases: subgroup 1 comprised patients with a tumor-positive sentinel node; subgroup 2, the patients in subgroup 1 plus those in subgroup 4 with a nodal recurrence after a negative result on biopsy; subgroup 3, those with nodal recurrence during observation; and subgroup 4, those with nodal recurrence after a negative result on biopsy. Panel C shows the melanoma-specific survival among patients without nodal metastases, according to the type of treatment (median follow-up, 59.8 months). Panel D shows the time to local or in-transit metastasis, according to the type of treatment.
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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REFERENCES

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APPENDIX


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