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Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases

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ABSTRACT

BACKGROUND

Trials evaluating the omission of completion axillary-lymph-node dissection in patients with clinically node-negative breast cancer and sentinel-lymph-node metastases have been compromised by limited statistical power, uncertain nodal radiotherapy target volumes, and a scarcity of data on relevant clinical subgroups.

METHODS

We conducted a noninferiority trial in which patients with clinically node-negative primary T1 to T3 breast cancer (tumor size, T1, ≤20 mm; T2, 21 to 50 mm; and T3, >50 mm in the largest dimension) with one or two sentinel-node macrometastases (metastasis size, >2 mm in the largest dimension) were randomly assigned in a 1:1 ratio to completion axillary-lymph-node dissection or its omission (sentinel-node biopsy only). Adjuvant treatment and radiation therapy were used in accordance with national guidelines. The primary end point was overall survival. We report here the per-protocol and modified intention-to-treat analyses of the prespecified secondary end point of recurrence-free survival. To show noninferiority of sentinel-node biopsy only, the upper boundary of the confidence interval for the hazard ratio for recurrence or death had to be below 1.44.

RESULTS

Between January 2015 and December 2021, a total of 2766 patients were enrolled across five countries. The per-protocol population included 2540 patients, of whom 1335 were assigned to undergo sentinel-node biopsy only and 1205 to undergo completion axillary-lymph-node dissection (dissection group). Radiation therapy including nodal target volumes was administered to 1192 of 1326 patients (89.9%) in the sentinel-node biopsy–only group and to 1058 of 1197 (88.4%) in the dissection group. The median follow-up was 46.8 months (range, 1.5 to 94.5). Overall, 191 patients had recurrence or died. The estimated 5-year recurrence-free survival was 89.7% (95% confidence interval [CI], 87.5 to 91.9) in the sentinel-node biopsy–only group and 88.7% (95% CI, 86.3 to 91.1) in the dissection group, with a country-adjusted hazard ratio for recurrence or death of 0.89 (95% CI, 0.66 to 1.19), which was significantly ($P<0.001$) below the prespecified noninferiority margin.

CONCLUSIONS

The omission of completion axillary-lymph-node dissection was noninferior to the more extensive surgery in patients with clinically node-negative breast cancer who had sentinel-node macrometastases, most of whom received nodal radiation therapy. (Funded by the Swedish Research Council and others; SENOMAC ClinicalTrials.gov number, NCT02240472.)

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CME

A Quick Take is available at NEJM.org

In 2010 and 2011, the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial[1,2] showed the safety of the omission of completion axillary-lymph-node dissection (the removal of additional axillary lymph nodes after biopsy of sentinel lymph nodes has revealed metastases) among patients with clinically node-negative (cN0) breast cancer undergoing breast-conserving surgery and whole-breast radiotherapy in whom sentinel-lymph-node biopsy had revealed one or two metastases. Since then, the use of completion axillary-lymph-node dissection has been steadily decreasing. In some countries, the adaptation of guidelines has been slow, owing mainly to underrecruitment in the ACOSOG Z0011 trial and the premature closure of that trial in combination with a large noninferiority margin, short follow-up, and uncertainties regarding irradiated nodal volumes and any consequences for adjuvant therapies.[3-5] In a later article,[6] the investigators reported that postoperative radiation therapy with the use of high tangents had been used in more than half the patients and that protocol-prohibited nodal radiation therapy had been used in 19%. Detailed treatment records were available for only 228 of 856 patients.[6]

In the European Organization for Research and Treatment of Cancer (EORTC) 10981-22023 Comparison of Complete Axillary Lymph Node Dissection with Axillary Radiation Therapy in Treating Women with Invasive Breast Cancer (AMAROS) trial, completion axillary-lymph-node dissection was replaced with axillary radiation therapy.[7] Mastectomy was not an exclusion criterion, but only 248 such patients (17.4%) underwent randomization. Although neither of these trials reached statistical power for their respective end points, no benefit of completion axillary-lymph-node dissection was observed after 10 years of follow-up.[8,9] Signs of lymphedema, however, were twice as common after completion axillary-lymph-node dissection than after axillary radiation therapy in the AMAROS trial.[7,9]

In 2015, we opened the SENOMAC trial for enrollment. The aim of this trial was to validate results from previous trials in a sufficiently large cohort focused only on patients with sentinel-node macrometastases and to extend eligibility criteria to include important underrepresented subgroups — namely, patients undergoing mastectomy, those with sentinel-node extracapsular extension or T3 tumors (tumor size, >50 mm in the largest dimension), and men.

Methods

Trial Design and Oversight

For this prospective, randomized, phase 3 trial, we chose a noninferiority design because of the known clinical advantages of sentinel-node biopsy regarding long-term complications to the arm (e.g., lymphedema). We aimed to show that the omission of completion axillary-lymph-node dissection would not worsen overall survival (the primary end point) by more than a small, clinically acceptable margin. The original trial protocol, which is available with the full text of this article at NEJM.org, has been published previously.[10] The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

The trial was conducted at 67 hospitals in Sweden, Denmark, Germany, Greece, and Italy. Ethics approval was obtained from the Swedish Ethical Review Authority in 2014 and from relevant ethics review boards in the participating countries. All the patients provided informed written consent. The trial was conducted and monitored according to Good Clinical Practice guidelines. Clinical data were recorded in an electronic case-report form, and data quality was thoroughly reviewed and optimized to address any outlying, missing, or incongruent values. The manuscript was written by the authors, and no one who is not an author contributed to the writing of the manuscript. The funders had no part in the design, performance, analysis, or reporting of the trial.

Patient Selection

Female and male adult patients who had cN0 breast cancer with a tumor stage of T1, T2, or T3 (tumor size, T1, ≤20 mm; T2, 21 to 50 mm; and T3, >50 mm in the largest dimension) and one or two sentinel-node macrometastases (metastasis size, >2 mm in the largest dimension) were eligible for inclusion. Preoperative ultrasonography of the axilla was mandatory. Patients were ineligible if they had extraaxillary regional or distant metastases, a history of invasive breast cancer, breast cancer in both breasts if one of the breasts met exclusion criteria, medical contraindications against radiation therapy or systemic

treatment, or an inability to understand the trial information. Additional micrometastases (metastasis size, ≤2 mm in the largest dimension) on sentinel-node biopsy and extracapsular extension were allowed. Patients who had suspicious but nonpalpable axillary lymph nodes on ultrasonography were eligible even if metastasis was confirmed by fine-needle aspiration. After a protocol amendment in 2016, primary systemic treatment was allowed if the sentinel-node biopsy was performed before the start of treatment.

TREATMENT AND FOLLOW-UP

After patients underwent sentinel-node biopsy, they underwent randomization by means of a computerized system either to completion axillary-lymph-node dissection or to no further axillary surgery (sentinel-node biopsy only). Depending on the use of intraoperative frozen section, which is sometimes used by hospitals to receive preliminary results of sentinel-node biopsy during surgery, completion axillary-lymph-node dissection was performed either during the same surgery (intraoperative randomization) or during a second surgery (postoperative randomization). Breast-conserving surgery and mastectomy were eligible interventions. Negative surgical margins were mandatory. Sites in Germany and Italy limited trial inclusion to patients undergoing mastectomy because the ACOSOG Z0011 criteria had been implemented in national guidelines.

A sentinel node was defined as any lymph node that had accumulated tracer material (blue dye or isotope) or was considered to be suspicious for cancer on intraoperative palpation. Lymph nodes that did not fulfill these criteria but that had been randomly removed during surgery were not classified as sentinel nodes, and metastases in such nonsentinel nodes did not lead to exclusion. The recommendations of the American Joint Committee on Cancer were applied for the assessment of histopathological specimens.[11]

Adjuvant systemic treatment was recommended according to relevant national guidelines and could consist of endocrine treatment or chemotherapy (or both), with or without targeted treatment. Whole-breast radiation therapy after breast-conserving surgery was mandatory. Indications for radiation-therapy boost to the tumor bed, radiation therapy to the chest wall after mastectomy, and radiation therapy to regional lymph nodes were in accordance with national guidelines. Quality control of radiation therapy was performed by means of source-data verification (with data from the registered electronic case-report form compared with the actual plans for radiation therapy) for all the patients who underwent randomization in Sweden or Denmark until May 31, 2019. Given that the protocol did not stipulate any specific radiation-therapy target volumes or doses, the occurrence of protocol-prohibited radiation therapy was not assessed. The concordance between data from the registered electronic case-report form regarding radiation therapy to the breast or chest wall and nodal target volumes (yes or no) and the actual radiation therapy received according to radiation-therapy plans was evaluated. A detailed radiation-therapy review to evaluate the clinical significance of specific nodal target volumes and doses is ongoing.

At enrollment, all the patients completed questionnaires about health-related quality of life and long-term complications to the arm (the EORTC Quality of Life Questionnaire [QLQ-C30], the breast cancer–specific QLQ-BR23 questionnaire, the EuroQol Group 5-Dimension questionnaire, and the Lymphedema Functioning, Disability, and Health Questionnaire), and according to the protocol, patients will receive these questionnaires again after 1, 3, 5, and 10 years. No clinical measurements of lymphedema were conducted. Although 1-year questionnaire data from a Swedish–Danish subpopulation were published in 2022,[12] the 3-year data for the entire trial population are not yet available.

Follow-up is being assessed by means of annual mammography for 5 years and another mammography after 10 years. Annual clinical examinations were mandatory initially, but owing to the interruption of some clinical services during the coronavirus disease 2019 pandemic, the requirement for clinical visits was replaced with the option of remote visits.

END POINTS

The primary end point was changed from breast cancer–specific survival to overall survival in 2020 on the basis of a recommendation from the independent data and safety monitoring board. Prespecified secondary end points were recurrence-free survival, breast cancer–specific survival, and patient-reported outcomes. The definition of

recurrence-free survival follows the updated Standardized Definitions for Efficacy End Points (STEEP) criteria[13] and includes invasive recurrence and death.

POWER COMPUTATION

Clinical noninferiority was defined as 5-year overall survival that was not worse by more than 2.5 percentage points when completion axillary-lymph-node dissection was omitted — that is, 94.0% in the dissection group and 91.5% in the sentinel-node biopsy–only group. This margin was intentionally small — half the margin that was used in the ACOSOG Z0011 trial — in order to increase clinical applicability and to be comparable with oncologic trials evaluating systemic therapies. Thus, we calculated that in order for the trial to have 80% power with a one-sided alpha of 10%, a total of 190 deaths would need to occur, with the upper one-sided 90% confidence interval for the hazard ratio (sentinel-node biopsy only vs. completion axillary-lymph-node dissection) being below 1.44. Owing to its clinical significance, the secondary end point of recurrence-free survival is being reported before the primary end point of overall survival, for which statistical power has not yet been obtained.

For the secondary end point of recurrence-free survival (reported here), the sample-size calculation was added to the protocol in June 2020, under an assumption that 5-year recurrence-free survival would be 90% in the dissection group, on the basis of the safety analysis of May 2020. With an unchanged threshold for the upper boundary of the confidence interval for the hazard ratio for recurrence or survival of 1.44, resulting in a prespecified noninferiority margin of 4.1 percentage points, we concluded that the trial would have sufficient power (80%) to conclude noninferiority once 190 events of recurrence or death had occurred.

DEFINITIONS OF TRIAL POPULATIONS

Among all the patients who underwent randomization, the modified intention-to-treat population excluded those who withdrew their informed consent within 21 days after randomization — that is, before a potential second surgery with completion axillary-lymph-node dissection. Patients who withdrew consent later had their data censored at the date of withdrawal of consent.

The per-protocol population consisted of all the patients who underwent axillary surgery according to their randomized group assignment. Patients who did not meet all the inclusion criteria or who met any of the exclusion criteria at the time of randomization, even if the situation was discovered later, were excluded from the per-protocol analyses.

STATISTICAL ANALYSIS

The present analysis pertains to the prespecified secondary end point of recurrence-free survival. Descriptive clinical data are summarized for the two treatment groups. Categorical variables are presented as frequencies and percentages, and continuous variables are presented as means with standard deviations or as medians with ranges. For each variable, the numbers and percentages of patients with missing observations are presented.

The time to an event was calculated from the randomization date to the date of recurrence or death or to the date of last recorded visit for patients without an event. Recurrence-free survival was descriptively evaluated with the use of Kaplan–Meier curves. The effect of the omission of completion axillary-lymph-node dissection on 5-year recurrence-free survival was assessed with the use of a Cox proportional-hazards model. Final analyses were adjusted for the stratification factor of country. Hazard ratios (sentinel-node biopsy only vs. completion axillary-lymph-node dissection) are presented with 95% confidence intervals. The proportional-hazards assumption was evaluated with the use of Schoenfeld residuals.

The per-protocol population was used for the main analysis because such a population is more conservative in the context of a noninferiority analysis.[14,15] The upper boundary of the confidence interval was required to be below the noninferiority margin of 1.44 for the analysis of the hazard ratio for recurrence or death. A complementary one-sided noninferiority statistical test was performed, and a P value of less than 0.025 was considered to indicate that the result was significantly below the noninferiority margin. Clinically relevant subgroups were assessed in the per-protocol population. These subgroup analyses were not prespecified, so results are presented as hazard ratios with 95% confidence intervals that were not adjusted for

multiplicity, without any formal statistical test. Sensitivity analyses were performed with the use of a model adjusted for calendar period as a potential factor that may predict nonadherence to the assigned treatment, in the modified intention-to-treat population, and with introduction of the requirement that at least nine lymph nodes were removed in the dissection group (as compared with the overall sentinel-node biopsy–only group).[16]

RESULTS

CHARACTERISTICS OF THE PATIENTS AND TUMORS

Trial enrollment opened on January 31, 2015, and closed on December 31, 2021. Overall, 6637 patients underwent screening at 67 sites internationally, and 2766 patients underwent randomization. The modified intention-to-treat population consisted of 2624 patients, and the per-protocol population of 2540 patients, of whom 1335 had been assigned to undergo sentinel-node biopsy only and 1205 to undergo completion axillary-lymph-node dissection (dissection group) (Fig. 1). The per-protocol population included 1553 patients (61.1%) from Sweden, 803 (31.6%) from Denmark, 86 (3.4%) from Germany, 52 (2.0%) from Greece, and 46 (1.8%) from Italy.

The median follow-up was 46.8 months (range, 1.5 to 94.5). A total of 17 patients (9 in the sentinel-node biopsy–only group and 8 in the dissection group) left the trial before the reporting of radiation therapy was due. Most of the patients who remained in the trial until at least 1 year of follow-up underwent postoperative radiation therapy targeting regional lymph nodes (1192 of 1326 [89.9%] in the sentinel-node biopsy–only group and 1058 of 1197 [88.4%] in the dissection group), and all but 26 patients received some systemic treatment. Patients 65 years of age or older were well represented in the trial (529 patients [39.6%] in the sentinel-node biopsy–only group and 496 [41.2%] in the dissection group). Table 1 shows the characteristics of the patients and tumors in the per-protocol population. Corresponding data for the modified intention-to-treat population are provided in

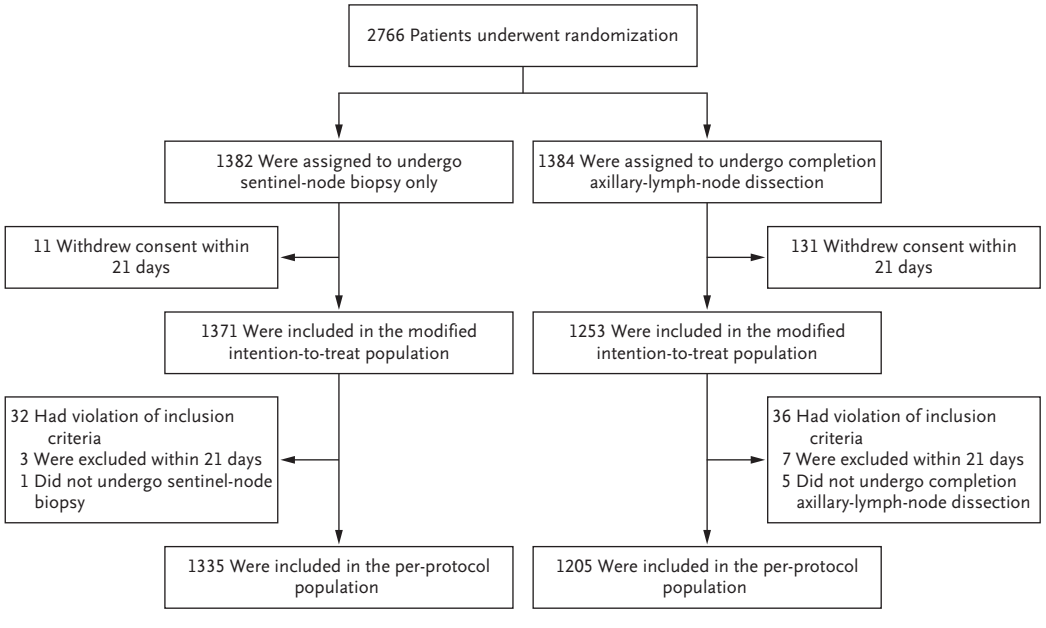

Figure 1. Randomization of the Patients and the Analysis Populations.

The modified intention-to-treat population excluded patients who withdrew their informed consent within 21 days after randomization (i.e., before a potential second surgery with completion axillary-lymph-node dissection). The per-protocol population consisted of patients who underwent axillary surgery corresponding to their randomized group assignment. Patients who did not meet all the inclusion criteria or who met any of the exclusion criteria at the time of randomization, even if discovered later, were excluded from the per-protocol analyses.

Table 1. Characteristics of the Patients and Tumors (Per-Protocol Population).*

Characteristic	Sentinel-Node Biopsy Only (N = 1335)	Completion Axillary-Lymph-Node Dissection (N = 1205)
Age		
Mean — yr	61.0±12.0	60.9±11.7
Median (range) — yr	61 (20–94)	61 (34–90)
Distribution — no. (%)		
<40 yr	37 (2.8)	32 (2.7)
40–49 yr	220 (16.5)	194 (16.1)
50–64 yr	549 (41.1)	483 (40.1)
65–74 yr	334 (25.0)	342 (28.4)
≥75 yr	195 (14.6)	154 (12.8)
Tumor size — mm†		
Mean	24.4±15.5	24.2±16.9
Median (range)	20 (0.2–155)	20 (1–155)
Tumor stage — no. (%)‡		
T1	710 (53.2)	651 (54.0)
T2	552 (41.3)	480 (39.8)
T3	73 (5.5)	74 (6.1)
No. of removed sentinel lymph nodes — no. (%)		
1 or 2	934 (70.0)	856 (71.0)
3 or 4	349 (26.1)	303 (25.1)
>4	52 (3.9)	46 (3.8)
Mean	2.1±1.2	2.1±1.2
Median (range)	2 (1–11)	2 (1–9)
No. of sentinel lymph-node macrometastases — no. (%)		
1	1143 (85.6)	1008 (83.7)
2	192 (14.4)	197 (16.3)
No. of axillary metastases		
Mean	1.3±0.5	2.3±3.0
Median (range)	1 (1–5)	1 (1–42)
Type of breast surgery — no. (%)		
Breast-conserving surgery	845 (63.3)	775 (64.3)
Mastectomy	490 (36.7)	430 (35.7)
Tumor histologic type — no. (%)		
Invasive carcinoma, no special type	997 (74.7)	939 (77.9)
Lobular carcinoma	278 (20.8)	226 (18.8)
Other	60 (4.5)	40 (3.3)
Nottingham histologic grade — no. (%)§		
Grade 1	243 (18.2)	211 (17.5)
Grade 2	786 (58.9)	717 (59.5)
Grade 3	298 (22.3)	263 (21.8)
Missing data	8 (0.6)	14 (1.2)

Table 1. (Continued.)

Characteristic	Sentinel-Node Biopsy Only (N=1335)	Completion Axillary-Lymph-Node Dissection (N=1205)
Tumor subtype — no. (%)¶		
ER-positive, HER2-negative	1166 (87.3)	1034 (85.8)
ER-positive, HER2-positive	84 (6.3)	88 (7.3)
ER-negative, HER2-positive	23 (1.7)	34 (2.8)
ER-negative, HER2-negative	57 (4.3)	46 (3.8)
Missing data	5 (0.4)	3 (0.2)
Ki-67 proliferation index		
Mean — %	24.6±17.2	24.8±17.7
Median (range) — %	20 (1–98)	20 (1–98)
Missing data — no. (%)	13 (1.0)	18 (1.5)

* Plus–minus values are means ±SD. The per-protocol population consisted of patients who underwent axillary surgery corresponding to their randomized group assignment. Patients who did not meet all the inclusion criteria or who met any of the exclusion criteria at the time of randomization, even if discovered later, were excluded from per-protocol analyses. Percentages may not total 100 because of rounding.

† A total of 55 patients (17 in the sentinel-node biopsy–only group and 38 in the dissection group) who received primary systemic treatment were excluded from this analysis.

‡ Tumor stage was deduced from the histopathological tumor size in the context of primary surgery and from the clinical tumor size in the context of primary systemic treatment. A stage of T1 indicates that the tumor size was no more than 20 mm in the largest dimension, T2 that the size was 21 to 50 mm, and T3 that the size was greater than 50 mm.

§ Nottingham histologic grades are based on information about the degree of tubular formation, nuclear pleomorphism, and mitosis. Grades range from 1 to 3, with higher grades indicating a higher risk of recurrence.

¶ Tumor subtype was based on estrogen receptor (ER) status and human epidermal growth factor receptor 2 (HER2; Erb2-neu) gene amplification. HER2 positivity was defined as a result of 3+ on immunohistochemical testing or a result of 2+ on immunohistochemical testing with a subsequent in situ hybridization test showing gene amplification.

Table S1 in the Supplementary Appendix, available at NEJM.org.

Approximately one third of the patients had extracapsular extension in the sentinel-node biopsy sample. Sentinel-node biopsy only removed a mean of 2 lymph nodes per patient, whereas sentinel-node biopsy followed by completion axillary-lymph-node dissection removed a mean of 15 lymph nodes per patient. Lymphovascular invasion in the primary tumor was present in approximately 28% of the patients. Approximately 65% of the patients received adjuvant chemotherapy, with endocrine therapy used in approximately 93% and human epidermal growth factor receptor 2 (HER2)–targeted therapy in approximately 9%. Approximately 88% of the patients received radiation therapy to the breast or chest wall plus regional lymph nodes. Details are provided in Table S2.

For radiation-therapy quality control, data from all 1360 patients in the per-protocol population who had undergone randomization in Sweden or Denmark until May 31, 2019, were considered, and 1154 radiation-therapy plans were evaluated (Fig. S1). Reported data from the electronic case-report form matched the radiation-therapy plan in 1146 patients (99.3%) with regard to radiation therapy to the breast or chest wall and in 1115 patients (96.6%) with regard to nodal target volumes.

Given that additional sentinel-node micrometastases were allowed, 49 patients in the trial had a total of three metastatic sentinel nodes, and 3 patients had four. On preoperative ultrasonography, 177 patients (13.3%) in the sentinel-node biopsy–only group and 170 patients (14.1%) in the dissection group had axillary lymph nodes that were suspicious for cancer. Fine-needle aspiration was confirmatory for lymph-node metastasis in 18 patients (1.3%) in the sentinel-node biopsy–only group and in 18 (1.5%) in the dissection group.

Owing to the varying use of intraoperative frozen section, completion axillary-lymph-node dissection was performed either during a second surgery (in 930 patients [77.2%]) or during the same session as the sentinel-node biopsy (in 275 patients [22.8%]). Additional non–sentinel-node metastases were found on completion axillary-lymph-node dissection in 403 of 1167 patients (34.5%) who had undergone primary surgery. Among patients with one sentinel-node macrometastasis, 31.3% had additional non–sentinel-node metastases; among patients with two sentinel-node macrometastases, 51.3% had additional non–sentinel-node metastases. The final pathological nodal classification among the 2485 patients undergoing primary surgery was pN1 (1 to 3 metastases) in 1311 patients (99.5%) in the sentinel-node biopsy–only group and in 1016 patients (87.1%) in the dissection group, pN2 (4 to 9 metastases) in 7 (0.5%) and in 116 (9.9%), respectively, and pN3 (≥10 metastases) in 35 patients (3.0%) in the dissection group.

END POINTS

Recurrence or death occurred in 191 patients. Table 2 shows the numbers of recurrences and deaths according to trial group in the per-protocol population during the entire follow-up period. Most deaths (117) occurred within 5 years after randomization, with 50 of those deaths being due to breast cancer. The estimated 5-year overall survival was 92.9% (95% confidence interval [CI], 91.0 to 94.9) in the sentinel-node biopsy–only group and 92.0% (95% CI, 89.9 to 94.1) in the dissection group. The estimated 5-year breast cancer–specific survival was 97.1% (95% CI, 95.8 to 98.3) in the sentinel-node biopsy–only group and 96.6% (95% CI, 95.3 to 97.9) in the dissection group.

Regional recurrences were in the ipsilateral axilla in three patients, in the ipsilateral axilla and infraclavicular nodes in two patients, and in the supra- or infraclavicular, internal mammary, or parasternal nodes in one patient each. In four patients, the location of the regional recurrence was unknown.

The calculation of the estimated 5-year recurrence-free survival was based on 180 patients (7.1%) who had an event within 5 years after randomization: 89 patients (6.7%) in the sentinel-node biopsy–only group and 91 (7.6%) in the dissection group. The estimated 5-year recurrence-free survival was 89.7% (95% CI, 87.5 to 91.9) in the sentinel-node biopsy–only group and 88.7% (95% CI, 86.3 to 91.1) in the dissection group (Fig. 2). After adjustment for the stratification factor of country, the hazard ratio for recurrence or death in the sentinel-node biopsy–only group as compared with the dissection group was 0.89 (95% CI, 0.66 to 1.19), which was significantly ($P<0.001$) below the noninferiority margin. The proportional-hazards assumption of the Cox model was not violated ($P=0.48$). The result in the modified intention-to-treat population (hazard ratio, 0.89; 95% CI, 0.67 to 1.19) was similar to that in the per-protocol population. The noninferiority of sentinel-node biopsy only to completion axillary-lymph-node dissection was confirmed in sensitivity analyses (Fig. 3).

Subgroup analyses were performed in clinically relevant subgroups (Fig. 3). Too few male patients (10 [0.4%]) had been enrolled for subgroup analysis to be possible. The hazard ratio for recurrence or death in the sentinel-node biopsy–only group as compared with the dissection group included 1.00 in all the subgroups except in the subgroup of patients with estrogen receptor–

Table 2. Recurrence-free Survival Analyses (Per-Protocol Population).*

Variable	Sentinel-Node Biopsy Only (N=1335)	Completion Axillary-Lymph-Node Dissection (N=1205)
Recurrence — no. (%)		
Local	12 (0.9)	10 (0.8)
Regional	6 (0.4)	6 (0.5)
Distant	44 (3.3)	53 (4.4)
Death — no. (%)	62 (4.6)	69 (5.7)
Cause of death — no./total no. (%)		
Breast cancer	24/62 (39)	31/69 (45)
Other cause	30/62 (48)	30/69 (43)
Unknown	8/62 (13)	8/69 (12)
Recurrence or death as first event — no. (%)		
No	1240 (92.9)	1109 (92.0)
Yes	95 (7.1)	96 (8.0)

* Shown are analyses of recurrence-free survival (secondary end point) in the per-protocol population during the entire follow-up period. Some patients may have more than one recurrence of breast cancer.

positive, HER2–positive disease, in which sentinel-node biopsy only appeared to be better.

DISCUSSION

In this randomized, controlled trial, the estimated 5-year recurrence-free survival after sentinel-node biopsy only was noninferior to that after completion axillary-lymph-node dissection among patients with breast cancer and one or two sentinel-node macrometastases. Most of the patients, regardless of trial-group assignment, received adjuvant systemic treatment and radiation therapy, including nodal target volumes.

The current results are in line with those of the ACOSOG Z0011 and AMAROS trials,[1,7] which enrolled patients in the periods of 1999–2004 and 2001–2010, respectively. The SENOMAC trial differs from these earlier trials in several aspects. First, patients who had only sentinel-node micrometastases were not enrolled, on the basis of the results of the International Breast Cancer Study Group (IBCSG) 23-01 trial.[17] In the ACOSOG Z0011 and AMAROS trials, however, patients with sentinel-node micrometastases constituted nearly 40% of the trial population, a notably higher percentage than has been observed in the clinical breast cancer population. Second, the SENOMAC trial allowed sentinel-node extracapsular extension; in the ACOSOG Z0011 trial, matted nodes and gross extranodal disease were an exclusion criterion, and extracapsular extension was not reported in the AMAROS trial. This lack of information resulted in substantial clinical uncertainty, which the results of the present trial may now resolve. Third, whereas the SENOMAC trial included a relevant proportion of patients with T3 tumors, only one such patient was enrolled in the previous two trials together, so our trial addressed an important knowledge gap. Fourth, mastectomy was not an eligible intervention in the ACOSOG Z0011 trial, and the AMAROS trial included only 248 such patients (17.4%). In our trial, more than one third of the patients underwent mastectomy, which corroborates the external validity of our trial, given that 34% of the patients with breast cancer in Sweden and 31% of those in Denmark undergo mastectomy.[18,19]

Results from two further trials evaluating the omission of completion axillary-lymph-node dissection in patients who had a sentinel node with metastases have been reported. The Optimal Treatment of the Axilla–Surgery or Radiotherapy (OTOASOR) trial, in which patients with a breast cancer up to 3 cm in the largest dimension were randomly assigned to completion axillary-lymph-node dissection or regional nodal irradiation, showed no significant between-group difference

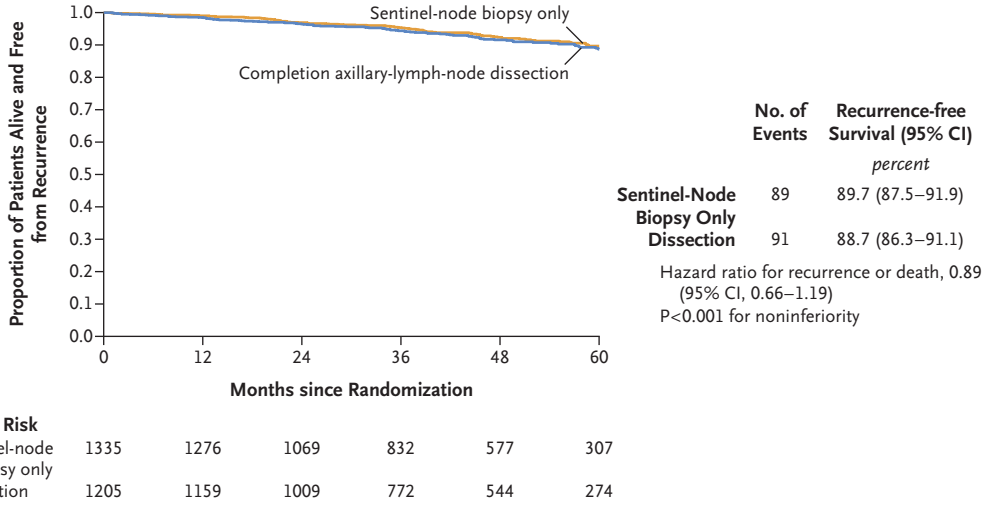

Figure 2. Recurrence-free Survival (Per-Protocol Population).
Shown are Kaplan–Meier curves for the secondary end point of recurrence-free survival.

in disease-free survival.[20] However, more than one third of the patients in that trial had only sentinel-node micrometastases or isolated tumor cells, extracapsular extension was not reported, and few patients underwent mastectomy. The SINODAR-ONE trial, in which patients with T1 or T2 tumors and sentinel-node macrometastases were randomly assigned to completion axillary-lymph-node dissection or sentinel-node biopsy only, showed equivalent recurrence-free survival in the two groups.[21] A subgroup analysis that included 218 patients undergoing mastectomy was confirmatory. Therefore, previous trials had certain clinical limitations regarding eligibility and the size of included subgroups but also had signs of selection bias toward a more low-risk population than the underlying population of persons with breast cancer. This situation has

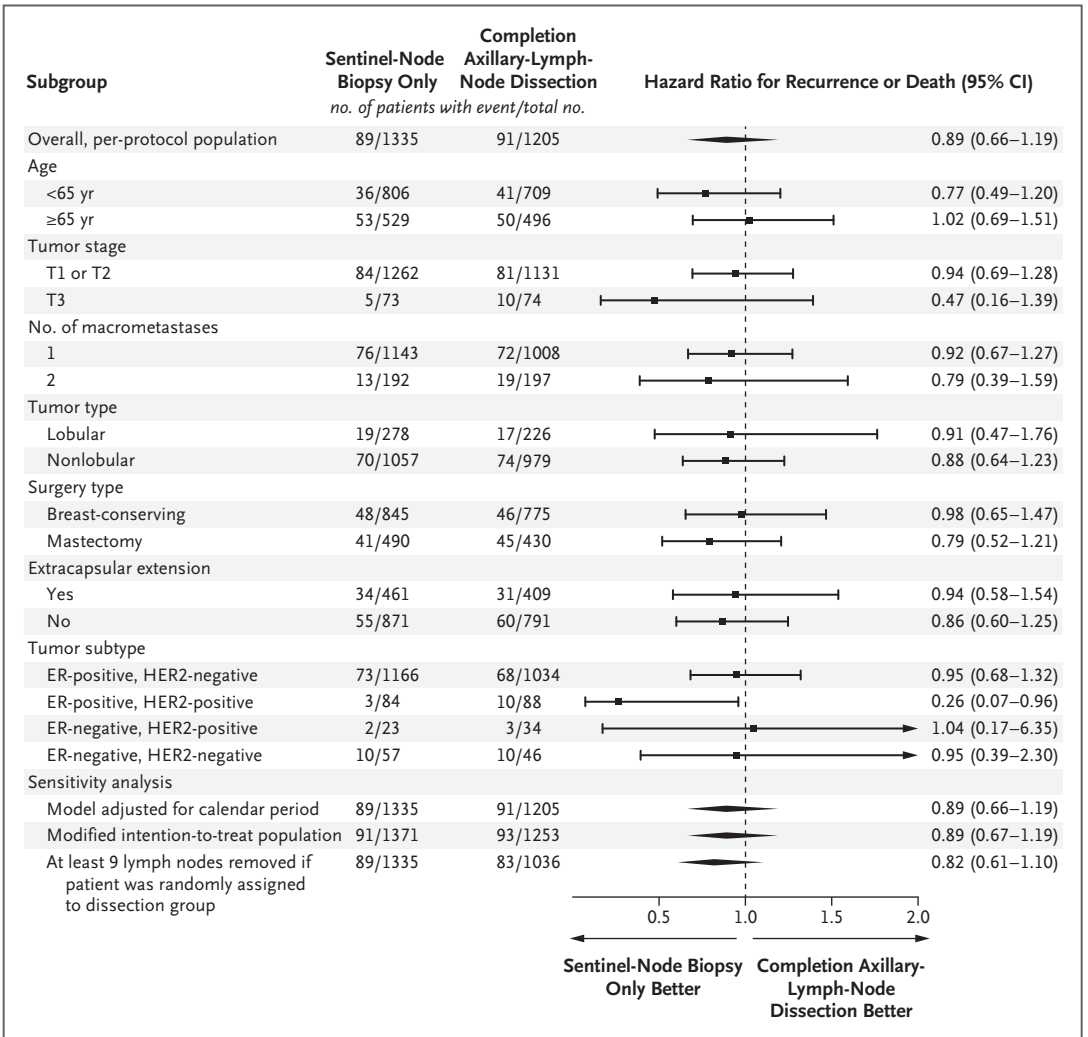

Figure 3. Subgroup Analysis of Recurrence-free Survival.

Subgroup analyses were conducted in the per-protocol population. Sensitivity analyses were conducted in a model that was adjusted for calendar year (as a potential factor that may predict nonadherence to the assigned treatment), in the modified intention-to-treat population, and with introduction of the requirement that at least nine lymph nodes were removed in the dissection group (with the overall sentinel-node biopsy–only group as the comparator). Arrows indicate that the 95% confidence interval exceeds the graphed area. Diamonds represent the overall estimate, with the width of the diamond indicating the 95% confidence interval. ER denotes estrogen receptor, and HER2 human epidermal growth factor receptor 2.

resulted in uncertainties about which patients should be offered the possibility of omitting completion axillary-lymph-node dissection. The present trial had highly representative proportions of such subgroups, a larger trial population, and extended eligibility criteria.

A common problem in clinical trials is the underrepresentation of older patients. Even though, of the trials mentioned above, only SINODAR-ONE had an age limit for enrollment, the reported populations in previous trials have had mean ages between 54 years and 56 years, which is lower than in a typical breast cancer population. Our trial enrolled a substantial number of older patients, and the median ages of 65 years in the Swedish breast cancer population and 62 years in the Danish breast cancer population support the external validity of our trial results.[18,22]

Other prospective randomized trials evaluating the omission of completion axillary-lymph-node dissection have been initiated. The Borstkanker Onderzoek Groep (BOOG) 2013-07 trial in the Netherlands was closed prematurely owing to slow enrollment.[23] The second randomization of the Intergroup-Sentinel-Mamma (INSEMA) trial in Germany (ClinicalTrials.gov number, NCT02466737) had not met the target enrollment when the trial closed enrollment in 2019, when its first randomization, in which patients were assigned to sentinel-node biopsy or its omission, had reached full enrollment. The results of the Positive Sentinel Node (POSNOC) trial in the United Kingdom, in which 1900 patients with cN0 breast cancer with a tumor stage of T1 or T2 were randomly assigned either to axillary treatment (completion axillary-lymph-node dissection or axillary radiation therapy) or to no axillary treatment, are awaited.[24]

Our trial has some limitations. First, the use of radiation therapy followed national guidelines, which led to a high proportion of patients undergoing nodal field irradiation, which is the standard care in Sweden and Denmark. Thus, the results of our trial are comparable with those of the AMAROS and OTOASOR trials rather than with those of the POSNOC, SINODAR-ONE, and ACOSOG Z0011 trials. The concordance between the data from the registered electronic case-report forms and the actual radiation-therapy plans was high. Detailed information about radiation-therapy target volumes and doses to specific nodal levels are not yet available. Second, the recruitment of male patients aimed to fill an important knowledge gap, but only 10 male patients could be enrolled over a 7-year period — a situation that prevented subgroup analysis according to sex. Third, given that most of the enrolled patients had breast cancer of the luminal subtype, and also given the predilection of this subtype to recur late, the current follow-up is relatively short. Fourth, as in previous trials, enrollment ran short of the prespecified target. However, statistical power relies on the occurrence of events rather than on the target sample size, and given the high number of events, the narrow confidence intervals, and the large distance between the noninferiority margin and the observed upper boundary of the confidence interval, the presented results reflect a high precision of estimates. Fifth, the incidence of withdrawal was clearly higher in the dissection group than the sentinel-node biopsy–only group, a situation that reflects patients' awareness and desire to avoid completion axillary-lymph-node dissection. Given the large size of the trial population and the balanced distribution of important variables between the two trial groups, however, this situation should not have affected the trial results.

This trial provides robust evidence that the omission of completion axillary-lymph-node dissection was safe in patients with clinically node-negative T1, T2, or T3 breast cancer and one or two sentinel-node macrometastases who received adjuvant systemic treatment and radiation therapy according to national guidelines.

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APPENDIX

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