ORIGINAL ARTICLE

Axillary Surgery in Breast Cancer — Primary Results of the INSEMA Trial

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ABSTRACT

BACKGROUND

Whether surgical axillary staging as part of breast-conserving therapy can be omitted without compromising survival has remained unclear.

METHODS

In this prospective, randomized, noninferiority trial, we investigated the omission of axillary surgery as compared with sentinel-lymph-node biopsy in patients with clinically node-negative invasive breast cancer staged as T1 or T2 (tumor size, ≤5 cm) who were scheduled to undergo breast-conserving surgery. We report here the per-protocol analysis of invasive disease–free survival (the primary efficacy outcome). To show the noninferiority of the omission of axillary surgery, the 5-year invasive disease–free survival rate had to be at least 85%, and the upper limit of the confidence interval for the hazard ratio for invasive disease or death had to be below 1.271.

RESULTS

A total of 5502 eligible patients (90% with clinical T1 cancer and 79% with pathological T1 cancer) underwent randomization in a 1:4 ratio. The per-protocol population included 4858 patients; 962 were assigned to undergo treatment without axillary surgery (the surgery-omission group), and 3896 to undergo sentinel-lymph-node biopsy (the surgery group). The median follow-up was 73.6 months. The estimated 5-year invasive disease–free survival rate was 91.9% (95% confidence interval [CI], 89.9 to 93.5) among patients in the surgery-omission group and 91.7% (95% CI, 90.8 to 92.6) among patients in the surgery group, with a hazard ratio of 0.91 (95% CI, 0.73 to 1.14), which was below the prespecified noninferiority margin. The analysis of the first primary-outcome events (occurrence or recurrence of invasive disease or death from any cause), which occurred in a total of 525 patients (10.8%), showed apparent differences between the surgery-omission group and the surgery group in the incidence of axillary recurrence (1.0% vs. 0.3%) and death (1.4% vs. 2.4%). The safety analysis indicates that patients in the surgery-omission group had a lower incidence of lymphedema, greater arm mobility, and less pain with movement of the arm or shoulder than patients who underwent sentinel-lymph-node biopsy.

CONCLUSIONS

In this trial involving patients with clinically node-negative, T1 or T2 invasive breast cancer (90% with clinical T1 cancer and 79% with pathological T1 cancer), omission of surgical axillary staging was noninferior to sentinel-lymph-node biopsy after a median follow-up of 6 years. (Funded by the German Cancer Aid; INSEMA ClinicalTrials.gov number, NCT02466737.)

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Axillary nodal status in invasive breast cancer has long been regarded as one of the most important prognostic factors, together with tumor size, and has been used to guide systemic therapy and radiotherapy. With the recognition that molecular tumor characteristics are relevant to the patient's response to therapy and survival, decisions on systemic therapy must be balanced according to both nodal status and tumor biology.[1] The publication of results from the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial[2,3] provided the basis for the design and funding of several de-escalation trials of the omission of axillary surgery in the treatment of early-stage breast cancer.

Four prospective, randomized trials — SOUND (Sentinel Node versus Observation after Axillary Ultrasound),[4] INSEMA (Intergroup Sentinel Mamma),[5] BOOG 2013-08 (Dutch Breast Cancer Research Group 2013-08),[6] and NAUTILUS (No Axillary Surgical Treatment for Lymph Node–Negative Patients after Ultra-Sonography)[7] — are investigating the omission of axillary-sentinel-lymph-node biopsy in patients with clinically node-negative (cN0) breast cancer who undergo upfront breast-conserving surgery. Recently, primary results from the SOUND trial showed that omission of axillary surgery was noninferior to sentinel-lymph-node biopsy in patients with small breast cancers up to 2 cm.[8] The primary outcome of the SOUND trial was distant disease–free survival at 5 years, analyzed in the intention-to-treat population (1405 patients) after a median follow-up of 5.7 years. Primary-outcome results of the BOOG trial, involving 1644 patients, are expected to be reported in 2025. Later, in 2027, data from the NAUTILUS trial, involving 1734 patients, are expected.

Here, we present the primary-outcome data from the INSEMA trial. A preplanned central quality-assurance review process for radiotherapy planning and axillary contouring was included in the INSEMA protocol (available with the full text of this article at NEJM.org), and the findings of the review were published in 2020.[9] Our recent analysis of patient-reported outcomes showed differences between the groups with respect to scores on a quality-of-life assessment of breast symptoms and arm symptoms, with better scores among patients who did not undergo sentinel-lymph-node biopsy than among those who did. In the assessment of arm symptoms, patients who underwent sentinel-lymph-node biopsy had significantly higher scores (indicating worse symptoms) for symptoms including pain, arm swelling, and impaired mobility at all postoperative visits.[10]

The goal of the INSEMA trial is to show that complete omission of axillary surgery in early-stage breast cancer treated with breast-conserving surgery is noninferior to sentinel-lymph-node biopsy with respect to invasive disease–free survival.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this prospective, randomized, noninferiority trial at 142 sites in Germany and 9 sites in Austria after obtaining approval from local independent review boards. The trial was designed by the University Medicine Rostock in cooperation with the German Breast Group. The German Breast Group performed data management, statistical analysis, project management, monitoring, and trial oversight. The Austrian Breast and Colorectal Cancer Study Group provided regulatory coordination at trial sites in Austria. All verification of source data was performed according to the standard operating procedures of the German Breast Group. The first author and the author who served as the statistician vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The first draft of the manuscript was written by the first author in collaboration with the German Breast Group. No one who is not an author contributed to the writing of the manuscript. All authors contributed substantially and approved the version of the manuscript that was submitted for publication.

PATIENTS

Women with breast cancer who planned to undergo upfront breast-conserving surgery were eligible for the trial if they were at least 18 years of age and had a clinical tumor stage of T1 or T2 (tumor size, ≤5 cm) and node-negative status according to clinical assessment (cN0) and imaging (iN0). All patients provided written informed consent. Patients were first randomly assigned in a 1:4 ratio to undergo treatment without axillary surgery (the surgery-omission group) or to undergo sentinel-lymph-node biopsy (the surgery group). Patients who underwent sentinel-lymph-

node biopsy and were found to have pathological sentinel-node–positive status (one to three macrometastases) underwent subsequent randomization in a 1:1 ratio to undergo completion axillary-lymph-node dissection or to proceed without dissection (having undergone sentinel-lymph-node biopsy alone). The results of the second randomization are not reported here. During follow-up, patients were assessed according to standard clinical practice. A medical history was taken and a physical examination was performed every 6 months for the first 36 months and yearly thereafter. Annual mammography and sonography were required; other testing was performed according to the patient's symptoms at the discretion of the investigator.

LOCAL TREATMENT

The preoperative diagnostic workup included routine axillary ultrasonography before biopsy. In cases of cN0 status in which ultrasonography indicated the presence of cancer in a lymph node (iN+ status), a negative core biopsy or a fine-needle aspiration biopsy of the lymph node was required before randomization. A cortical thickness greater than 2.5 mm or the absence of a fatty hilum were recommended as criteria for the identification of metastatic lymph nodes by axillary ultrasonography.[11]

All patients underwent unilateral breast-conserving surgery with postoperative whole-breast irradiation regardless of the intrinsic cancer subtype. Conventional fractionation or moderate hypofractionation could be used. Radiation therapy could be delivered with the use of three-dimensional conformal or intensity-modulated techniques. The axilla was not specifically targeted. Use of high tangents or regional nodal irradiation was not permitted except for patients with four or more axillary lymph node metastases in the surgery group. A boost of radiotherapy to the tumor bed was generally recommended but could be omitted in patients at lower risk for local recurrence (those >60 years of age with a small tumor size and favorable tumor biology). The use of partial breast irradiation was not allowed. Procedures to ensure the quality of radiotherapy included a central review of radiotherapy plans for the first three patients treated at each center.[9] Dosimetric data were collected in the electronic case report forms for the entire trial population.

TRIAL OUTCOMES

The primary outcome for the first randomization was invasive disease–free survival, prespecified as the period between randomization and the first primary-outcome event (recurrence of local, axillary, or distant invasive disease; death from any cause; occurrence of contralateral invasive breast cancer; or occurrence of second primary invasive cancer of a type other than breast cancer).[12] Because fewer patients had positive sentinel-lymph-node biopsies than expected, invasive disease–free survival was downgraded from a primary to a secondary outcome for the second randomization (in which patients were assigned to undergo sentinel-lymph-node biopsy alone or completion axillary-lymph-node dissection) according to protocol amendment 5. Other secondary outcomes were overall survival, locoregional disease–free survival, ipsilateral axillary recurrence, distant disease–free survival, quality-of-life measures, and dose distribution in ipsilateral axilla levels I through III during radiotherapy.

Patient-reported outcomes were assessed with the use of the European Organisation for Research and Treatment of Cancer (EORTC) 30-item Quality of Life of Cancer Patients questionnaire QLQ-C30 and the EORTC Breast Cancer questionnaire QLQ-BR23 at baseline (before surgery) and 1, 3, 6, 12, and 18 months after surgery.[10] Scores for all the multi-item scales and single-item measures range from 0 to 100. Higher scores on measures of global health status and quality of life indicate a higher quality of life, but higher scores on multi-item symptom scales or individual symptom-related items indicate worse symptoms. Short-term surgical complications within 4 weeks after the final surgery were recorded, and selected long-term complications were documented during the complete follow-up period.

STATISTICAL ANALYSIS

To calculate sample size, we considered the 5-year invasive disease–free survival rate among patients with cN0 or iN0 and T1 or T2 disease to be 88%. To show clinical noninferiority of the omission of axillary surgery, we specified that the surgery-omission group would need to have a 5-year invasive disease–free survival rate of at least 85%, and the upper end of the 95% confidence interval for the hazard ratio for invasive disease or death in the surgery-omission group as compared with the surgery group would need

to be less than 1.271. The overall error rate for a false-positive outcome (alpha) was set to 5%. The error rate for a false-negative result (beta) was set to 20% — that is, the trial was calculated to have 80% power to confirm noninferiority according to the specified criteria.

After adjustment for randomization in a 1:4 ratio according to the method of Hsieh,[13] we calculated that a total of 851 primary-outcome events and a per-protocol population of 5230 (1046 in the surgery-omission group and 4184 in the surgery group) would be needed for the first randomization. With the assumption that 5% of patients would have to be excluded from the per-protocol analysis, approximately 5505 patients would be needed for the first randomization. We planned for the final efficacy analysis to be event driven and to be performed when 851 primary-outcome events for the first randomization had occurred in the per-protocol population. In the case of lower rates of events than expected, we planned for a time-driven analysis to be performed after the last-recruited patient had completed a follow-up of 5.5 years.

The analysis of the primary outcome was performed with the per-protocol population because of the noninferiority design of the trial.[14,15] Primary-outcome results for the per-protocol and intention-to-treat populations and the results of a sensitivity analysis that does not exclude patients who did not undergo radiotherapy are reported.

The analyses were performed with data available as of August 30, 2024, after nearly 5.5 years of follow-up for the last patient enrolled, because 851 events had not yet accrued. The Kaplan–Meier product-limit method was used to estimate rates of 5-year invasive disease–free survival (reported with two-sided 95% confidence intervals). Noninferiority was tested on the basis of the confidence interval of the hazard ratio from the Cox proportional-hazards model to exclude a hazard ratio of 1.271 or above for invasive disease or death. A multivariate Cox proportional-hazards model was used to adjust hazard ratios according to stratification factors (age, tumor size, and tumor grade). The homogeneity of findings among subgroups stratified according to age, tumor size, tumor grade, and histologic subtype was explored with the use of univariate Cox regressions. The Pocock minimization method[16] was used for trial-group assignment, with groups stratified according to specified stratification criteria.

Analyses were performed with the use of SAS, version 9.4, with SAS Enterprise Guide version 8.3. No adjustment for multiple comparisons was made. All confidence intervals and tests were two-sided; the widths of the confidence intervals have not been adjusted for multiple comparisons and should not be used in place of hypothesis testing of secondary outcomes.

RESULTS

PATIENT CHARACTERISTICS

Between September 2015 and April 2019, a total of 5502 patients were recruited for the first randomization, and 5154 were included in the intention-to-treat population (1030 assigned to undergo treatment without sentinel-lymph-node biopsy and 4124 to undergo sentinel-lymph-node biopsy). A total of 348 patients (6.3%) withdrew from the trial; the main reasons for withdrawal were secondary mastectomy and withdrawal of consent before completion of breast surgery. After exclusion of an additional 296 patients for various reasons (e.g., lack of postoperative radiotherapy), a total of 4858 patients (962 assigned to undergo treatment without sentinel-lymph-node biopsy and 3896 to undergo sentinel-lymph-node biopsy) were included in the per-protocol population (Fig. 1). Characteristics of the patients in the per-protocol population are presented in Table 1. All baseline characteristics were well balanced between trial groups, and the demographic and clinical characteristics of the trial population were similar to those of the general population of patients who undergo treatment for breast cancer in Germany and Austria. Although data on race or ethnic group were not collected specifically as part of the trial, the majority of the patients were White, which reflects the general population in the areas surrounding the trial sites but may not be representative of patients with breast cancer in other geographic regions. The median age at cancer diagnosis was 62.0 years (range, 24.0 to 89.0; interquartile range, 53.0 to 68.0). Only 527 patients (10.8%) were enrolled at less than 50 years of age. The median preoperative tumor size was 15 mm (interquartile range, 10 to 20) as assessed by palpation and 11 mm (interquartile range, 8 to 16) as assessed

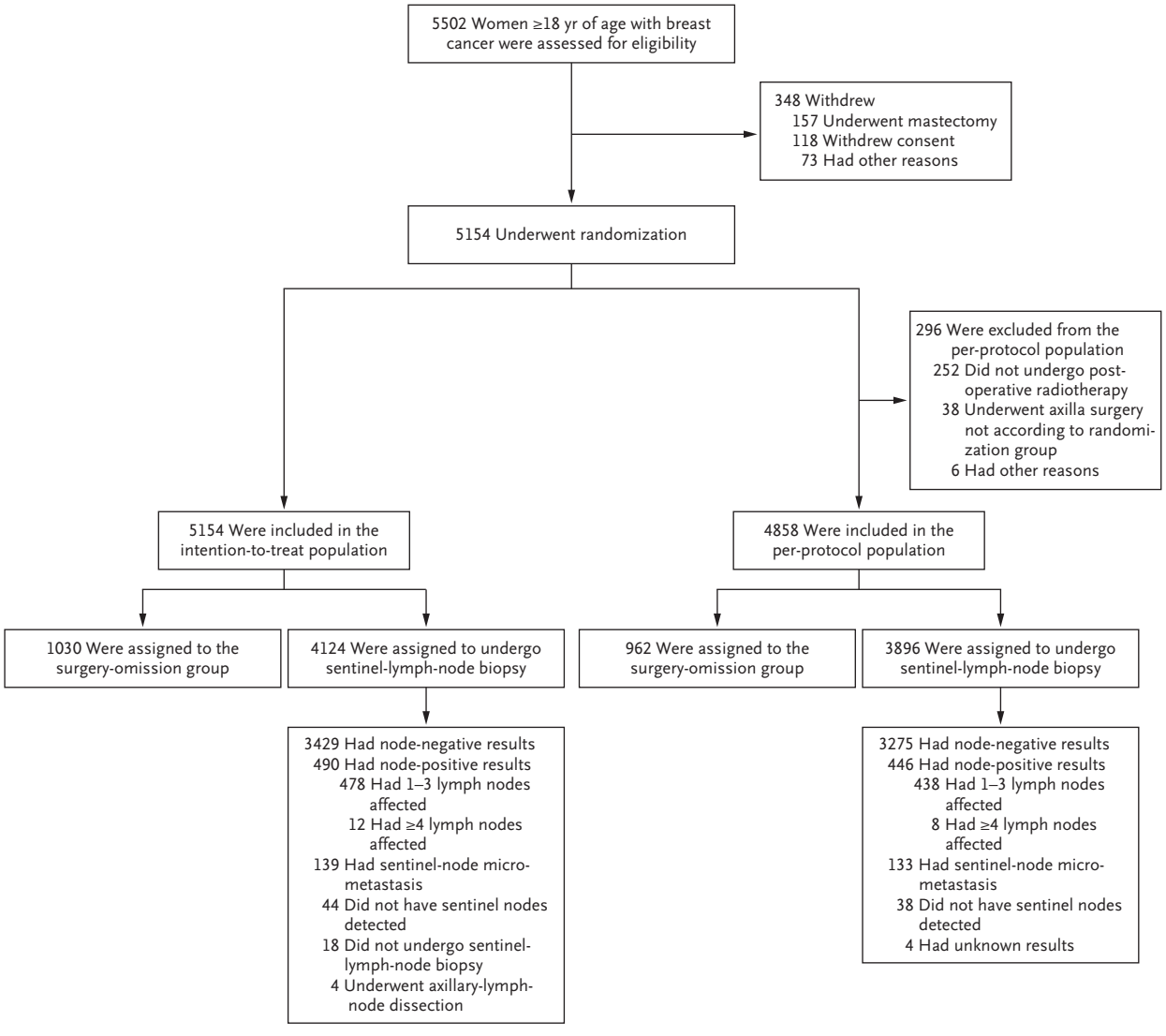


Figure 1. Randomization and Analysis.

Failed sentinel-lymph-node mapping was an indication for axillary-lymph-node dissection according to the trial protocol, based on the guideline released by the American Society of Breast Surgeons in November 2014.

by imaging (94.7% of patients who underwent imaging underwent sonography); 4392 patients (90.4%) had cancer staged as clinical T1, and 3855 (79.4%) had pathological T1 cancer. Among the subgroup of 466 patients (9.6%) with clinical T2 cancer, the median tumor size in both trial groups was 25 mm (interquartile range in the surgery-omission group, 22 to 29; interquartile range in the surgery group, 22 to 28). In the surgery group, 579 of 3854 patients (15.0%) with sentinel lymph nodes detected and a known nodal status had cancer-positive sentinel nodes; 133 patients (3.5%) had micrometastases, 438 (11.4%) had one to three macrometastases, and 8 (0.2%) had at least four positive nodes. The incidence of sentinel-node positivity for micro- and macrometastases was higher in the subgroup of patients with T2 cancer than in the subgroup with T1 cancer (Table S1 in the Supplementary Appendix, available at NEJM.org). Among the 253

Table 1. Demographic and Clinical Characteristics of Patients in the Per-Protocol Population.*

Characteristic	No Sentinel-Lymph-Node Biopsy (N=962)	Sentinel-Lymph-Node Biopsy (N=3896)	All Patients (N=4858)
Age — no. (%)			
<35 yr	4 (0.4)	6 (0.2)	10 (0.2)
35 to <50 yr	110 (11.4)	407 (10.4)	517 (10.6)
50 to <60 yr	295 (30.7)	1278 (32.8)	1573 (32.4)
60 to <70 yr	355 (36.9)	1454 (37.3)	1809 (37.2)
≥70 yr	198 (20.6)	751 (19.3)	949 (19.5)
BMI — no./total no. (%)†			
<30	716/961 (74.5)	2913/3896 (74.8)	3629/4857 (74.7)
≥30	245/961 (25.5)	983/3896 (25.2)	1228/4857 (25.3)
Unknown	1	0	1
Preoperative tumor size — no (%)‡			
≤2 cm	871 (90.5)	3521 (90.4)	4392 (90.4)
>2 cm	91 (9.5)	375 (9.6)	466 (9.6)
Pathological tumor stage — no. (%)§			
pT0, pTis, or pTX	6 (0.6)	34 (0.9)	40 (0.8)
pT1	773 (80.4)	3082 (79.1)	3855 (79.4)
pT2	177 (18.4)	756 (19.4)	933 (19.2)
pT3 or pT4	6 (0.6)	24 (0.6)	30 (0.6)
Nodal status — no./total no. (%)¶			
Sentinel lymph nodes			
pN0		3275/3854 (85.0)	
pN1mi		133/3854 (3.5)	
pN1		438/3854 (11.4)	
pN2		8/3854 (0.2)	
Unknown		4	
All lymph nodes			
pN0		50/253 (19.8)	
pN1mi		1/253 (0.4)	
pN1		169/253 (66.8)	
pN2		33/253 (13.0)	
ER and PR status — no./total no. (%)‖			
Negative	15/961 (1.6)	58/3893 (1.5)	73/4854 (1.5)
Positive	946/961 (98.4)	3835/3893 (98.5)	4781/4854 (98.5)
Unknown	1	3	4
HER2 status — no./total no. (%)			
Negative	914/958 (95.4)	3755/3885 (96.7)	4669/4843 (96.4)
Positive	44/958 (4.6)	130/3885 (3.3)	174/4843 (3.6)
Unknown	4	11	15

Table 1. (Continued.)

Characteristic	No Sentinel-Lymph-Node Biopsy (N=962)	Sentinel-Lymph-Node Biopsy (N=3896)	All Patients (N=4858)
Intrinsic subtype — no./total no. (%)			
HR positive, HER2 negative	905/958 (94.5)	3705/3884 (95.4)	4610/4842 (95.2)
HER2 positive	44/958 (4.6)	130/3884 (3.3)	174/4842 (3.6)
Triple-negative breast cancer**	9/958 (0.9)	49/3884 (1.3)	58/4842 (1.2)
Tumor grade — no. (%)††			
G1	372 (38.7)	1463 (37.6)	1835 (37.8)
G2	552 (57.4)	2294 (58.9)	2846 (58.6)
G3	38 (4.0)	139 (3.6)	177 (3.6)
Ki-67 index — no./total no. (%)‡‡			
≤20%	800/909 (88.0)	3220/3705 (86.9)	4020/4614 (87.1)
>20%	109/909 (12.0)	485/3705 (13.1)	594/4614 (12.9)
Unknown	53	191	244
Histologic subtype — no./total no. (%)			
Invasive carcinoma (no special type)	726/962 (75.5)	2828/3895 (72.6)	3554/4857 (73.2)
Invasive or mixed lobular carcinoma	125/962 (13.0)	491/3895 (12.6)	616/4857 (12.7)
Other	111/962 (11.5)	576/3895 (14.8)	687/4857 (14.1)
Unknown	0	1	1

* When numbers and total numbers are given, patients with missing data are not included in the total numbers. Percentages may not total 100 because of rounding. HER2 denotes human epidermal growth factor receptor 2, and HR hormone receptor.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

‡ Tumor sizes were determined with the use of sonography. If sonography results were unavailable, results from mammography or magnetic resonance imaging were used, in that order.

§ Pathological (p) stages indicate the following tumor sizes and characteristics: T0, no evidence of primary tumor; Tis, carcinoma in situ; TX, the primary tumor cannot be assessed; T1, the tumor is 2 cm across or less; T2, the tumor is more than 2 cm across but not more than 5 cm; T3, the tumor is more than 5 cm across; and T4, the tumor (of any size) is growing into the chest wall or skin.

¶ The involvement of lymph nodes is indicated as follows: pN0, no nodes involved; pN1mi, micrometastases (≥0.2 mm to ≤2 mm) are present in one to three axillary lymph nodes; pN1, cancer has spread to one to three axillary lymph nodes; and pN2, cancer has spread to four to nine lymph nodes. The involvement of sentinel nodes was assessed by sentinel-lymph-node biopsy, and the involvement of all nodes (sentinel and nonsentinel) was assessed by sentinel-lymph-node biopsy plus completion axillary-lymph-node dissection. A total of 3858 patients had sentinel lymph nodes detected, but the biopsy result was unavailable for 4 patients.

‖ Negative indicates that breast cancer cells were negative for both estrogen receptors (ER) and progesterone receptors (PR); positive indicates that cells were positive for ER, PR, or both.

** Triple-negative breast cancer is negative for HR (ER and PR) and HER2.

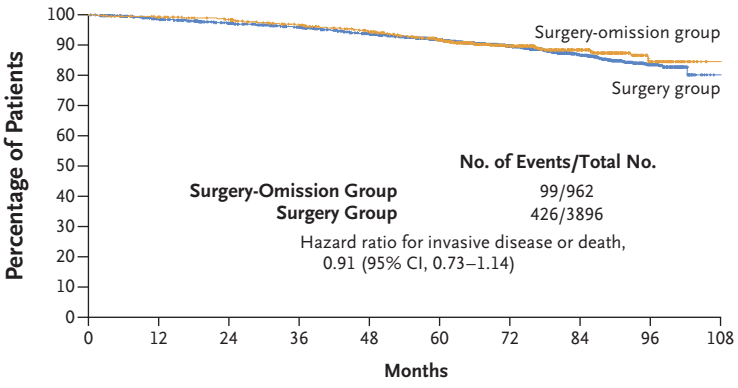
†† Tumor grade refers to the appearance of cancer cells; grades range from G1 to G4, with higher numbers indicating greater abnormality of cells.

‡‡ Ki-67 is a protein in the nucleus of cancer cells. The Ki-67 index indicates the percentage of cancer cells that are actively growing and dividing.

patients who underwent completion axillary-lymph-node dissection, 169 (66.8%) had pathological N1 (pN1) cancer (one to three macrometastases) and 33 (13.0%) had pN2 cancer (at least four positive nodes) according to results for both sentinel and nonsentinel nodes.

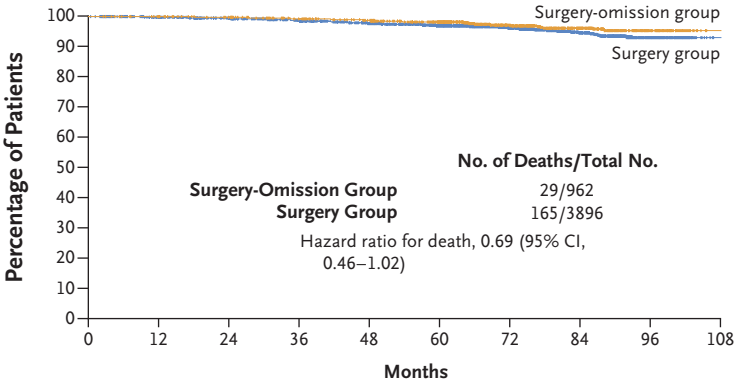
No differences between trial groups with respect to the application of postoperative systemic

A Invasive Disease–free Survival in the Per-Protocol Population



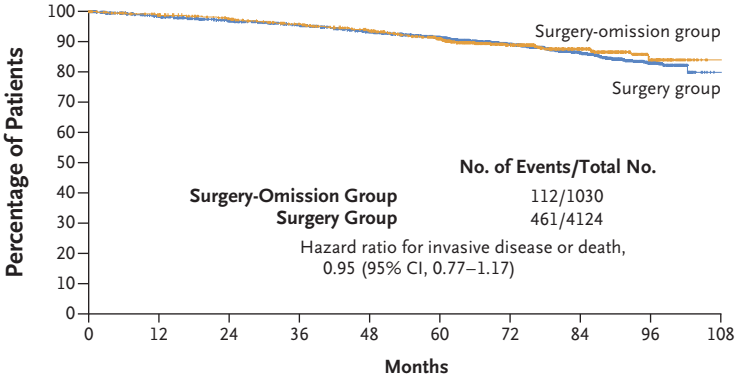
No. at Risk										
Surgery-omission group	962	942	918	877	832	743	477	272	82	0
Surgery group	3896	3726	3582	3459	3286	2950	1842	1008	329	0

B Overall Survival in the Per-Protocol Population



No. at Risk										
Surgery-omission group	962	950	931	900	871	793	517	289	88	0
Surgery group	3896	3769	3659	3554	3417	3110	1978	1098	360	0

C Invasive Disease–free Survival in the Intention-to-Treat Population



No. at Risk										
Surgery-omission group	1030	997	961	917	865	774	494	283	83	0
Surgery group	4124	3891	3732	3597	3409	3051	1907	1039	336	0

Figure 2 (facing page). Kaplan–Meier Estimates of Primary and Secondary Outcomes in the Per-Protocol and Intention-to-Treat Populations.

Shown are Kaplan–Meier curves of invasive disease–free survival (Panel A) and overall survival (Panel B) in the per-protocol population and invasive disease–free survival in the intention-to-treat population (Panel C). Patients were assigned to undergo breast-conserving therapy without sentinel-lymph-node biopsy (the surgery-omission group) or with sentinel-lymph-node biopsy (the surgery group).

treatment were observed, except for chemotherapy (Table S2); the percentage of patients who received adjuvant chemotherapy was higher in the surgery group than in the surgery-omission group (12.9% vs. 10.4%).

OUTCOME ANALYSES

The median follow-up was 73.6 months (interquartile range, 61.3 to 86.4), with an overall completeness of follow-up of 88.5% as calculated according to the method of Clark et al.[17] The primary analysis of invasive disease–free survival among the per-protocol population shows that the omission of axillary surgery was noninferior to sentinel-lymph-node biopsy (hazard ratio, 0.91; 95% confidence interval [CI], 0.73 to 1.14) according to the prespecified noninferiority margin of 1.271 for the upper end of the confidence interval for the hazard ratio (Fig. 2A). The estimated 5-year invasive disease–free survival rate was 91.9% (95% CI, 89.9 to 93.5) in the surgery-omission group and 91.7% (95% CI, 90.8 to 92.6) in the surgery group. The analysis of 5-year invasive disease–free survival with respect to tumor size yielded a broader confidence interval for the subgroup of patients with T2 cancer (hazard ratio, 0.71; 95% CI, 0.39 to 1.32) than for those with T1 cancer but was generally consistent with the results obtained for the group with T1 cancer (hazard ratio, 0.95; 95% CI, 0.75 to 1.20) (Fig. S1A and S1B).

Although an event-driven analysis was planned, fewer than 851 primary-outcome events had occurred by 5.3 years after the last patient was enrolled; therefore, according to the prespecified plan, the analysis of invasive disease–free survival was conducted without waiting for additional events to occur. This analysis includes 525 events, which provides the trial with less power than was estimated with 851 events. The first primary-outcome events (occurrence or recurrence of invasive disease or death) in the surgery-omission group and the surgery group are listed in Table 2. No major differences with respect to numbers of primary-outcome events were observed between patients with T1 tumors and those with T2 tumors (Table S1). The estimated 5-year overall survival rate was 98.2% (95% CI, 97.1 to 98.9) in the surgery-omission group and 96.9% (95% CI, 96.3 to 97.5) in the surgery group (Fig. 2B).

All similar intention-to-treat and sensitivity analyses confirmed the primary-outcome result in the per-protocol population. Among the intention-to-treat population, the analysis of invasive disease–free survival shows that the omission of axillary surgery was noninferior to sentinel-lymph-node biopsy; this analysis included 573 primary-outcome events (an incidence of 11.1%). The Kaplan–Meier plot (Fig. 2C) shows no significant difference between the curves, with a hazard ratio of 0.95 (95% CI, 0.77 to 1.17) for invasive disease or death in the surgery-omission group as compared with the surgery group. The distribution of the first primary-outcome events in the surgery-omission group as compared with the surgery group was similar to that in the per-protocol analysis (invasive locoregional recurrence, 2.1% vs. 1.6%; axillary recurrence, 1.0% vs. 0.4%; invasive contralateral breast cancer, 1.1% vs. 0.6%; distant metastases, 2.6% vs. 2.8%; secondary cancer, 3.3% vs. 3.7%; and death, 1.7% vs. 2.5%). The estimated 5-year invasive disease–free survival rate among the intention-to-treat population was 91.1% (95% CI, 89.1 to 92.7) in the surgery-omission group and 91.4% (95% CI, 90.4 to 92.2) in the surgery group.

The multivariate Cox regression according to stratification factors provided a hazard ratio for invasive disease or death among the per-protocol population similar to that in the primary analysis. An age of 65 years or more, a preoperative tumor size of greater than 2 cm, and a tumor grade of G3 were associated with shorter invasive disease–free survival (Table S3). The univariate Cox regression for invasive disease–free survival among subgroups stratified according to age, tu-

Table 2. Summary of Primary-Outcome Events in the Per-Protocol Population.

Event	No Sentinel-Lymph-Node Biopsy (N=962)	Sentinel-Lymph-Node Biopsy (N=3896)	All Patients (N=4858)
Any primary-outcome event — no. (%)			
No	863 (89.7)	3470 (89.1)	4333 (89.2)
Yes	99 (10.3)	426 (10.9)	525 (10.8)
First primary-outcome event — no. (%)			
Invasive locoregional relapse	18 (1.9)	54 (1.4)	72 (1.5)
Invasive contralateral breast cancer	10 (1.0)	25 (0.6)	35 (0.7)
Distant relapse	26 (2.7)	104 (2.7)	130 (2.7)
Secondary cancer	32 (3.3)	150 (3.9)	182 (3.7)
Death	13 (1.4)	93 (2.4)	106 (2.2)
Locoregional relapse — no. (%)			
Axillary recurrence	10 (1.0)	12 (0.3)	22 (0.5)
Invasive ipsilateral breast recurrence	8 (0.8)	42 (1.1)	50 (1.0)
Death from any cause — no./ total no. (%)			
Breast cancer	0	1/93 (1.1)	1/106 (0.9)
Second, nonbreast cancer	0	3/93 (3.2)	3/106 (2.8)
Other known cause	7/13 (53.8)	43/93 (46.2)	50/106 (47.2)
Unknown cause	6/13 (46.2)	46/93 (49.5)	52/106 (49.1)

mor size, tumor grade, and histologic subtype showed no substantial heterogeneity in hazard ratios (in the surgery-omission group as compared with the surgery group) among subgroups (Fig. 3).

SURGICAL COMPLICATIONS

The incidence of short-term surgery-related complications (Table S4) confirmed previously published data.[10] The long-term safety analysis indicates that patients in the surgery-omission group as compared with those in the surgery group had reduced incidence of lymphedema (1.8% vs. 5.7%), restriction of arm or shoulder mobility (2.0% vs. 3.5%), and pain with arm or shoulder movement (2.0% vs. 4.2%), all conditions that were unresolved at the last follow-up visit (Table S5).

DISCUSSION

In this trial involving patients with cN0, T1 or T2 invasive breast cancer (90% of whom had clinical T1 cancer), omission of surgical axillary staging was noninferior to sentinel-lymph-node biopsy after a median follow-up of approximately 6 years. The 5-year invasive disease–free survival in our trial is consistent with the results of the SOUND trial.[8] Both trials have shown the noninferiority of omitting standard sentinel-lymph-node biopsy in patients with cN0 breast cancer and upfront breast-conserving surgery.

According to current guidelines from Ontario Health (Cancer Care Ontario) and the American Society of Clinical Oncology, sentinel-lymph-node biopsy is not required for patients 70 years of age or older with T1cN0 invasive breast cancer that is hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER2) negative.[18] This recommendation is based on long-term follow-up of the Cancer and Leukemia Group B (CALGB) 9343,[19] Milan,[20] and International Breast Cancer Study Group (IBCSG) 10-93 trials.[21] The general statement on axillary staging in the current guidelines for breast cancer from the National Comprehensive Cancer Network (version 5.2024) and the National Institute for Health and Care Excellence (last updated in January 2024) has not been modified since the publication of SOUND data.[22,23]

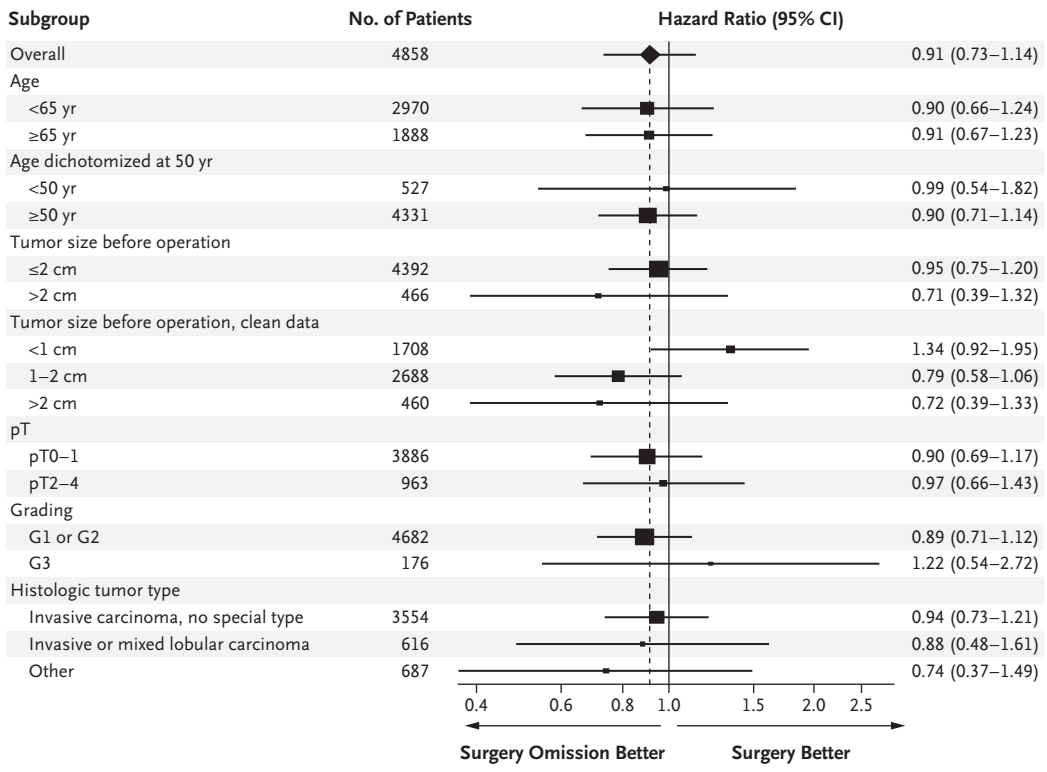


Figure 3. Invasive Disease–free Survival According to Subgroup.

The forest plot was created with the use of univariate Cox regression. The preoperative tumor size was determined on the basis of sonography. If results from sonography were unavailable, results from mammography or magnetic resonance imaging were used, in that order. The abbreviation pT indicates pathological tumor stage, as follows: pT0–1, no evidence of tumor or tumor is ≤2 cm across; pT2–4, tumor is >2 cm across. The size of the squares is proportional to the number of patients in the subgroup.

Although invasive disease–free survival was the primary outcome, axillary recurrence was an important secondary outcome in a trial focused on the omission of axillary surgery. The incidence of recurrence of 1.0% in the surgery-omission group and 0.3% in the surgery group warrants mention, even though the incidence was low in both groups. This difference between groups is in line with the results of randomized trials in the era before sentinel-lymph-node biopsy, which all showed higher incidence of axillary recurrence with no axillary surgery than with axillary-lymph-node dissection but no effect of this difference on disease-free or overall survival.[21,24-26]

Our trial differs from the SOUND trial in some aspects of the trial design. We recruited 5502 patients with early-stage breast cancer (T1 or T2; tumor size, ≤5 cm), and the SOUND trial enrolled 1405 patients with smaller carcinomas up to 2 cm. However, the median tumor size in the two trials was practically the same (approximately 11 mm as assessed by imaging), probably owing to selection bias. As mentioned above, the primary outcomes differed (invasive disease–free survival in our trial vs. distant disease–free survival in the SOUND trial), which led to higher rates of primary-outcome events in our trial. The median age of patients, the median follow-up, and the dominant intrinsic subtype of breast cancer (HR positive and HER2 negative) seem comparable between the two trials. In both trials, patients with HER2-positive and triple-negative (HR-negative and HER2-negative) breast cancer, who are candidates for neoadjuvant systemic therapies, were underrepresented. For patients with small, HER2-positive tumors, the nodal status

seems particularly important with regard to the decision between de-escalated adjuvant systemic therapy and neoadjuvant systemic therapy in light of results from the Adjuvant Paclitaxel and Trastuzumab (APT) trial.[27]

The de-escalation of axillary surgery during breast-conserving surgery must be discussed in the context of radiotherapy treatment to interpret oncologic outcomes accurately. Given the frequent use of protocol-prohibited nodal fields in the ACOSOG Z0011 trial,[28] a preplanned central quality-assurance process was included in our trial protocol.[9] At least 50% of 276 patients included in the central review received at least 80% of the radiotherapy dose prescribed for the breast in axillary level I. Median incidental doses in axillary levels I and II were 85.4% and 14.9% of the dose prescribed for the breast, respectively. No differences between trial groups with respect to the incidental dose to the axilla were observed. Subgroup analyses revealed that the incidental radiation dose in patients with obesity was significantly higher than that in other patients, but the dose in patients who received a boost of radiation to the tumor bed was not significantly higher, a finding that is contrary to the quality-assurance data from the BOOG 2013-08 trial.[29]

Preoperative axillary ultrasonography was performed for nodal evaluation in our trial and the SOUND trial, and the incidence of false-negative findings from axillary ultrasonography is reported to be approximately 10% in the sentinel-node-biopsy group in both trials (11.5% in our trial vs. 8.7% in the SOUND trial for patients with pathological T1 or higher-stage tumors). However, sentinel-lymph-node biopsy itself has a false-negative rate of 6 to 10%,[30] which means that the true incidence of false-negative findings from axillary ultrasonography in both trials may be higher than reported. No clear criteria have been defined for simple but reproducible and validated categorization of cancer as iN0 in the preoperative setting. Recently, a review by van Nijnatten et al. provided an overview of four de-escalation trials and compared differences in protocols for axillary ultrasonography and techniques for axillary ultrasonography–guided biopsy.[31] Of note, no consensus has been reached on the cutoff value for cortical thickness in axillary ultrasonography.

Our trial provides important information with regard to patient selection for the omission of sentinel-lymph-node biopsy.[32] Approximately 90% of patients in our trial were 50 years of age or older, and 95% presented with a luminal intrinsic tumor subtype (HR positive and HER2 negative); patients with the combination of these two characteristics can be considered to be eligible for the omission of sentinel-lymph-node biopsy. The trial included few patients with tumors larger than 2 cm, and the results for this subgroup had wide confidence intervals, which precludes definitive conclusions.

The lack of information on nodal status may have a considerable effect on the management of treatment for patients with early-stage breast cancer. The importance of nodal involvement in clinical decision making with regard to adjuvant systemic therapy in postmenopausal patients with one to three involved lymph nodes has decreased.[33,34] However, information on nodal involvement is still a major factor in the indication of regional nodal irradiation in node-positive disease,[35] as well as in the selection of de-escalation strategies, such as partial breast irradiation or the omission of whole-breast irradiation in proven node-negative disease.[36] The potential consequences of the omission of sentinel-lymph-node biopsy for postoperative radiotherapy must be weighed against the benefits in terms of improved quality of life and reduced risk of short-term and persistent long-term complications.

This trial has numerous strengths. First, data from the comparison between the omission of axillary surgery and the inclusion of sentinel-lymph-node biopsy have been obtained from an extensive trial population. The results showing noninferiority in both the intention-to-treat and per-protocol analyses led to increased confidence in the trial results. Second, this publicly funded academic trial reached the planned target recruitment numbers within a shorter period than expected (<4 years), which reduced the potential for imbalances in systemic therapies. Finally, patient-reported outcomes and incidental axillary irradiation doses during whole-breast irradiation (assessed prospectively) are secondary outcomes for the entire trial population.

However, our trial has several limitations. First, the significance of reported results is restricted to a low-risk population (patients ≥50 years of age with grade G1 or G2 tumors) with HR-positive, HER2-negative invasive breast cancer

and a tumor size up to 3 cm. Only 20% of patients in this trial had pT2 lesions (>2 cm but ≤5 cm); thus, the evidence for that subgroup is not as robust as that for patients with lesions up to 2 cm. The median preoperative tumor size (11 mm) is far below the eligible tumor size, which has implications for external validity and implementation. The percentage of high-grade G3 tumors (3.6%) in this trial was comparable to the 7% of G3 tumors in the low-risk cohort of the TAILORx (Hormone Therapy with or without Combination Chemotherapy in Treating Women Who Have Undergone Surgery for Node-Negative Breast Cancer) trial, which included patients with HR-positive, HER2-negative breast cancer and a recurrence score of no more than 10 based on a 21-gene assay.[37] One reason for the low percentage of G3 tumors in our trial is that patients with higher-risk tumors, such as HER2-positive or triple-negative breast cancer, were not enrolled in this trial because these patients are candidates for neoadjuvant systemic therapy. Another reason is the importance of nodal status as a factor in the decision to use chemotherapy for G3 tumors (multigene signatures such as those provided by the Oncotype DX and MammaPrint tests were not available during the recruitment period). In addition, the assumed 5-year invasive disease–free survival rate of 88% contrasts with the observed rates of 91.9% and 91.7% in each trial group. Finally, the median follow-up of 73.6 months is appropriate for reporting 5-year survival data but can miss late recurrences of HR-positive diseases.[38]

Our trial shows that the omission of axillary-sentinel-lymph-node biopsy does not compromise survival in patients with early-stage, cN0 breast cancer who plan to undergo primary breast-conserving surgery. This de-escalation concept may be suitable for patients 50 years of age or older who present with low-risk (grade G1 or G2), HR-positive, HER2-negative invasive breast cancer and clinical T1 tumors.

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APPENDIX

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