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Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial

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Summary

Background—Sentinel node surgery was designed to minimize side effects of lymph node surgery but still offer outcomes equivalent to axillary dissection. The aims of NSABP Protocol B-32 were to determine whether sentinel node resection in breast cancer patients achieves the same survival and regional control as axillary dissection but with fewer side effects.

Methods—5611 women with invasive breast cancer were randomly assigned to sentinel node resection plus axillary dissection (Group 1) or to sentinel node resection alone with axillary dissection only if sentinel nodes were positive (Group 2). Random assignment was done at the NSABP Biostatistical Center and accomplished via using a biased coin minimization approach. Stratification variables were age at entry (≤ 49,≥ 50), clinical tumor size (≤ 2.0 cm, 2.1 – 4 cm, ≥ 4.1 cm), and surgical plan (lumpectomy, mastectomy). Sentinel node resection was done using blue dye and radioactive tracer. As pre-specified in the protocol, analyses of endpoint data were performed according to the randomized group assignments on patients who were assessed at the time of randomization as having pathologically negative sentinel nodes (3989 patients). The endpoint analyses were performed on all such patients who had follow-up information regardless of their eligibility status (3986 patients). The primary endpoint for the study was overall survival. All deaths regardless of cause were included. The mean time on study for the 3986 sentinel node-negative patients with follow-up information was 95.6 months (range: 70.1 – 126.7 months).

Findings—A total of 309 deaths were reported in the 3986 sentinel node-negative patients with follow-up information. Log-rank comparison of overall survival in Groups 1 and 2 yielded an unadjusted hazard ratio of 1.20 (95% confidence interval [CI]; 0.96 –1.50, P = 0.12). Eight-year Kaplan-Meier estimates for overall survival are 91.8% in Group 1 and 90.3% in Group 2. Treatment comparisons for disease-free survival yielded an unadjusted hazard ratio of 1.05 (95% CI: 0.90 – 1.22, P=0.54). Eight-year Kaplan-Meier estimates for disease-free survival are 82.4% in Group 1 and 81.5% in Group 2. There were 8 regional node recurrences as first events in Group 1 and 14 in Group 2 (P=0.22). Patients are continuing follow up for longer term evaluation of survival and regional control.

Interpretation—Overall survival, disease-free survival, and regional control were statistically equivalent between groups. When the sentinel node is negative, sentinel node surgery alone with no further axillary dissection is an appropriate, safe, and effective therapy for breast cancer patients with clinically negative lymph nodes.

Keywords

sentinel node; breast cancer; randomized trial; survival; axillary dissection

INTRODUCTION

Axillary node dissection for breast cancer is a procedure originally designed to maximize survival and regional control and to determine the nodal classification. This procedure is associated with short and long term side effects in a substantial number of patients.[1,2]

Sentinel node resection was designed to minimize side effects of lymph node surgery but still offer outcomes equivalent to axillary node dissection. The National Surgical Adjuvant

Breast and Bowel Project (NSABP) B-32 trial was designed to determine whether sentinel node resection achieves the same therapeutic outcomes as axillary dissection but with fewer side effects. The primary endpoints of the B-32 trial are survival, regional control, and morbidity. Technical outcomes and assessment of the training methods for this trial have been previously reported.[3,4] Patient-reported outcomes and morbidity related to range of motion, edema, pain, and sensory defects are also being reported.[5,6] An ancillary pathology study evaluating the survival related to detection of occult node metastases in 3887 sentinel node negative cases has been completed and will be reported separately.

Herein we report the primary outcomes data from the largest randomized sentinel node trial, NSABP Protocol B-32. The data presented are based on a controlled, randomized trial that used standardized surgical and pathological methods to ensure that the primary outcomes were as comparable as possible between the treatment groups.

Methods

NSABP Protocol B-32 (ClinicalTrials.gov., NCT00003830, CONSORT diagram) was undertaken after approval from local institutional review boards and in accord with assurances filed with and approved by the US Department of Health and Human Services. Informed written consent was obtained from each participant in this study.

Trial Design

Women with invasive breast cancer and clinically negative nodes were eligible to be randomly assigned to sentinel node resection plus axillary dissection (Group 1) or to sentinel node resection alone with axillary dissection only if sentinel nodes were positive (Group 2) (Schema, Fig 1). Patients in both groups with pathologically negative sentinel nodes were monitored at 4 to 6 month intervals for the primary outcomes of overall survival, disease-free survival, and regional control. Patients in Group 1 with negative sentinel nodes and positive non-sentinel nodes were included in Group 1 as sentinel node-negative. This trial was designed to detect a survival difference of 2% between sentinel node-negative patients in the two groups at 5 years. All primary outcomes reported here are on the sentinel node-negative patients.

From May 1, 1999 through February 29, 2004, 5611 women were enrolled in the study by 233 surgeons from 80 academic and community institutions in the United States and Canada. Patients were randomly assigned at an overall allocation ratio of 1:1 to a treatment group via a centralized mechanism at the NSABP Biostatistical Center. A stratified randomization was performed using a biased coin minimization approach.[7] The stratification factors included age at entry (≤ 49, ≥ 50), clinical tumor size (≤ 2.0 cm, 2.1 – 4.0 cm, ≥ 4.1 cm), and surgical treatment plan (lumpectomy, mastectomy).

As pre-specified in the protocol, 300 deaths were required in order to trigger the definitive endpoint analysis. This requirement was met in December 2009. Formal interim endpoint analyses were presented to an external Data Monitoring Committee (DMC) after 71, 148, and 242 deaths had been reported. In all cases, the committee recommended continuation of the trial without divulging early results.

Training and Quality Control

Details of training and quality control have been previously reported.[3] Surgeons and pathologists were required to follow specific protocols for performing sentinel node surgery, labeling of lymph nodes, and for pathological analysis of the lymph nodes. Performance audits documented excellent adherence to protocol.[4]

Surgical and Pathological Procedures

Technetium-99m sulfur colloid was injected into the breast around the tumor and intradermally over the tumor from 30 minutes to 8 hours before surgery. Isosulfan blue was injected into the breast around the tumor 5 minutes before incision.[8] Lymph nodes that were radioactive, blue, or clinically positive were considered sentinel nodes. If a non-sentinel node was removed during a sentinel node procedure it was submitted to pathology separate from the sentinel nodes and labeled as a non-sentinel node. Sentinel nodes from both Groups 1 and 2 were evaluated postoperatively with routine stains at approximately 2mm intervals through the node. Immunohistochemistry, except for confirmation of suspicious findings on routine hematoxylin and eosin stains, was not permitted. In addition, sentinel nodes from Group 2 were evaluated intraoperatively using cytology.

Statistical Methods

The calculation of the primary endpoint, overall survival, includes all deaths. Calculation of disease-free survival includes all local, regional, or distant breast cancer recurrences, all second cancers (opposite breast and non-breast), and all deaths.

As pre-specified in the protocol, analyses of endpoint data were performed according to the randomized group assignments on patients who were assessed at the time of randomization as having pathologically negative sentinel nodes (3989 patients). The endpoint analyses were performed on all such patients who had follow-up information regardless of their eligibility status (3986 patients). The follow-up information for the patients who withdrew consent to be followed after they were randomized only included information up to the time of consent withdrawal and did not include any information beyond that time. The B-32 trial was designed so that if a difference in survival of 2% or less between groups for the sentinel node-negative patients was observed, the groups would be declared to be equivalent. 95% confidence intervals [CIs] are reported for the trial primary and secondary endpoints. All CIs and P values are two-sided. The α-level for declaring statistical significance is set at 0.05. Analyses are based on information received through December 31, 2009.

Simple log-rank tests and Cox proportional hazard models were employed to make formal inferences about group comparisons and Kaplan-Meier curves were used to quantify the values of overall survival and disease-free survival over time.[9] In the Cox regression analyses, adjustments were made for the stratification variables.[10] Tests of the validity of the proportionality assumption were conducted via the method proposed by Grambsch and Therneau.[11] Cox models were also used to determine if significant treatment by stratification variable interactions existed with respect to the endpoints.[12] Site-specific failure rates were calculated by using cumulative incidence curves.13,14 These estimates appropriately adjust for competing risks of failure.13 P values for treatment comparisons of cumulative incidence curves were obtained by using cause-specific hazard rates.[15] In the forest plots used to display subset analyses, because the comparisons involve stratification variables, the hazard ratios reflect adjusted treatment comparisons. Statistical analyses were performed using SAS version 8.4 (Cary, NC) and R version 2.8.0.

Results

Patient Characteristics

5611 women were randomized to Group 1 (2807 patients) or Group 2 (2804 patients). Of the 5611 patients, 3989 (71.1%) were sentinel node-negative, of which 3986 (99.9%) had follow-up information. The mean time on study for the 3986 sentinel node-negative patients was 95.6 months (range: 70.1 – 126.7 months). Random assignment of patients to the two treatment arms were balanced according to age, clinical tumor size, and surgical treatment

plan (Table 1). The use of systemic adjuvant therapy was well balanced: 85% of Group 1 and 84.1% of Group 2 patients received systemic adjuvant therapy. Radiation therapy was also well balanced: 82.3% of Group 1 and 82.2% of Group 2 received radiation therapy.

Overall Survival

Among the 3986 women with follow-up information 309 deaths were reported (140/1975 in Group 1 and 169/2011 in Group 2). The average annual mortality rate across the two groups was 1.12% (1.02% and 1.22% in Group 1 and Group 2, respectively). Of the 309 deaths, 109 occurred after the first event was a breast cancer recurrence (50 in Group 1 and 59 in Group 2). Of these 109 deaths, 15 were after a local recurrence (8 in Group 1 and 7 in Group 2), 10 after regional recurrence (3 in Group 1 and 7 in Group 2), and 84 after systemic recurrence (39 in Group 1 and 45 in Group 2). There were 7 deaths after a new contralateral breast cancer (5 in Group 1 and 2 in Group 2). There were 84 deaths after the first event was a second non-breast cancer (37 in Group 1 and 54 in Group 2). Another 109 died (53 in Group 1 and 56 in Group 2) without a recurrence of their breast cancer or a second cancer. In the subset of patients in Group 1 who had positive axillary nodes and negative sentinel nodes, 5 of 75 died (average annual mortality rate=0.98%).

Log-rank comparison of overall survival in Group 1 and Group 2 yielded an unadjusted hazard ratio of 1.20 (95% CI: 0.96 – 1.50, P = 0.12). On average, the patient mortality in Group 1 was favorable to that in Group 2. However, as indicated by inclusion of 1 in the 95% CI for the mortality hazard ratio, the two groups were statistically equivalent to Group 2. Cox proportional hazard analyses adjusting for stratification variables yielded results very similar to those given above (hazard ratio= 1.19, 95% CI: 0.95 – 1.49, P=0.13). The test for the interaction of treatment with all stratification variables combined for overall survival yielded a non-significant result (P=0.25). Furthermore, none of the individual stratification variables had significant interactions with treatment.

Five-year Kaplan-Meier estimates for overall survival are 96.4% in Group 1 and 95.0% in Group 2; the 8-year estimates are 91.8% and 90.3%, respectively (Fig. 2).

Disease-Free Survival

Treatment comparisons for disease-free survival yielded an unadjusted hazard ratio of 1.05 (95% CI: 0.90 – 1.22, P=0.54); the adjusted hazard ratio was 1.07 (95% CI: 0.90 – 1.22, P=0.57). The location of first treatment failure is presented in Table 2. No substantial differences are evident across sites. The average annual event rate pooled across the two arms is 2.49% (2.43% in Group 1 and 2.55% in Group 2). In the subset of patients in Group 1 who had positive axillary nodes but negative sentinel nodes, 10 of 75 had events (average annual event rate=2.06%).

Five-year Kaplan-Meier estimates for disease-free survival are 89.0% in Group 1 and 88.6% in Group 2; the 8-year estimates are 82.4% and 81.5%, respectively (Fig. 3).

A forest plot summarizing the hazard ratios and 95% confidence intervals comparing the two groups for all sites of first treatment failures is given in Fig. 4. No significant differences were observed.

Local and Regional Recurrences

There were 54 local recurrences in Group 1 and 49 in Group 2 (P=0.55). Ninety-nine of the 103 local recurrences were ipsilateral breast tumor recurrences (51 in Group 1 and 48 in Group 2), three were in the chest wall (2 in Group 1 and 1 in Group 2), and one (in Group 1) was in the area of the surgical scar.

There were 8 regional node recurrences as first events in Group 1 and 14 in Group 2 (P=0.22). Among the 22 regional events, 10 were in the axilla (2 in Group 1 and 8 in Group 2), 7 were in the supraclavicular area (3 in Group 1 and 4 in Group 2), one (in Group 1) in the parasternal region, one (in Group 1) in the subclavicular area, and 3 that occurred in both local and regional areas (one in Group 1 and two in Group 2).

Adverse Events—Allergic reactions were reported in 46 patients (0.8%) and 24 were Grade 1, 9 Grade 2, 3 Grade 3 and 10 Grade 4 reactions. The majority of these reactions were related to blue dye.

Discussion

This trial demonstrates that overall survival, disease-free survival, and regional control were all statistically equivalent in sentinel node negative patients who had a completion axillary dissection or sentinel node surgery alone. The observed survival difference between the two groups was less than 2% and any variation observed under that threshold is not significant. Indeed, in a trial of this magnitude exact numerical duplication of events are not expected. There did appear to be a non-significant trend in favor of Group 1. In Group 1, 75 patients had at least one positive non-sentinel node and 95% of this subset was treated with systemic adjuvant therapy. The outcome of these patients was not inferior to the group as a whole (average annual mortality rate: 0.99% vs. 1.02% respectively) even though they were node-positive. In Group 2, a similar subset of non-sentinel node-positive patients was expected. Since their node-positive status was not known, their adjuvant therapy was likely to be similar to the remaining Group 2 patients (84%). This may have modestly contributed to the observed survival trend. Also, following a second non-breast cancer there were 37 deaths in Group 1 and 54 in Group 2. This apparently random event (as indicated by the inclusion of 1 in the HR confidence interval in Fig 4) in favor of Group 1 may have also contributed to the observed trend.

Disease-free survival was not different between the two treatment groups. Comparisons based on sites of first treatment failures also showed no significant differences across all sites. This data further confirms the similarity in outcomes between the two treatment arms.

Each treatment group had less than 1% regional recurrences as first events. Similar to several nonrandomized reports,[16] the B-32 results confirm the low rate of regional node recurrences following sentinel node surgery. The B-32 trial also validates that when the sentinel nodes are negative there is no significant difference in regional node recurrence between axillary node dissection and sentinel node resection.

The results from Protocol B-32 confirm previous reports[1] that patient-reported outcomes and morbidity related to range of motion, edema, pain, and sensory defects is lower in the sentinel node group compared with the axillary dissection group.[5,6] Sentinel node surgery is not without complications and there is a small increase over baseline of extremity edema and functional and neurological deficits.

Randomized trials have been instrumental in effecting changes in the surgical management of breast cancer. One of the last major surgical trial that led to safe reduction of surgery, NSABP Protocol B-06, was initially reported in 1985.[17] The long-standing importance of this trial is demonstrated by the current use of breast-conserving therapy as a major indicator of quality care.[18] Sentinel node surgery represents the next major step in reducing the extent of surgical procedures to treat breast cancer.

The design of randomized trials for breast-conserving therapy and lymph node-sparing surgery are similar. The goals are to preserve tissue but still achieve the same cancer control. A reduction in morbidity is an obvious goal but the more challenging metric is demonstrating that survival is not adversely affected. The B-32 trial was designed so that even a 2% difference in survival would be detected. This narrow difference in survival was chosen to ensure that reduced morbidity would not occur at the expense of reduced survival. This required high total accrual and is why the B-32 trial is the largest randomized surgical trial in breast cancer yet performed.

One measure of quality in trial design is the clarity of the goals.[19] The primary outcomes of B-32 were clearly stated and the trial was monitored regularly by an independent Data Monitoring Committee. Disclosure of trial results was allowed only when overall survival endpoints were met. Assessing narrow differences in the primary outcomes in such a large group of patients mandated careful control of the trial conditions. Patient factors in this trial were well controlled and balanced. This was further validated by the survival results which, when evaluated with all of the stratification variables combined, yielded no significant differences.

Potential imprecision was possible because of the complexity of surgical and pathological procedures. Variation was controlled by a careful preregistration training program that focused on protocol compliance.20 In addition, extensive auditing of enrolled cases evaluated 94 specific items per case. Of the 224 surgeons audited, the outcomes were excellent.[4] The quality of the trial is further supported by the extent of follow-up information (99.9% of cases).

Other sentinel node trials include the American College of Surgeons Oncology Group trial Z0011 that randomized 891 patients with pathologically positive sentinel nodes to axillary dissection or sentinel node only.[21] This study closed prior to meeting accrual goals. A trial from Milan has reported data with follow up to 10 years.[22-24] The primary objective for the Milan trial was “the predictive power of the status of the sentinel node.” Explicit survival data comparing patients who were treated only with sentinel node resection do not appear to be present. The primary outcomes from the ALMANAC trial and the SNAC trials are morbidity, although these well-designed trials do not address survival.[25,26]

The AMAROS trial (EORTC 10981-22023) is another well-designed randomized trial comparing axillary surgery to sentinel node and radiation therapy with no further axillary surgery.[27] The primary objectives for the AMAROS trial are local and regional control and morbidity.

Data combined from available randomized trials of axillary dissection versus no axillary surgery indicated a modest survival advantage to axillary dissection.[28] Survival has also been significantly associated with the number of nodes removed.[29] Sentinel node surgery is neither observation-only nor removal of suspicious nodes from a fixed anatomic location. It is a highly targeted removal of the lymph nodes receiving direct drainage from a solid tumor in the breast. The results from B-32 demonstrate that in the sentinel node-negative population, any survival advantage to full axillary dissection is fully mitigated by simply removing the sentinel nodes.

Surgeons should continue to strive to optimize the methods of sentinel node surgery. For example, removal of only a single sentinel node increases the risk for false-negative sentinel node resection. Improving methods to validate that the nodes removed are in fact on the immediate drainage pathway from the cancer is important.[3] Life-threatening anaphylactic reactions related to dyes occur in approximately 0.25% to 0.5% of cases.[30] Genotoxity of blue dyes in the form of DNA strand breaks and increased levels of oxidative DNA lesions

have been reported after very brief exposure to cells in vitro.[31] There are clearly unfinished areas of research in the field of sentinel node surgery.

Conclusion

In summary, in NSABP Protocol B-32, overall survival, disease-free survival, and regional control between the treatment groups were statistically equivalent. We conclude that when the sentinel node is negative, sentinel node surgery alone with no further axillary dissection is an appropriate, safe, and effective therapy for breast cancer patients with clinically negative lymph nodes.

Research in Context

Systematic Review

A systematic review was done by reading all articles available through PubMed that matched the query “sentinel” and “breast.” This number currently totals 3108. No randomized trial results addressing survival or regional control were published at the time that NSABP Protocol B-32 began accruing patients. At present, there are references to twenty different sentinel node studies in breast cancer patients in which there was a randomization component. None of these twenty trials report survival data explicitly comparing sentinel node versus axillary dissection in sentinel node-negative patients. All sentinel node studies with a randomization component that have reported on more than 1000 patients are described in the report presented here.

Interpretation

NSABP Protocol B-32 adds to the totality of evidence in breast cancer patients by definitively demonstrating that there is no significant difference in survival between axillary dissection and sentinel node surgery alone in patients with negative sentinel nodes. It also adds information to existing reports related to regional control and morbidity.

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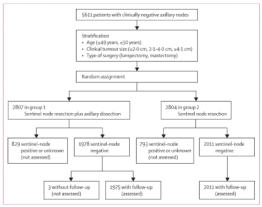

Figure 1. NSABP B-32 trial profile

Group 2 patients in whom a sentinel lymph node (SLN) was not identified received an axillary lymph node dissection (ALND).

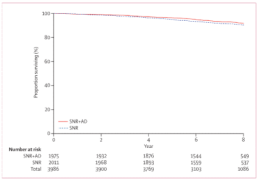

Figure 2. Overall survival for sentinel-node (SLN)-negative patients

Data as of Dec 31, 2009. For sentinel node resection (SNR) plus axillary dissection (AD), N=1975, 140 deaths. For SNR, N=2011, 169 deaths. Hazard ratio 1.20, 95% CI 0.96–1.50; p=0.12.

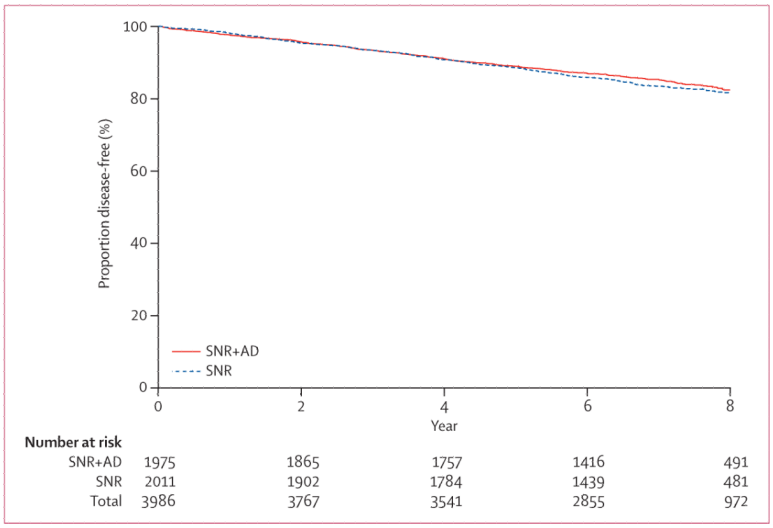

Figure 3. Disease-free survival for sentinel-node (SLN)-negative patients

Data as of Dec 31, 2009. For sentinel node resection (SNR) plus axillary dissection (AD), N=1975, 315 events. For SNR, N=2011, 336 events. Hazard ratio 1.05, 95% CI 0.90–1.22; p=0.54.

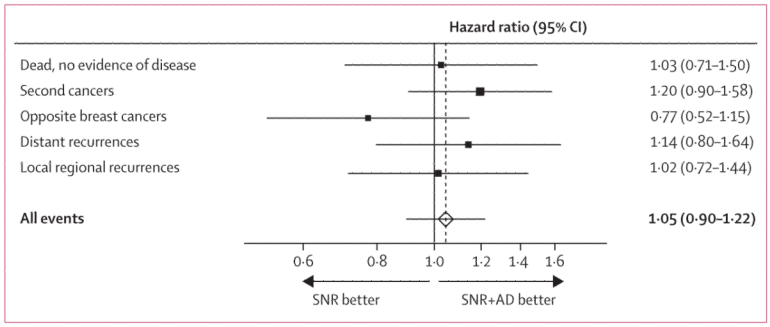

Figure 4. Forest plot for sentinel-node (SLN)-negative patients

SNR=sentinel node resection. SNR+AD=sentinel node resection plus axillary dissection.

Table 1

Clinical characteristics for sentinel node (SLN)-negative patients only

Characteristic	Sentinel node resection + axillary dissection	Sentinel node resection	TOTAL
No. patients			
Entered	1978	2011	3989
Ineligible	6	7	13
Withdrew consent	45	28	73
Without follow-up	3	0	3
With follow-up	1975	2011	3986
Mean time on study (mos)*	95.6	95.6	95.6
Range (mos)*	70.1 – 125.8	70.1 – 126.7	70.1 – 126.7
Age†,‡			
≤ 49 years	488 (24.7%)	491(24.4%)	979 (24.5%)
≥ 50 years	1490 (75.3%)	1520(75.6%)	3010 (75.5%)
Race ‡			
White	1780 (90.0%)	1829 (90.9%)	3609 (90.5%)
Black	99 (5.0%)	87 (4.3%)	186 (4.7%)
Other	99 (5.0%)	95 (4.7%)	194 (4.9%)
Clinical tumor size†,‡			
≤ 2.0 cm	1655 (83.7%)	1689 (84.0%)	3344 (83.8%)
2.1 - 4.0 cm	291 (14.7%)	294 (14.6%)	585 (14.7%)
≥ 4.1 cm	32 (1.6%)	28 (1.4%)	60 (1.5%)
Surgical treatment plan†,‡			
Lumpectomy	1735 (87.7%)	1755 (87.0%)	3490 (87.5%)
Modified radical	243 (12.3%)	256 (13.0%)	499 (12.5%)

*Based on all sentinel node patients with follow-up information as of December 31, 2009

†As reported at the time of random assignment.

‡Denominators for percent based on the number sentinel node-negative patients in each group

Table 2

First reported site of treatment failure for sentinel-node (SLN)-negative patients

	Sentinel node resection + axillary disection		Sentinel node resection	
Location of failure	**No.**	**%**	**No.**	**%**
Local recurrence	54	2.7	49	2.4
Regional node recurrence	8	0.4	14	0.7
Distant metastasis	55	2.8	64	3.2
Opposite breast	56	2.8	44	2.2
Second non-breast cancer	89	4.5	109	5.4
Dead, no evidence of disease	53	2.7	56	2.8
Total First Events	**315**	**15.9**	**336**	**16.7**
Alive, event free	1660	84.1	1675	83.3
Patients followed	1975	100.0	2011	100.0