VOLUME 28 · NUMBER 25 · SEPTEMBER 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Patient-Reported Outcomes in Sentinel Node–Negative Adjuvant Breast Cancer Patients Receiving Sentinel-Node Biopsy or Axillary Dissection: National Surgical Adjuvant Breast and Bowel Project Phase III Protocol B-32

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Submitted January 19, 2010; accepted June 2, 2010; published online ahead of print at www.jco.org on August 2, 2010.

Supported by the Grants No. U10-CA-12027, U10-CA-69651, U10-CA-37377, U10-CA-69974, and 5RO1-CA-074137 (D.N.K.) from the National Cancer Institute, Department of Health and Human Services, Public Health Service, and by Grant No. P30 CA22435 from the Vermont Cancer Center.

Presented in part at the 44th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 30-June 3, 2008.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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0732-183X/10/2825-3929/$20.00

DOI: 10.1200/JCO.2010.28.2491

ABSTRACT

Purpose
Sentinel lymph node resection (SNR) may reduce morbidity while providing the same clinical utility as conventional axillary dissection (AD). National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 is a randomized phase III trial comparing SNR immediately followed by AD (SNAD) to SNR and subsequent AD if SN is positive. We report the definitive patient-reported outcomes (PRO) comparisons.

Patients and Methods
Eligible patients had clinically node-negative, operable invasive breast cancer. The PRO substudy included all SN-negative participants enrolled May 2001 to February 2004 at community institutions in the United States (n = 749; 78% age ≥ 50; 87% clinical tumor size ≤ 2.0 cm; 84% lumpectomy; 87% white). They completed questionnaires presurgery, 1 and 2 to 3 weeks postoperatively, and every 6 months through year 3. Arm symptoms, arm use avoidance, activity limitations, and quality of life (QOL) were compared with intent-to-treat two-sample *t*-tests and repeated measures analyses.

Results
Arm symptoms were significantly more bothersome for SNAD compared with SNR patients at 6 months (mean, 4.8 *v* 3.0; $P < .001$) and at 12 months (3.6 *v* 2.5; $P = .006$). Longitudinally, SNAD patients were more likely to experience ipsilateral arm and breast symptoms, restricted work and social activity, and impaired QOL ($P \leq .002$ all items). From 12 to 36 months, fewer than 15% of either SNAD or SNR patients reported moderate or greater severity of any given symptom or activity limitation.

Conclusion
Arm morbidity was greater with SNAD than with SNR. Despite considerable fears about complications from AD for breast cancer, this study demonstrates that initial problems with either surgery resolve over time.

J Clin Oncol 28:3929-3936. © 2010 by American Society of Clinical Oncology

INTRODUCTION

National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-32 is a randomized phase III trial, launched in 1999, designed to determine whether sentinel node resection (SNR) alone in patients with early-stage breast cancer provides reduction in morbidity, with the same prognostic information, regional control, and survival, as conventional axillary dissection (AD). Important secondary outcomes of B-32 were patient-reported outcome (PRO) measures of morbidity as well as observer-rated arm edema and function. The American Society for Clinical Oncology recommendations note that decreased morbidity is a motivation for avoiding AD.[1]

This report presents our definitive, planned comparison of treatment groups with respect to PROs. We hypothesized that PRO end points would indicate greater morbidity in the sentinel node resection followed by axillary dissection (SNAD) group. Our study differs from other published phase III studies (which were conducted in other countries) in several respects.[2-5] We provide data in the early postoperative period (1 and 2 to 3 weeks after surgery) and the long term (36 months). We assessed symptoms in the breast (in addition to the arm), ability to perform specific tasks, daily activities, and overall quality of life (QOL).

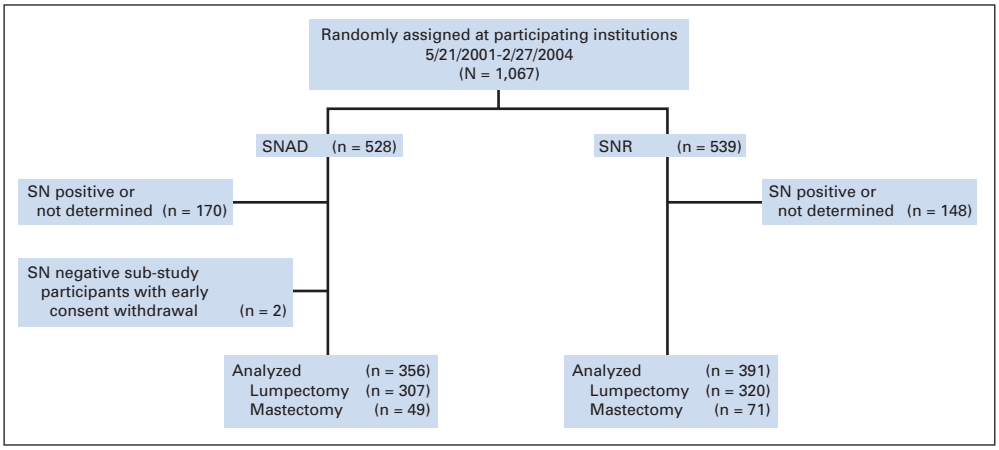

Fig 1. CONSORT diagram. SN, sentinel node; SNAD, SN resection followed by axillary dissection; SNR, sentinel node resection.

We also report results separately for patients who received lumpectomy or mastectomy. Our study was conducted in community settings, providing broad representation across the United States. Finally, our study is restricted to patients who were sentinel node negative, hence SNR group patients were not expected to receive a secondary AD.

PATIENTS AND METHODS

Participants

Eligible patients had clinically node-negative operable invasive breast cancer. Primary surgery (mastectomy or breast-conserving) and systemic therapy were given at the discretion of the treating physician. Patients were stratified by age ($\leq$ 49 years, $\geq$ 50 years), clinical tumor size (eg, $\leq$ 2.0, 2.1 to 4.0, $\geq$ 4.1 cm), and surgical treatment plan (eg, mastectomy, lumpectomy), and randomly assigned to either SNR immediately followed by conventional AD (SNAD), or SNR alone (Fig 1). Patients found to be SN-positive intraoperatively or during pathology review, or for whom a SN could not be identified, subsequently underwent AD (Fig 2). The primary comparison groups for all analyses are SN-negative patients. The random assignment is preserved because the determination of SN status was made the same way in both treatment groups. More information about B-32, including the SN surgical training, has been reported elsewhere.[6-9]

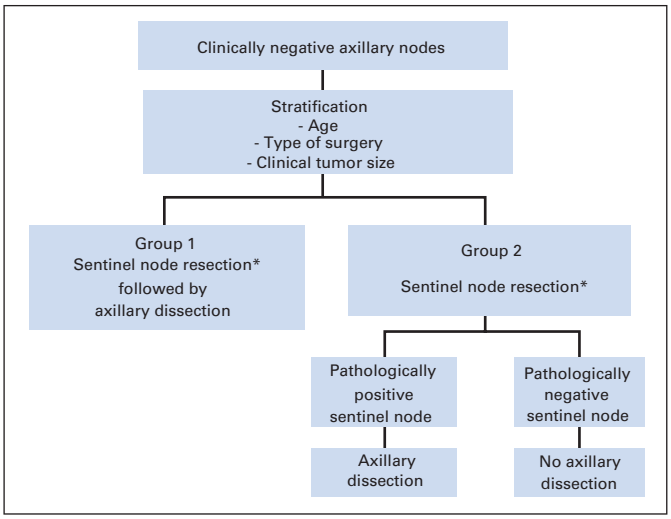

Fig 2. National Surgical Adjuvant Breast and Bowel Project B-32 schema. (*) Patients in whom a sentinel lymph node is not identified will go on for axillary dissection.

The B-32 trial required a large sample size for the primary clinical outcomes. The PRO substudy required a much smaller sample size and thus accrual to the PRO substudy began 2 years after B-32 opened. By design, the substudy included all SN-negative patients randomly assigned at participating institutions designated as members of the Community Clinical Oncology Program, a National Cancer Institute program that encourages clinical trial participation by community-based physicians. The protocol and consent form were approved by the National Cancer Institute and the institutional review boards of all participating institutions. All participants provided written informed consent.

Instruments

The PRO assessments were primarily focused on arm-related morbidity. There was, at the time of study design, no generally accepted measure of QOL related to axillary node dissection. We adapted items from previous studies and from the validated Disabilities of Arm, Shoulder and Hand Scale,[10-13] and used a validated single-item health-related QOL rating scale (0 to 10) adapted from previous NSABP studies.[14-16] Twenty-six items (response scale 0 to 4) assessed how bothered patients were by the following symptoms: (1) tenderness, (2) swelling, (3) discomfort or pain, (4) numbness and "pins and needles," (5) skin sensitivity, (6) tightness, pulling or stretching, and (7) weakness. Symptoms 1 to 6 were assessed for the right and left arms (where arms included underarms, arms, hands, and fingers) and the right and left breast and chest; weakness was assessed only for arms. It also included items (response scale 0 to 3) regarding avoidance of arm use and the difficulty of pushing large objects, lifting objects, and reaching. Social and occupational activity limitations were assessed with two items (response scale 0 to 4; see full questionnaire in Appendix Fig A1 [online only]). The questionnaire is not a psychometric instrument in that it does not use multiple items to measure the same attribute. Rather, it is a clinimetric instrument: most items measure distinct symptoms, and these are summed to form indexes.[17,18] The questionnaire also collected the most recent surgical procedure (eg, biopsy, mastectomy, or breast reconstruction).

Questionnaires were given before surgery, 1 week postoperatively, 2 to 3 weeks postoperatively, and every 6 months through year 3. Questionnaires were completed in the physician's office when possible; otherwise by telephone or mail. Patients were expected to complete the questionnaires on schedule until they were diagnosed as sentinel node-positive, had a documented breast cancer recurrence or second primary cancer, died, or withdrew consent from the parent B-32 study. Institution staff completed a QOL missing data form when efforts to administer the questionnaire failed. The QOL missing data form provided reasons that the questionnaire was not done.

Statistical Methods

All analyses were intent-to-treat, grouping patients according to their random assignment, and were carried out separately on patients who received mastectomy versus lumpectomy. Questionnaire compliance (submission of

expected forms) was compared between treatment groups with logistic mixed effects modeling.[19] All available data were used for all analyses.

In patients who received lumpectomy, we compared the ipsilateral arm symptom subscale (change from baseline) between SNAD and SNR at 6 months and 1 year using two-sample *t*-tests. This subscale was formed by summing ipsilateral arm symptom scores (Cronbach's α .90). These two tests, along with six other comparisons between dominant and nondominant sides (not presented here), were defined in the protocol as primary analyses, and were to be one-sided at significance level 0.05/8 = 0.00625 (Bonferroni correction). However, two-sided *P* values are presented in this report per *Journal* recommendations.

Longitudinal analyses: for the QOL rating scale, we performed a repeated measures mixed effects regression to compare SNAD with SNR through 36 months of follow-up. For every other item (severity > 0 *v* 0), we performed a separate repeated-measures logistic mixed effects regression. Effects included time as a three level factor (baseline, postoperative = 1 to 3 weeks, long-term = 6 to 36 months), baseline severity, treatment group, systemic therapy (chemotherapy or hormone therapy, as a time-varying effect), a factor indicating whether the surgical procedure was on the dominant or nondominant side, the interaction between time and treatment group, and, for analyses involving mastectomy patients, breast reconstruction. Secondary analyses were performed at a two-sided significance level of .05.

We estimated that 663 lumpectomy patients and 156 mastectomy patients would be SN negative and enroll in the substudy, based on the number expected to enroll in the parent B-32 study. That was estimated to provide 87% power for the comparison of means of the ipsilateral arm symptom scale at 6 months, assuming a true mean difference of 2 points (standard deviation [SD], 7).

Analyses were carried out in SAS version 9.1.3 (SAS Institute, Cary, NC), including PROC GLIMMIX (SAS Institute) for the repeated measures analyses.

RESULTS

Participants and Assessments

The PRO study enrolled 749 participants from May 2001 to February 2004 (Fig 1). Two patients withdrew consent for B-32 early in the study, leaving 747 participants with follow-up (356 SNAD *v* 391 SNR). Eleven patients in the SNR group with negative nodes underwent elective AD. The mean number of nodes removed was 14.3 (SD, 5.8) in the SNAD group and 3.1 (SD, 2.9) in the SNR group. There were differences between PRO substudy participants and other B-32 participants, reflecting differences between the participating Community Clinical Oncology Programs and other institutions (Table 1). There were no significant differences between treatment groups. Among patients with PRO data at baseline and the 6-month time point, 550 had received only lumpectomy or excisional biopsy as the most extensive breast surgery, 116 had received mastectomy, and seven had received neither. Radiation therapy was administered to 91% of lumpectomy-treated patients and to 11% of mastectomy-treated patients. Among 116 patients who received mastectomy by the 6-month time point, 67 (29 SNAD, 38 SNR) had not received breast reconstruction. The most extensive breast surgery was on the dominant side for 370 patients and on the nondominant side for 379 patients.

Submission of expected questionnaires ranged from 99% at baseline (742 of 749) and 92% at 6 months (676 of 738 forms expected) to 84% at 36 months (584 of 699 expected). In longitudinal analyses, the

Table 1. National Surgical Adjuvant Breast and Bowel Project B-32 Patient Characteristics

Characteristic	PRO Substudy Patients With Follow-Up Treatment: SNAD (n = 356) No.	SNAD (n = 356) %	SNR (n = 391) No.	SNR (n = 391) %	All (N = 747) No.	All (N = 747) %	Other B-32 Patients With Follow-Up, Enrolled During Substudy Accrual Period (n = 2,000) No.	Other B-32 Patients With Follow-Up, Enrolled During Substudy Accrual Period (n = 2,000) %	*P* for Substudy *v* Parent Study Participant Characteristics*
Age, years									.14
≤ 49	73	20.5	90	23	163	21.8	490	24.5	
50+	283	79.5	301	77	584	78.2	1,510	75.5	
Clinical tumor size, cm									.004
≤ 2.0	308	86.5	343	87.7	651	87.1	1,645	82.3	
2.1-4.0	46	12.9	45	11.5	91	12.2	320	16.0	
≥ 4.1	2	0.6	3	0.8	5	0.7	35	1.8	
Surgery plan									< .001
Lumpectomy	307	86.2	320	81.8	627	83.9	1,778	88.9	
Mastectomy	49	13.8	71	18.2	120	16.1	222	11.1	
Race									< .001
White	314	88.2	338	86.4	652	87.3	1,827	91.4	
Black	30	8.4	40	10.2	70	9.4	62	3.1	
Other	12	3.4	13	3.3	25	3.3	111	5.6	
Systemic adjuvant therapy†									.36
Yes	308	87.8	336	87.1	644	87.4	1,666	86.0	
No	43	12.3	50	13.0	93	12.6	271	14.0	
Radiation therapy									< .001
Yes	276	77.5	309	79.0	585	78.3	1,683	84.2	
No	80	22.5	82	21.0	162	21.7	317	15.9	

Abbreviations: PRO, patient-related outcomes; SNAD, sentinel node resection followed by axillary dissection; SNR, sentinel node resection.
**P* value represents comparison of substudy participants with other B-32 participants enrolled during the substudy accrual period.
†Use of systemic adjuvant therapy is unknown for some of the participants.

Table 2. Symptoms, Arm Use Avoidance, and Social/Occupational Limitations at 6 and 12 Months in National Surgical Adjuvant Breast and Bowel Project B-32 Patient-Reported Outcomes Substudy

Parameter	Response at Follow-up						Change From Baseline			
	Baseline*		6 Months†		12 Months†		Baseline to 6 Months		Baseline to 12 Months	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Ipsilateral arm symptoms (scale 0-28)										
SNAD	1.9	1.3 to 2.5	4.8	4.1 to 5.4	3.6	3 to 4.2	3.6	2.9 to 4.3	2.3	1.6 to 2.9
SNR	2.1	1.3 to 2.8	3	2.5 to 3.5	2.5	2 to 3	1.7	1.2 to 2.2	1.2	0.7 to 1.7
SNAD *v* SNR	−0.2	−1.1 to 0.8	1.7	0.9 to 2.6	1.1	0.4 to 1.9	1.9	1 to 2.7	1.1	0.3 to 1.8
P								< .001		.006
Ipsilateral breast symptoms (scale 0-24)										
SNAD	3.1	2.4 to 3.7	3.5	3 to 4	2.8	2.3 to 3.2	1.2	0.6 to 1.7	0.4	−0.1 to 0.9
SNR	3.2	2.4 to 3.9	2.6	2.2 to 3.1	2.1	1.7 to 2.5	0.5	0 to 0.9	−0.2	−0.6 to 0.3
SNAD *v* SNR	−0.1	−1 to 0.9	0.8	0.1 to 1.5	0.7	0.1 to 1.3	0.7	0 to 1.4	0.5	−0.1 to 1.2
P								.06		.10
Ipsilateral arm avoidance (scale 0-3)										
SNAD	0.5	0.3 to 0.6	0.5	0.4 to 0.6	0.4	0.4 to 0.5	0.2	0.1 to 0.3	0.2	0.1 to 0.2
SNR	0.4	0.3 to 0.5	0.3	0.2 to 0.4	0.3	0.2 to 0.3	0.1	0 to 0.2	0	−0.1 to 0.1
SNAD *v* SNR	0.1	−0.1 to 0.2	0.2	0.1 to 0.3	0.2	0.1 to 0.3	0.1	0 to 0.3	0.2	0 to 0.3
P								.09		.021
Social/occupational limitations (scale 0-8)										
SNAD	0.7	0.5 to 1	0.7	0.6 to 0.9	0.4	0.2 to 0.5	0.4	0.2 to 0.6	0	−0.2 to 0.2
SNR	0.6	0.3 to 0.8	0.4	0.3 to 0.5	0.4	0.3 to 0.5	0.0	−0.1 to 0.2	0	−0.2 to 0.2
SNAD *v* SNR	0.2	−0.2 to 0.5	0.3	0.1 to 0.5	0	−0.2 to 0.2	0.4	0.1 to 0.6	0	−0.2 to 0.2
P								.004		1.0

Abbreviations: SNAD, sentinel node resection followed by axillary dissection; SNR, sentinel node resection.
*Patients with baseline regardless of having 6 months or 1 year follow-up.
†Among patients with baseline data.

compliance rate differed significantly between treatment groups ($P = .006$). However, the differences were of small magnitude (91% SNAD *v* 92% SNR at 6 months; 90% SNAD *v* 93% SNR at 1 year). Furthermore, 46% of missed forms were attributed to staff oversight or understaffing, reasons unrelated to PROs. Compliance was reported in detail previously.[19]

Treatment Group Comparisons at 6 Months and 1 Year

Among patients who received lumpectomy, symptoms in the ipsilateral arm at 6 months were significantly greater with SNAD (mean change from baseline 3.6; SD, 5.7, on a 0-28 scale) than SNR (mean 1.7; SD, 4.3), with a mean treatment difference of 1.9 ($P < .001$). Differences were reduced by 1 year, with a mean change of 2.3 (SD, 5.0) with SNAD versus 1.2 (SD, 4.0) with SNR, but remained significant according to the protocol-defined Bonferroni-adjusted criterion (mean difference 1.1; $P = .006$). Other cross-sectional comparisons are presented in Appendix and in Table 2.

Longitudinal Analysis

Among patients whose intended surgery was lumpectomy, SNAD patients were significantly more likely to experience difficulty over time on study (through 3 years) in the following end points: pushing large objects, lifting objects, reaching, and conducting social and work activities ($P < .001$). They were more likely to avoid ipsilateral arm use and more likely to experience all the symptoms assessed on the ipsilateral side ($P = .002$ breast tenderness; $P < .001$ all other items). For some items, the treatment difference diminished significantly over time (moving or lifting objects; reaching; arm: pain, numbness, skin sensitivity, tightness, or weakness; social or work activities; Fig 3A and Table 3). For other items, the difference persisted throughout the study (avoidance of arm use; arm or breast tenderness or swelling; breast: pain, numbness, skin sensitivity, or tightness; Fig 3B; other data not shown). All symptoms were significantly associated with the baseline response and diminished over time ($P < .001$ all items). Patients who received systemic therapy reported significantly more arm symptoms: tenderness, pain, skin sensitivity, tightness (all $P < .001$), and weakness ($P = .007$); breast symptoms: tenderness, swelling, pain, numbness, skin sensitivity (all $P < .001$), tightness ($P = .004$), and occupational limitations ($P = .030$) than those who did not receive systemic therapy. Overall QOL, adjusted for baseline levels, was significantly better among SNR patients ($P < .001$), lower among patients who received systemic therapy ($P = .028$) and improved significantly over time ($P < .001$); the difference between treatment groups diminished significantly over time ($P < .001$). The time course of activity limitations and overall QOL indicate that the impact of the procedures was seen mainly in the few weeks after surgery (Figs 3A to 3C).

Among patients whose surgical plan was mastectomy, longitudinal analysis revealed that SNAD patients reported significantly greater arm use avoidance ($P = .044$), arm swelling ($P = .021$), arm and breast numbness ($P < .001$; $P = .017$ respectively), arm skin sensitivity ($P = .032$), arm tightness ($P = .001$) and social limitations ($P = .026$) than SNR patients. Patients with breast reconstruction experienced more breast swelling ($P = .015$) and tightness ($P = .007$) over time. Overall QOL did not differ significantly by SNAD versus SNR or

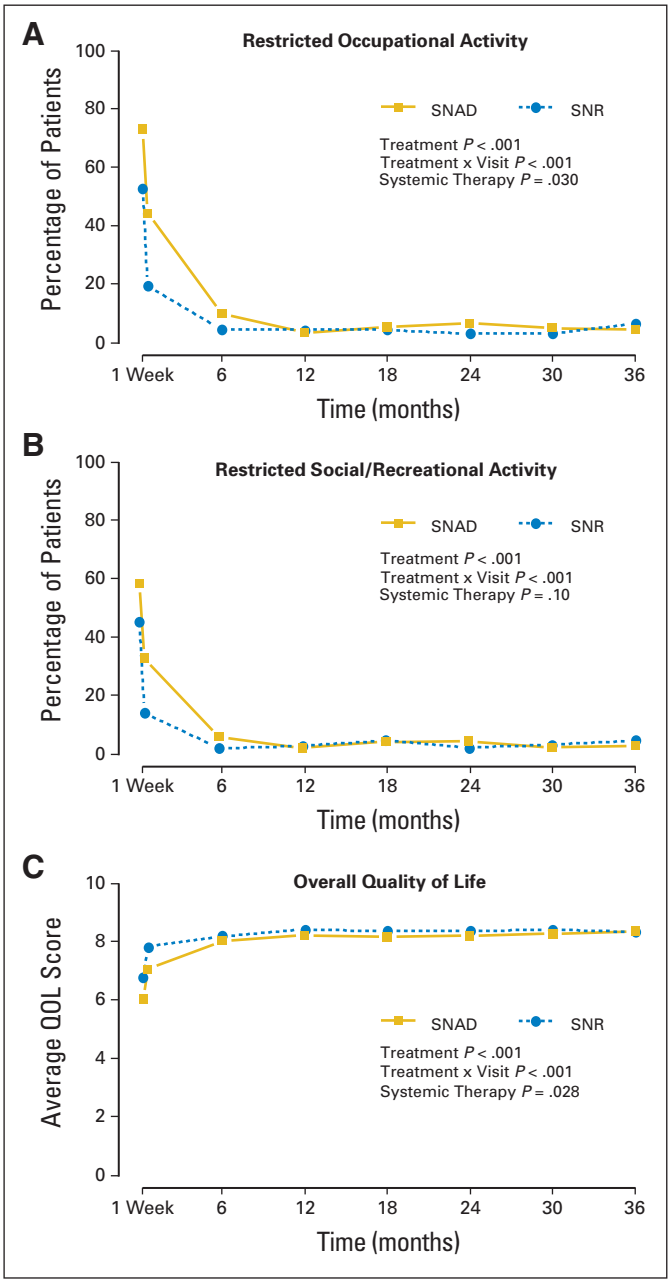

Fig 3. (A) Longitudinal graph of the proportion of patients with any restriction in recreational or social activity, among those with no restriction at baseline. *P* values from repeated measures logistic regression are shown. (B) Longitudinal graph of the percentage of patients with any restriction in occupational activity, among those with no restriction at baseline. *P* values from repeated measures logistic regression are shown. (C) Longitudinal graph of the mean quality of life score. *P* values from repeated measures linear regression are shown. SNAD, sentinel node resection followed by axillary dissection; SNR, sentinel node resection; QOL, quality of life.

reconstruction. The treatment difference in arm swelling diminished over time ($P = .009$); other differences persisted. Systemic therapy was associated with arm tenderness ($P = .005$) and tightness ($P = .020$) in this group. Presurgery symptom severity significantly predicted post-treatment values for nearly all items (data not shown). Scores for all items diminished significantly over time.

DISCUSSION

At the time B-32 was launched, several other randomized comparisons of SNR and AD opened elsewhere[20]: the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial of the British Association of Surgical Oncology,[2,3,21] the Sentinella-Gruppo Interdisciplinare Veneto Oncologia Mammaria (GIVOM) trial,[4,22] and the Royal Australasian College of Surgeons (RACS) Sentinel Node Biopsy versus Axillary Clearance (SNAC) trial,[5,23-25] (Table 4) as well as two smaller trials.[26-28]

Our finding of significant differences favoring SNR in arm-related symptoms was consistent with the three other large trials. However, women in our trial reported less severe symptoms. For example, arm numbness at 6 months was at least moderately bothersome for 19.3% of SNAD patients in B-32, compared with 26.5% in ALMANAC. Arm numbness appears to be a sensitive indicator of surgical change in the axilla. This may be related to direct cutaneous nerve injury or subsequent seroma/hematoma formation. For the SNR group, this was considerably lower at 9.3%, reflecting less cutaneous nerve trauma from sentinel node only removal and less surgical trauma. The greater severity in other trials might be because all randomly assigned patients were included in the analysis, whereas in B-32 only sentinel node–negative patients from both treatment groups were included. Therefore, according to the protocol, the SNR group did not receive AD, and the SNAD group received SNR immediately followed by AD. The differences might also be related to how the symptoms were elicited and rated.

In addition to the decreased severity for lumpectomy-treated, node-negative B-32 patients as compared with patients in the other trials, the patterns of symptom differences during early postoperative and long-term follow-up in B-32 were informative. A prospective patient could, for example, conclude from Table 3 that she will have a 73% chance of restricted work activity one week after SNAD, or a 53% chance after SNR; but that by 6 months, those rates will be reduced to 10% and 4%, respectively. The differences between treatment groups during the second year in B-32 were similar to the other randomized trials. For example, the percentages of patients bothered by numbness were about double in the AD versus SNR groups in the second year of GIVOM and ALMANAC. The proportions were similarly about double in B-32 patients through 30 months and remained different (9.6% *v* 6.4%) at 36 months in B-32. Arm pain differed between treatment groups in the first year but became similar between groups during the second year in ALMANAC, GIVOM, and B-32. However, the third year in B-32 revealed persistent differences in arm pain between groups.

Interestingly, increased morbidity due to AD was not limited to the arms. Breast tenderness, swelling, pain, numbness, sensitivity, and tightness were all significantly increased in the SNAD group, and the differences did not diminish significantly over time. This is important because most concerns have focused on the arm, and breast symptoms have not been reported from other randomized studies. The arm may have better circulation of lymph fluid after AD than the breast because of natural arm movement and because that area has collateral channels that are less compromised during surgery. This is likely further compounded by breast irradiation.

This study also provides new information about social and occupational activity. We found that restrictions in activity were severe in

Table 3. Percentages of Lumpectomy Patients Without Each Symptom Listed at Baseline Who Experienced Each Ipsilateral Symptom at Moderate or Severe Levels, at Selected Time Points

	SNAD						SNR					
Parameter	Week 1	Weeks 2-3	Month 6	Month 12	Month 24	Month 36	Week 1	Weeks 2-3	Month 6	Month 12	Month 24	Month 36
Move objects*	57	32	7	7	9	7	43	16	3	3	3	5
Lift objects*	64	39	9	6	6	6	46	19	6	4	3	6
Reach above shoulders*	39	14	3	3	1	1	14	6	2	1	1	2
Avoid using arm†	70	38	10	8	8	6	51	20	8	3	4	4
Arm tenderness	74	52	22	10	10	12	58	28	13	11	7	5
Arm swelling	39	27	13	8	10	8	30	10	4	4	4	3
Arm pain	70	44	20	11	10	10	48	22	11	11	8	7
Arm numbness	46	36	19	14	13	10	16	10	8	9	7	6
Arm skin sensitivity	45	37	15	8	7	7	26	15	8	5	5	2
Arm tightness	66	49	20	11	9	10	40	15	9	7	4	2
Arm weakness	49	30	12	9	9	8	28	9	8	8	5	6
Breast tenderness	50	30	13	9	9	9	48	25	14	10	7	5
Breast swelling	30	21	9	7	3	5	28	12	5	3	3	3
Breast pain	52	28	14	10	8	5	38	20	14	9	4	3
Breast numbness	25	19	8	7	7	3	13	8	4	5	3	2
Breast skin sensitivity	34	22	12	6	4	4	23	15	10	4	3	3
Breast tightness	46	31	11	8	5	7	31	14	8	6	4	1
Restricted social activity	59	33	6	3	5	3	45	15	3	3	3	5
Restricted work activity	73	44	10	3	7	4	53	19	4	4	3	6

Abbreviations: SNAD, sentinel node resection followed by axillary dissection; SNR, sentinel node resection.
*Response categories are: "very difficult" or more severe (score 2 to 3 of the 0 to 3 range).
†Response categories are: "often avoided" or more severe (score 2 to 3 of the 0 to 3 range). All other response categories: "somewhat bothered" or more severe (score of 2 to 4 of the 0 to 4 range).

both groups during the postoperative period, and greater for the SNAD group, but diminished by 12 months. Nonetheless, for some patients in both treatment groups, limitations persisted to 36 months.

In our study, we found that overall QOL was significantly better for SNR patients during the postoperative period. This confirms that the symptoms experienced by the women undergoing AD are important for their overall perception of QOL. However, the treatment difference was slight by 6 months, and no difference remained at 36 months. Similarly, there was no negative effect of SNR on mental or emotional function in either GIVOM or ALMANAC. GIVOM also showed better psychological well-being in the SNR group. The authors concluded that SNR was associated with reduced arm morbidity and better QOL, with no increase in anxiety.

Longer-term follow-up is available from small observational studies that have been conducted in recent years.[29-36] For example, in one study with a mean follow-up of 6.6 years after AD and of 4.9 years after SNR, AD was associated with significantly greater likelihood of subjective arm numbness, chest or axillary numbness, and arm and hand swelling.[37] A Memorial Sloan-Kettering study collected PROs up to 60 months after surgery from 187 patients.[38] They found that symptoms were moderate but were greater among patients who received AD, even after 5 years.

A limitation of this study is that no widely used, well-validated instruments to measure arm and breast morbidity in this setting were available for our use. However, the items development was based on prior research, and items demonstrated responsiveness to

Table 4. PROs in Phase III Randomized Trials of SNR *v* AD

Trial	PRO Analysis Sample Size	PROs	PRO Time Points Reported
ALMANAC[2,3,21]	829	QOL, arm symptoms, anxiety (FACT-B, additional questions about arm symptoms and function, and the STAI)	Baseline, 1, 3, 6, 12, 18 months
Sentinella-GIVOM[4,22]	697 (pain); 310 (QOL)	Pain, MOS SF-36, and the PGWB Index	Every 6 months (pain); 6, 12, 24 months (SF-36 and PGWB)
RACS SNAC[5,23-25]	1,028	Symptoms, function, disabilities (SNAC Study-Specific Scales) [Other quality-of-life outcomes were assessed but have not yet been reported.]	Baseline, 1, 6, 12 months
NSABP B-32[6-9]	747	Symptoms, function, activity limitations, overall QOL	Baseline, 1 and 2-3 weeks post-operative; 6, 12, 18, 24, 30, 36 months

Abbreviations: PRO, patient-reported outcomes; SNR, sentinel node resection; AD, axillary dissection; ALMANAC, the Axillary Lymphatic Mapping Against Nodal Axillary Clearance trial; QOL, quality of life; FACT-B, Functional Assessment of Cancer Therapy–Breast Cancer; STAI, State/Trait Anxiety Inventory; GIVOM, Gruppo Interdisciplinare Veneto Oncologia Mammaria; MOS SF, Medical Outcomes Study Short Form; PGWB, Psychological General Well Being; RACS, Royal Australasian College of Surgeons; SNAC, Sentinel Node Biopsy Versus Axillary Clearance; NSABP, National Surgical Adjuvant Breast and Bowel Project.

differences between treatments and over time. A second potential limitation is that some differences existed between participants in the B-32 substudy and parent study, which was anticipated in the design by conducting this sub-study among community-based institutions. Thus, these results are more representative of the patients treated in community settings rather than tertiary centers, which serves to make the substudy conclusions more generalizable.

Ultimately, the differences in PROs will be weighed against differences in clinical outcomes, including survival, to be reported separately. In forthcoming articles, our group will also report the observer-reported arm function, and a comparison between arm function and PROs.[39] In the meantime, SNR is available to many patients. Two studies of preferences suggest that approximately half of women elect SNR as an alternative to AD when presented with a one in 10 rate of arm morbidity with AD and a one in 1,000 rate of increased 5-year mortality with SNR.[40,41] B-32 provides critical information regarding the patient experience. A major finding was that symptoms were less severe than expected with AD, which will reassure patients who may require this surgery as part of their cancer treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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