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ORIGINAL REPORT

Randomized Trial Comparing Axillary Clearance Versus No Axillary Clearance in Older Patients With Breast Cancer: First Results of International Breast Cancer Study Group Trial 10-93

International Breast Cancer Study Group

From the International Breast Cancer Study Group. Appendix lists the names and affiliations of the writing committee, and participants and authors of Trial 10-93.

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ABSTRACT

Purpose
Axillary clearance in early breast cancer aims to improve locoregional control and provide staging information but is associated with undesirable morbidity. We therefore investigated whether avoiding axillary surgery in older women would result in improved quality of life (QL) with similar disease-free survival (DFS) and overall survival (OS).

Patients and Methods
Between 1993 and 2002, women ≥ 60 years old with clinically node-negative operable breast cancer in whom adjuvant tamoxifen was considered indicated regardless of pathologic nodal status were randomly assigned to primary surgery plus axillary clearance (Sx + Ax) followed by tamoxifen (Tam) versus Sx without Ax followed by Tam for 5 consecutive years. The primary end point was QL reported by the patient and by physician assessment.

Results
A total of 473 patients (234 to Sx + Ax, 239 to Sx) were randomly assigned. The median age was 74 years; 80% had estrogen receptor–positive disease. In both the patients' subjective assessment of their QL and the physicians' perception of the patients' QL, the largest adverse QL effects of Ax were observed from baseline to the first postoperative assessment, but the differences tended to disappear in 6 to 12 months. At a median follow-up of 6.6 years, results for Sx + Ax and Sx yielded similar DFS (6-year DFS, 67% *v* 66%; hazard ratio [HR] Sx + Ax/Sx, 1.06; 95% CI, 0.79 to 1.42; $P = .69$) and OS (6-year OS, 75% *v* 73%; HR Sx + Ax/Sx, 1.05; 95% CI, 0.76 to 1.46; $P = .77$).

Conclusion
Avoiding axillary clearance for women ≥ 60 years old who have clinically node-negative disease and receive Tam for endocrine-responsive disease yields similar efficacy with better early QL.

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INTRODUCTION

The incidence of breast cancer increases with age[1] and breast cancer is the most common cancer in women older than 70 years old.[2] In Western countries, approximately 50% of women with breast cancer are older than 65 years old. Given that populations are aging, increasing numbers of breast cancer occurrences can be expected among older women.

Comorbid conditions also increase with age.[3] Because these conditions may limit the duration and extent of a surgical procedure, there is a potential advantage to avoiding axillary surgery if it does not compromise tumor control. Avoiding axillary surgery might also reduce postoperative effects on arm pain, mobility, and lymphedema.

Recent data[4,5] suggest that there is an association between increasing age at diagnosis and the presence of more favorable biologic characteristics of the tumor, such as greater expression of steroid hormone receptors, lower proliferative rates, diploidy, normal p53 expression, and the absence of overexpression of epidermal growth factor receptor and c-*erb*B-2. We therefore investigated whether older patients with clinically node-negative and primarily endocrine-responsive early breast cancer might benefit from a change to the surgical approach that eliminates axillary lymph node dissection. This surgery usually represents the main cause of morbidity after a breast cancer resection, especially because such patients would receive adjuvant treatment with tamoxifen. Our study compares older patients undergoing breast surgery treated

with axillary surgery versus patients who received no axillary surgery to determine the effect of axillary surgery on quality of life (QL), disease-free survival (DFS), and overall survival (OS).

PATIENTS AND METHODS

Study Design

From May 1993 through December 2002, 473 postmenopausal patients 60 years or older with clinically node-negative operable breast cancer were randomly assigned preoperatively to receive breast surgery with axillary clearance followed by tamoxifen (20 mg) for 5 years or breast surgery without axillary clearance followed by tamoxifen (20 mg) for 5 years. At the time of random assignment, estrogen receptor (ER) status and pathologic nodal status were unknown. Informed consent was required according to the criteria established within the individual countries. The protocol was reviewed and approved by institutional review boards.

Random assignment was performed centrally (at the coordinating centers in Bern, Switzerland, or Sydney, Australia) after stratification according to whether primary surgery was performed before random assignment (yes or no), age (60 to 70 or $>$ 70 years), and by participating institution. The permuted-blocks randomization schedule was produced by use of pseudorandom numbers generated by a congruence method.

All patients had a histologically proven unilateral breast cancer of stage T1a, T1b, T2a, T2b, T3, N0, or M0 (Union Internationale Contre le Cancer 1987), with either ER-positive or ER-negative primary tumors. Steroid hormone receptor concentrations in the primary tumors were determined by standard methods. ER concentrations of $\geq$ 10 fmol/mg of cytosol protein were considered positive; lower values were considered negative. Steroid hormone receptor determination by immunohistochemistry was allowed in a later phase of the study (52% of the patients). Staging before random assignment included chest x-ray, contralateral mammogram, bone scintigram (if clinically indicated), and hematologic, liver, and renal function tests.

In August 2002, the International Breast Cancer Study Group (IBCSG) Scientific Committee made a recommendation to discontinue tamoxifen for patients with endocrine-nonresponsive tumors. Surgery to remove the primary tumor was either a total mastectomy or breast-conserving surgery. On April 15, 1999, the original protocol was amended to allow institutions to perform sentinel node biopsy (SNB) in patients who had been randomly assigned to surgery, provided they then proceeded to axillary clearance. However, only two patients used this option. Radiotherapy using two tangential fields was recommended after breast-conserving surgery.

Clinical, hematologic, and biochemical assessments were required every 3 months for the first year, every 6 months during years 2 through 5, and yearly thereafter. Modified WHO toxicity grading criteria were used. Yearly mammography was optional. The data management and medical staff reviewed all study records (initial data, treatment, toxicity, and recurrence) and conducted regular site visit audits. In particular, the study chairs (D.C. and C-M.R.) reviewed the records of all patients for eligibility and adverse effects.

Patient self-assessments of QL using the IBCSG approach[6-9] were obtained before surgical treatment; postoperatively; at months 3, 6, 9, 12, 18, and 24; and yearly thereafter for 6 years. Single-item linear analog self-assessment scales that were scored between 0 and 100 were used; higher values represented better QL or less severe symptoms. The QL form consisted of a one-page core questionnaire[8] and a surgical QL module specific to this trial. Four scales on the core questionnaire were used from the start of the trial to measure physical well-being, mood, appetite, and perceived adjustment/coping. After May 1, 1993, six additional linear analog self-assessment scales were added to the core questionnaire to measure tiredness, hot flashes, nausea/vomiting, perceived social support, arm restriction, and subjective health estimation. The surgical QL module was first introduced on July 1, 1995, to measure swelling, numbness, weakness, pain, stiffness, performance of daily activities compared with the time before surgery, and a global measure of being bothered by any problems with hand, arm, shoulder, or chest.[6] We expected the latter to be less precise for specific effects but responsive to the whole spectrum of sequelae and selected it as the primary end point. QL scores were transformed to reduce skewing, and the statistical significance of treatment differences at each time point was assessed with analysis of variance, adjusting for country/language group.[7,8]

Physician assessments of the patients' QL were collected at the beginning of treatment; at first follow-up after discharge from final surgery; and at months 3, 6, 9, 12, 18, and 24. QL measures assessed by the physician included ipsilateral arm movement; arm, shoulder, and chest wall pain; arm circumference; and performance of daily activities with respect to preoperative levels.

End Points and Statistical Considerations

Axillary recurrence was defined as positive cytology or histology, or progression of disease if only indirect methods were used. DFS was defined as the length of time from the date of random assignment to any recurrent disease (including ipsilateral breast recurrence), the appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. OS was defined as the length of time from the date of random assignment to death as a result of any cause.

DFS and OS percentages, SEs, and treatment effect comparisons were obtained from the Kaplan-Meier method,[10] Greenwood's formula,[11] and log-rank tests,[12] respectively. Cox proportional hazards regression models[13] were used to estimate relative risks and 95% CIs for the treatment comparisons. Cumulative incidence of breast-related events is reported with nonbreast cancer events (ie, nonbreast second primary cancer or death without prior recurrence) as competing risks.[14] Classification according to nodal status was not used in a primary analysis because the opportunity to determine nodal status depended on the randomization option. All probability values were obtained from two-sided tests. Results are reported at a median follow-up of 6.6 years.

The trial was originally designed to assess equivalence between the axillary clearance and no axillary clearance treatment groups in terms of DFS. Using a one-sided .05-level test, a sample size of 1,020 patients (or 455 events) would provide 90% power to reject the hypothesis of equal treatment effectiveness. As of August 3, 2000, accrual was 430 patients. On the basis of the yearly accrual rate, it would have taken more than 20 additional years of accrual to reach the target sample size of 1,020 patients. On November 2, 2000, the study was redesigned to assess whether avoiding axillary clearance improved QL results. For consideration of sample size, we focused on one question from the surgical QL module assessed at 24 months: "Overall, how much are you bothered by any problems with your hand, arm, shoulder, or chest?" To detect a decrease of 13% in the percentage of patients bothered by hand, arm, shoulder, or chest (defined as a score of 85 or less) for patients not receiving axillary clearance with 80% power required a total of 472 randomly assigned patients. The Wilcoxon rank sum test[15] was used for testing differences between continuous variables, and associations between categoric variables were assessed by a Fisher's exact test.[16]

The Data and Safety Monitoring Committee reviewed accrual and safety data twice a year. The original study plan called for an interim analysis after 112 DFS events or 25 axillary recurrences had been observed. The first interim analysis took place after the last patient was enrolled.

RESULTS

Patient Eligibility and Characteristics

Of the 473 patients randomly assigned, 19 patients (4%) did not meet protocol eligibility criteria for the following reasons: incorrect stage (n = 9: five T4, three in situ only, one bone metastasis), prior or concurrent malignancy (n = 6), non-Hodgkin's lymphoma (n = 1), did not have breast cancer (n = 1), medically unsuitable (n = 1), and treatment started before random assignment (n = 1). However, all 19 ineligible patients are included in the intent-to-treat analyses.

The characteristics of the 473 patients are shown in Table 1. Baseline characteristics were balanced according to randomly assigned treatment arm. The median age was 74 years in both randomly assigned treatment groups. Twenty-two percent of the patients had

Table 1. Patients' Characteristics According to Treatment (percentages in parentheses)

Characteristic	Sx + Ax		Sx		Total	
	No.	%	No.	%	No.	%
Total No. of patients	234	100	239	100	473	100
Surgery before randomization						
No	214	91	212	89	426	90
Yes	20	9	27	11	47	10
Age, years						
Median	74		74		74	
Range	60-91		60-91		60-91	
ER status						
Positive	179	76	201	84	380	80
Negative	46	20	31	13	77	16
Unknown	9	4	7	3	16	3
Tumor Size						
≤ 2 cm	126	54	137	57	263	56
> 2 cm	100	43	100	42	200	42
Unknown	8	3	2	1	10	2
No. of positive nodes						
0	166	71	4	2	170	36
1-3	46	20	1	1	47	10
≥ 4	18	8	2	1	20	4
Axilla not dissected	4	2	232	97	236	50
Received HRT						
No	184	79	184	77	368	78
Yes	50	21	52	22	102	22
Unknown	0	0	3	1	3	0.6
Mastectomy	105	45	106	44	211	45
Breast-conserving surgery						
With radiotherapy	78	33	77	32	155	33
Without radiotherapy	51	22	56	23	107	23

Abbreviations: Sx, primary surgery; Ax, axillary clearance; ER, estrogen receptor; HRT, hormone-replacement therapy.

received prior hormone replacement therapy and 80% of the patients had primary tumors classified as ER positive. Twenty-eight percent of the patients who had axillary clearance were found to have involved nodes. The median number of examined lymph nodes was 13. Forty-five percent of the patients were treated with mastectomy, 33% had breast-conserving surgery with radiotherapy, and 23% had breast-conserving surgery without radiotherapy.

QL

Physicians were asked whether the patient experienced restricted ipsilateral arm movement and whether the patient experienced arm pain. For both end points, we found a statistically significant increase in physician-reported adverse effects in the first postoperative period for patients who had an axillary clearance. At the first postoperative assessment, there was a statistically significant increase in the restriction of arm movement in the group that received axillary clearance (39% *v* 15% in the group with no axillary clearance; $P = .000001$; Fig 1A). However, after the immediate postoperative period, the percentage of patients for whom the physicians reported restricted arm movement approached the preoperative values in both groups. Similar results were observed for physician-reported arm pain. For this end point physicians reported 23% of patients with arm pain among those receiving axillary clearance versus 7% in the other group at the first postoperative assessment ($P = .00006$; Fig 1B). This difference between treatments was no longer statistically significant at later follow-up assessments. The two other physician-reported QL end points, arm circumference and performance of daily activities, were not significantly different between treatments. The proportion of patients that developed lymphedema, defined as a 5% or greater increase in arm circumference from baseline, was also not significantly different between treatments.

Patient self-assessment of QL was available for 394 patients for the core questionnaire and 257 assessable patients for the study-specific module. For the protocol-specific question about being bothered by hand, arm, shoulder, or chest problems, patient responses showed similar differences between the two treatments as the evaluation performed by the physicians (Fig 2A). The largest difference was observed from baseline to the first postoperative assessment ($P = .01$), and there was a return to baseline levels over time. Other surgery-related symptoms assessed by the patient included restriction in arm movement and numbness. At the first postoperative assessment, patients in the group with axillary clearance reported more restriction in the use of their arm (Fig 2B; $P < .0001$) and more severe postsurgery numbness (Fig 2C; $P = .04$). For those measures not specifically related to surgery sequelae, no significant differences were

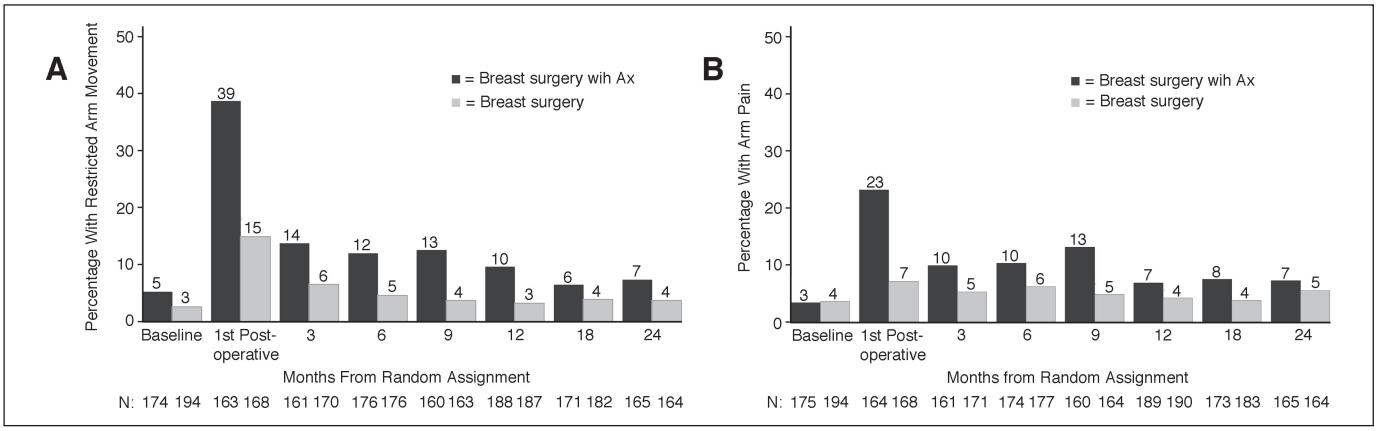

Fig 1. Physician-reported end points. Percentage of patients for whom the physicians reported (A) restricted arm movement and (B) arm pain by treatment group during the first 24 months. Ax, axillary clearance.

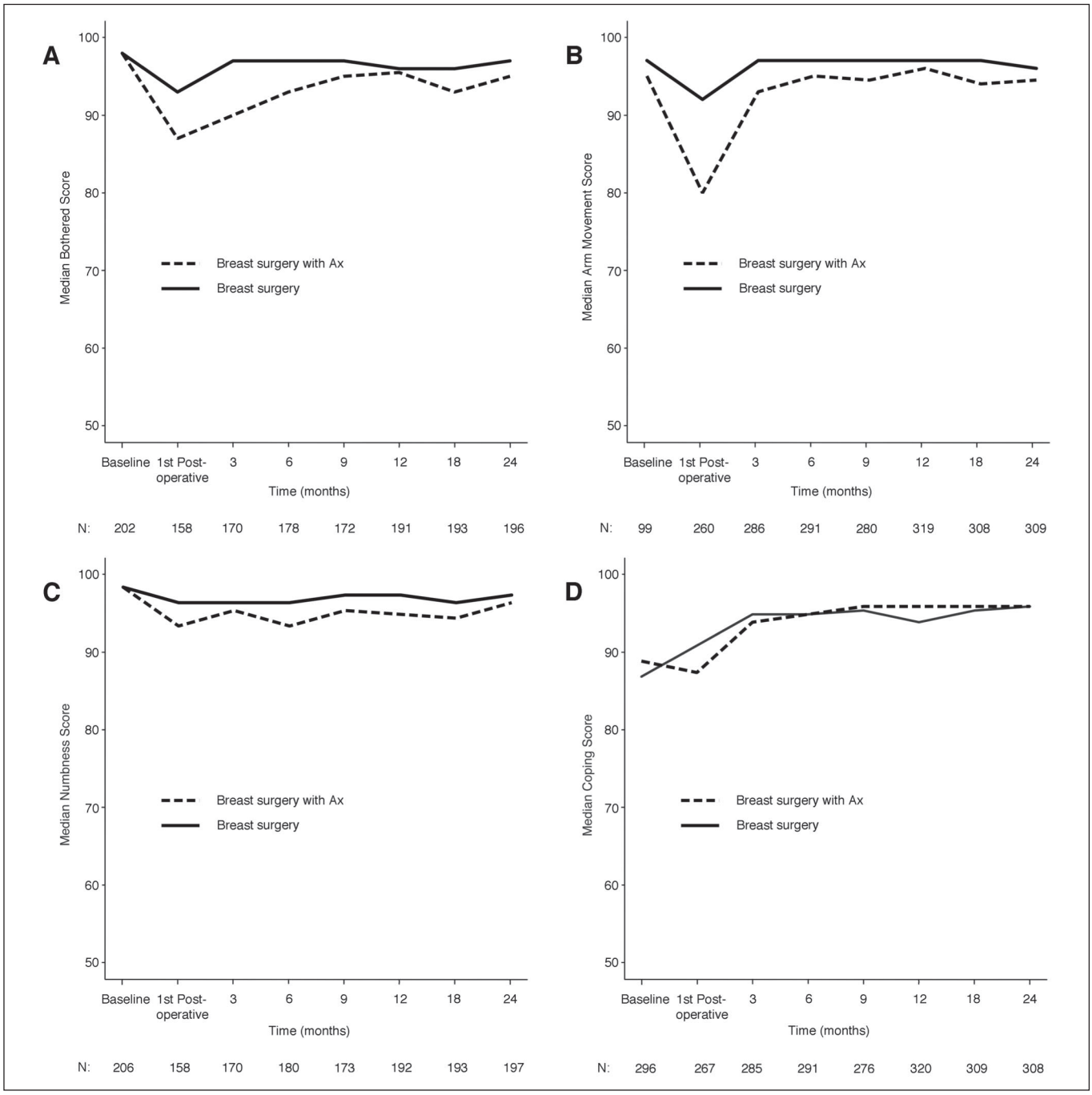

Fig 2. Patient-reported quality of life. Median (A) bothered scores, (B) arm movement scores, (C) numbness scores, and (D) coping scores by treatment group during the first 24 months. Higher values indicate better quality of life. Ax, axillary clearance.

observed at any of the time points. In addition, patients reported similar efforts to cope with their disease regardless of treatment assignment (Fig 2D).

DFS and OS

Overall, the two treatment groups were similar with respect to both DFS (6-year DFS = 67% with axillary clearance *v* 66% without axillary clearance; HR = 1.06; 95% CI, 0.79 to 1.42; *P* = .69; Fig 3A) and overall survival (6-year OS = 75% with axillary clearance *v* 73% without axillary clearance; HR = 1.05; 95% CI, 0.76 to 1.46; *P* = .77; Fig 3B). Within the ER-positive cohort the two treatment groups were similar with respect to both DFS (6-year DFS = 68% with axillary clearance [n = 179] *v* 66% without axillary clearance [n = 201]; HR = 1.01; 95% CI, 0.72 to 1.41; *P* = .95) and OS (6-year OS = 76% with axillary clearance [n = 179] *v* 74% without axillary clearance [n = 201]; HR = 0.97; 95% CI, 0.66 to 1.42; *P* = .87). Similarly, no treatment difference was observed for the ER-negative cohort for DFS (6-year DFS = 62% with axillary clearance [n = 46] *v* 64% without axillary clearance [n = 31]; HR = 1.35; 95% CI, 0.68 to 2.65; *P* = .39)

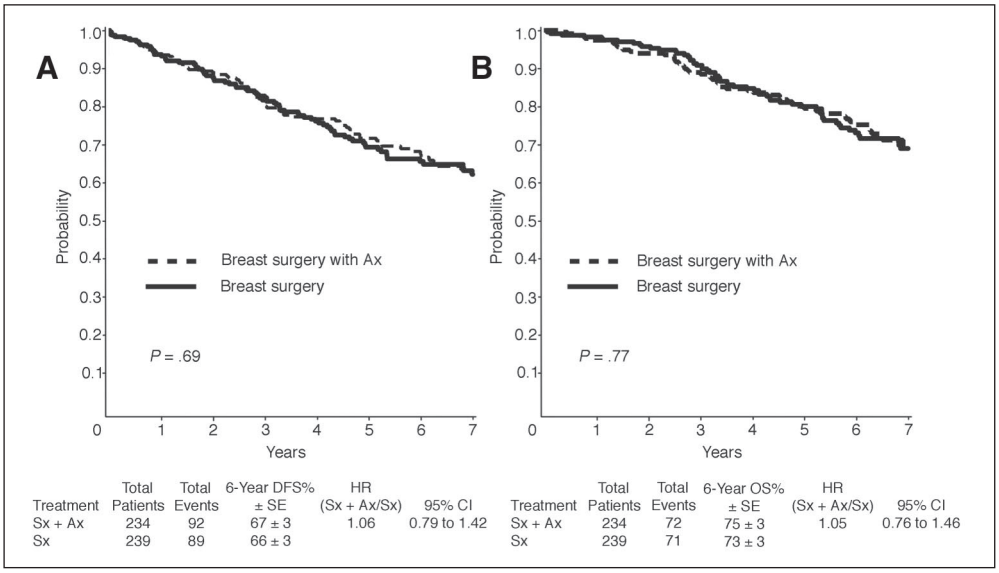

Fig 3. (A) Disease-free survival (DFS) and (B) overall survival (OS) according to treatment group. The median follow-up was 6.6 years. Ax, axillary clearance; Sx, primary surgery; HR, hazard ratio.

and OS (6-year OS = 68% with axillary clearance [n = 46] *v* 69% without axillary clearance [n = 31]; HR = 1.51; 95% CI, 0.72 to 3.17; $P = .28$).

Sites of First Event

Sites of first event were similar between the two treatment groups (Table 2). We observed only a 2% incidence of axillary recurrence overall (as first event) and no statistically significant difference between the two treatment options. One patient, who did not receive an axillary clearance, experienced a subsequent axillary recurrence. All of the patients who had an axillary recurrence received a late axillary clearance after recurrence. Seventeen percent of the patients experienced a breast cancer–related recurrence, whereas 21% experienced a nonbreast second primary cancer or death without recurrence. Because a high percentage of patients had competing events related to nonbreast cancer, we examined the cumulative incidence of breast and nonbreast cancer events by treatment. No differences were observed according to treatment group (Fig 4).

Table 2. Sites of First Event

Patient Data	Sx + Ax→Tam No.	%	Sx→Tam No.	%	Total No.	%
Total Patients	234		239		473	
Failures	92	39	89	37	181	38
Deaths	72	31	71	30	143	30
Site of first event						
Local	9	4	4	2	13	3
Contralateral breast	3	1	4	2	7	1
Axillary recurrence*	2	1	6	3	8	2
Other regional site	0	0	0	0	0	0
Distant	29	12	24	10	53	11
Soft tissue	1	0	3	1	4	1
Bone	12	5	9	4	21	4
Viscera	16	7	12	5	28	6
Total breast cancer events	43	18	38	16	81	17
Second (non-breast) primary	14	6	13	5	27	6
Death w/o recurrence	35	15	38	16	73	15

Abbreviations: Sx, primary surgery; Ax, axillary clearance; Tam, tamoxifen; w/o, without.
*Includes both axillary recurrence among patients with axillary dissection and reappearance of tumor in the undissected axilla.

Tamoxifen Treatment and Toxicity

At the time of this report, 185 patients (39%) had completed 5 years of tamoxifen and 16 patients (3%) received no tamoxifen (six with ER-positive tumors; five with ER-negative tumors; five with ER status unknown). Reasons for not receiving tamoxifen included recurrence (n = 4), patient refusal (n = 2), no invasive breast cancer (n = 4), clinical decision (n = 5), and early death (n = 1). Grade 3 or worse toxicities were experienced by 7% of patients during the tamoxifen therapy (7% with axillary clearance and 8% without axillary clearance). Grade 3 or worse toxicities that were observed included mostly thromboembolic events and cerebral vascular toxicities.

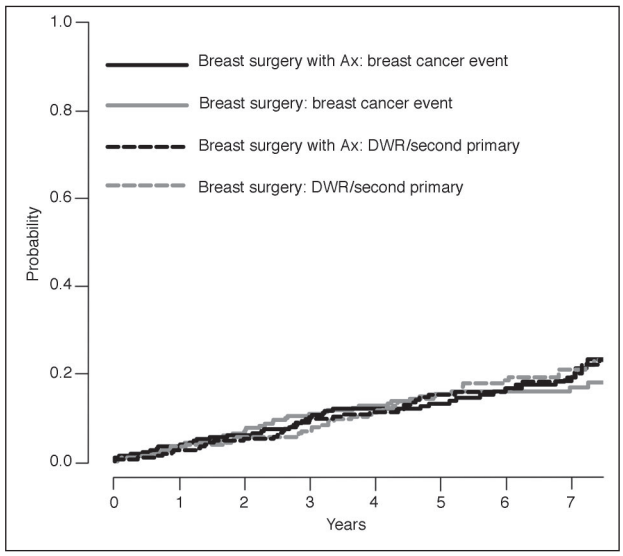

Fig 4. Cumulative incidence of breast and nonbreast cancer events by treatment. Ax, axillary clearance; DWR, death without recurrence.

DISCUSSION

The morbidity of axillary dissection has led some investigators to question its necessity,[17] whereas others have studied alternatives such as axillary radiation therapy[18] and SNB.[19,20] This randomized study examines the option of avoiding axillary surgery altogether and shows that in older women with clinically negative axillary examination, this transiently improves QL (mainly during the first year as assessed by both patients and their physicians) apparently without compromising DFS or OS results. The median age of the patients enrolled onto IBCSG Trial 10-93 was 74 years, which is substantially older than the median age in most adjuvant therapy trials conducted for postmenopausal patients. QL measurements by both physician and patient showed significantly inferior arm-related QL scores after axillary surgery. A similar comparison of arm-related complaints by Veronesi et al[21] showed similar but larger differences between complete axillary surgery and SNB in women of all ages.

The trial was originally designed to assess equivalence between the axillary clearance and no axillary clearance treatment groups in terms of DFS and OS, but the accrual was slower than anticipated; the primary goal shifted to assessing the QL end point. Therefore, the study was not powered to establish treatment equivalence. However, based on our current results, a predictive power calculation indicates that the chance that a fully accrued trial would have found a statistically significant benefit in DFS for patients who received axillary clearance was less than 3%. We conclude that axillary clearance does not contribute greatly to DFS or OS.[22] Nevertheless, no obvious differences were observed in DFS or OS up to 6.6 years of median follow-up. Regional recurrence or reappearance of disease in the axilla was observed for only 2% of the patients overall (3% without axillary clearance and 1% with axillary clearance). Results of our earlier IBCSG Trial IV (patients 66 to 80 years old at random assignment) demonstrated that adjuvant tamoxifen plus low-dose prednisone administered for 1 year provided significant improvement in DFS and OS (evident principally in improved locoregional control) compared with no adjuvant therapy for elderly patients with more than 20 years of follow-up,[23] although at present, we consider 1 year of tamoxifen a suboptimal duration of this therapy. Thus, we deduce that 5 years of tamoxifen included in this study may have prevented at least some axillary recurrences.

Given the postoperative morbidity and the decrease in QL associated with axillary surgery, especially for this elderly population, the trial results provide important evidence to support the option of avoiding axillary clearance. Maunsell et al[24] studied the frequency of reported arm problems and described that 3 months postsurgery, as much as 82% of the patients (n = 223) reported at least one arm problem, the most frequent being numbness (54%) and pain (55%); at the 18-month assessment, the percentage of patients reporting at least one problem remained almost unchanged (79%).

Eighty percent of the women enrolled onto our study had tumors that were classified as ER positive, and 96% of all patients received at least some tamoxifen as adjuvant therapy. This high proportion of patients with an endocrine-responsive disease who received an effective adjuvant endocrine treatment must be taken into account when interpreting the results of the trial. A recent randomized study conducted by the Cancer and Leukemia Group B (CALGB) investigators[25] evaluated the role of radiotherapy in older women with clinical stage I (T1, N0, M0) and ER-positive breast carcinoma treated with lumpectomy and tamoxifen for 5 years. In the CALGB trial, the axillary node dissection was allowed but discouraged, confirming our hypothesis that this approach is common in clinical practice in populations of women older than 70 years. In the CALGB trial, only two isolated axillary recurrences were found in women treated with lumpectomy and tamoxifen. Conversely, avoiding axillary clearance for older women with ER-negative tumors may not be as safe, as suggested by the overall outcomes reported in our study.

It may be argued that axillary surgery might still be worthwhile to determine whether to offer chemotherapy to these patients. Although knowing the axillary nodal status may be necessary to choose the best adjuvant systemic therapy, it is less relevant in an elderly population at low risk and with an inherently shorter life expectancy. Thus, the recent trend to substitute SNB can also be called into question, given that our present results seem to support avoidance of axillary dissection. [25] This line of reasoning is based on the older supposition that chemotherapy should be used for older patients with node-positive disease, but not for patients with node-negative disease. More recently, the endocrine responsiveness of the primary tumor, not the nodal status, is the relevant feature used for guidance in the decision whether to use chemotherapy.[26] Data for the 50- to 69-year age group from the Early Breast Cancer Trialists' Collaborative Group Overview[27] demonstrate that for patients with endocrine-responsive disease, endocrine therapy (specifically tamoxifen) provides the majority of the advantage associated with adjuvant treatments. Thus, because nodal status is less relevant for determining whether chemotherapy is indicated, there may be no need to perform even SNB procedures for an older woman with endocrine-responsive and clinically node-negative disease.

For older women who do require axillary dissection either because of clinical node involvement or because of a positive SNB, the results of this study are reassuring, demonstrating that for most of these women, there is little effect from this surgery on their long-term daily functioning or their QL.

Younger women reported higher rates of arm morbidity than older women, perhaps because these symptoms have a greater impact on their functioning.[28] In a recent study assessing long-term morbidity after axillary surgery for breast cancer, Taylor[29] reported that three fourths of 208 patients had at least one long-term symptom (3 to 6 years). Similar findings were reported by another group,[30] supporting the need to study less invasive procedures at least for clinically node-negative patients. Although several studies have specifically compared arm morbidity between women undergoing standard axillary clearance and those receiving SNB,[19-21,31,32] these have not focused on the elderly patient population.

In summary, IBCSG Trial 10-93 has demonstrated that avoiding axillary clearance for older women with clinically node-negative breast cancer who receive adjuvant tamoxifen seems safe and results in early improved QL for this older population of patients. These results apply primarily for patients with endocrine-responsive disease in whom the use of tamoxifen is associated with substantial benefit in terms of disease control. For older women with endocrine-nonresponsive disease, the tailored use of adjuvant systemic chemotherapy is being investigated in an ongoing randomized clinical trial (Chemotherapy Adjuvant Study for Women at Advanced Age: CASA), coordinated by the IBCSG on behalf of the Breast International Group.

REFERENCES

1. Greenlee RT, Hill-Harmon MB, Murray T, et al: Cancer statistics, 2001. CA Cancer J Clin 51:15-36, 2001

2. Yancik R: Cancer burden in the aged: An epidemiologic and demographic overview. Cancer 80:1273-1283, 1997

3. Yancik R, Wesley MN, Ries LA, et al: Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 285: 885-892, 2001

4. Diab SG, Elledge RM, Clark GM: Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst 92:550-556, 2000

5. Pierga JY, Girre V, Laurence V, et al: Characteristics and outcome of 1755 operable breast cancers in women over 70 years of age. Breast 13:369-375, 2004

6. Bernhard J, Maibach R, Thürlimann B, et al: Patients' estimation of overall treatment burden: Why not ask the obvious? J Clin Oncol 20:65-72, 2002

7. Hürny C, Bernhard J, Coates AS, et al: Impact of adjuvant therapy on quality of life in women with node-positive operable breast cancer. International Breast Cancer Study Group. Lancet 347:1279-1284, 1996

8. Bernhard J, Hürny C, Coates AS, et al: Quality of life assessment in patients receiving adjuvant therapy for breast cancer: The IBCSG approach—The International Breast Cancer Study Group. Ann Oncol 8:825-835, 1997

9. Bernhard J, Sullivan M, Hürny C, et al: Clinical relevance of single item quality of life indicators in cancer clinical trials. Br J Cancer 84:1156-1165, 2001

10. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

11. Greenwood M: The Natural Duration of Cancer. London, United Kingdom, Her Majesty's Stationary Office, 1926, pp 1-26

12. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966

13. Cox DR: Regression models and life-tables (with discussion). J R Stat Soc 34:187-220, 1972

14. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 16:1141-1154, 1988

15. Wilcoxon F: Individual comparisons by ranking methods. Biometrics 1:80-83, 1945

16. Cox DR: Analysis of Binary Data. London, United Kingdom, Methuen and Co, 1970

17. Parmigiani G, Berry DA, Winer EP, et al: Is axillary lymph node dissection indicated for early-stage breast cancer? A decision analysis. J Clin Oncol 17:1465-1473, 1999

18. Louis-Sylvestre C, Clough K, Asselain B, et al: Axillary treatment in conservative management of operable breast cancer: Dissection or radiotherapy? Results of a randomized study with 15 years of follow-up. J Clin Oncol 22:97-101, 2004

19. Schrenk P, Rieger R, Shamiyeh A, et al: Morbidity following sentinel lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. Cancer 88:608-614, 2000

20. Burak WE, Hollenbeck ST, Zervos EE: Sentinel lymph node biopsy results in less postoperative morbidity compared with axillary lymph node dissection for breast cancer. Am J Surg 183:23-27, 2002

21. Veronesi U, Paganelli G, Viale G, et al: A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 349:546-553, 2003

22. Jennison C, Turnbull BW: Statistical approaches to interim monitoring of medical trials: A review and commentary. Stat Sci 5:299-317, 1990

23. Crivellari D, Price K, Gelber RD, et al: Adjuvant endocrine therapy compared with no systemic therapy for elderly women with early breast cancer: 21-year results of International Breast Cancer Study Group Trial IV. J Clin Oncol 21:4517-4523, 2003

24. Maunsell E, Brisson J, Deshenes L: Arm problems and psychological distress after surgery for breast cancer. Can J Surg 36:315-320, 1993

25. Hughes KS, Schnaper LA, Berry D, et al: Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med 351:971-977, 2004

26. Goldhirsch A, Wood WC, Gelber RD, et al: Meeting highlights: Updated international expert consensus on the primary therapy of early breast cancer. J Clin Oncol 21:3357-3365, 2003

27. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effect of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687-1717, 2005

28. Liljegren G, Holmberg L: Arm morbidity after sector resection and axillary dissection with or without postoperative radiotherapy in breast cancer stage I: Results from a randomised trial—Uppsala-Orebro Breast Cancer Study Group. Eur J Cancer 33:193-199, 1997

29. Taylor KO: Morbidity associated with axillary surgery for breast cancer. ANZ J Surg 74:314-317, 2004

30. Kuehn T, Klass W, Darsow M, et al: Long-term morbidity following axillary dissection in breast cancer patients: Clinical assessment, significance for life quality and the impact of demographic, oncologic, and therapeutic factors. Breast Cancer Res Treat 64:275-286, 2000

31. Siberman AW, McVay C, Cohen JS, et al: Comparative morbidity of axillary lymph node dissection and the sentinel lymph node technique: Implications for patients with breast cancer. Ann Surg 240:1-6, 2004

32. Peintinger F, Reitsamer R, Stranzl H, et al: Comparison of quality of life and arm complaints after axillary lymph node dissection vs sentinel lymph node biopsy in breast cancer patients. Br J Cancer 89:648-652, 2003

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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