Axillary lymph node dissection for sentinel lymph node micrometastases may be safely omitted in early-stage breast cancer patients: long-term outcomes of a prospective study*

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Oncology 2010

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*This article was originally published in
Ann Surg Oncol (2009) 16:3366–3374
DOI 10.1245/s10434-009-0661-8 and is
published here in its entirety.

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Abstract

Objectives. To evaluate the long-term disease-free and overall survival of patients with sentinel lymph node (SLN) micrometastases, in whom a completion axillary lymph node dissection (ALND) was systematically omitted.

Background. The use of step sectioning and immunohistochemistry for SLN analysis results in a more accurate histopathologic examination and a higher detection rate of micrometastases. However, the clinical relevance and therapeutic implications of SLN micrometastases remain a matter of debate.

Methods. In this prospective study, 236 SLN biopsies were performed in 234 consecutive early-stage breast cancer patients (T1, T2 ≤ 3 cm, cN0 M0) between 1998 and 2002. The SLN were examined by step sectioning and stained with hematoxylin and eosin and immunohistochemistry. None of the patients with negative SLN or SLN micrometastases (International Union Against Cancer classification, >0.2 to ≤ 2 mm) underwent a completion ALND or radiation to the axilla. Long-term overall and disease-free survivals were compared between patients with negative SLN and those with SLN micrometastases by log rank tests.

Results. The SLN was negative in 55% of patients (123 of 224). SLN micrometastases were detected in 27 patients (27 of 224, 12%). After a median follow-up of 77 months (range, 24–106 months), neither locoregional recurrences nor distant metastases occurred in any of the 27 patients with SLN micrometastases. There were no statistically significant differences for overall ($P = 0.656$), locoregional ($P = 0.174$), and axillary and distant disease-free survival ($P = 0.15$) between patients with negative SLN and SLN micrometastases.

Conclusions. This analysis of unselected patients provides evidence that a completion level I and II ALND may be safely omitted in early-stage breast cancer patients with SLN micrometastases.

Introduction

THE sentinel lymph node (SLN) biopsy has emerged as the standard staging method in evaluating the axillary

lymph node status in early-stage breast cancer patients and has replaced level I and II axillary lymph node dissection (ALND) in many institutions. Many studies have proved the accuracy and the high negative predic-

tive value of the SLN procedure.^{1,2} The main advantage of SLN biopsy is that node-negative patients can be spared the substantial short- and long-term morbidity of a level I and II ALND.^{3–5} Furthermore, compared with analysis with hematoxylin and eosin (HE) only in ALND specimen, the use of step sectioning and immunohistochemistry in the SLN results in a more accurate histopathologic examination and is associated with a higher detection rate of micrometastases.^{6,7} Although the step sectioning and immunohistochemistry can be routinely applied to evaluate one or a few SLN, the systematic use of these techniques is not feasible in the assessment of ALND specimens because of time and financial constraints. However, the prognostic significance and therapeutic implications of SLN micrometastases in terms of axillary recurrence and long-term survival remain a matter of great debate.⁸ Therefore, the objective of the present prospective study was to evaluate the long-term disease-free and overall survival of patients with SLN micrometastases in whom a completion ALND was systematically omitted.

Patients and methods

Between April 1998 and September 2002, a total of 234 patients with early-stage breast cancer were prospectively enrolled into our study. Two patients had bilateral breast cancer, and thus a total of 236 SLN procedures were performed. Inclusion criteria for the present study were as follows: (1) presence of palpable breast cancer, (2) tumor size clinically B3 cm in diameter, and (3) absence of clinically palpable suspicious axillary lymph nodes. Written informed consent was obtained from all patients.

Lymphatic mapping and operative technique

SLN mapping was performed by using a combination of a radiolabeled colloid and a vital blue dye. ^{99m}Tc-labeled nanocolloid (Nanocoll, Nycomed AG, Wädenswil, Switzerland) at a dose of 4 × 20 MBq was injected, 3 × 20 MBq peritumorally and 1 × 20 MBq subdermally above the tumor site. Lymphoscintigraphy was performed preoperatively to identify lymphatic flow to axillary and/or parasternal lymph nodes. Hot spots were marked on the skin. The technique of SLN biopsy has been described previously.⁹ Briefly, SLN were intraoperatively identified first by use of a handheld gamma probe (Navigator, USSC, RMD Waterton, MA) to allow a precise and short incision of the overlying skin. Two to 5 mL of isosulfan blue (Lymphazurin, Ben Venue Labs, Bedford, OH) were injected in the same fashion as the radioactive tracer 5 min before incision. All hot and/or blue lymph nodes were excised and labeled separately as SLNs. Dissection

was continued until all hot and blue nodes had been removed, and the background count of the axilla was <10% of the hottest lymph node.

Before the present investigation was initiated, the SLN procedure has been validated at our institution on the basis of 44 breast cancer patients in whom both SLN and ALND level I and II were performed. For that group, the SLN identification rate was 93%, sensitivity 94%, specificity 100%, and negative predictive value 95%.⁹

Pathologic examination of lymph nodes

Frozen section was routinely performed intraoperatively. Lymph nodes >5 mm in diameter were bisected; lymph nodes ≤5 mm in diameter were not bisected but totally submitted for frozen section analysis. The SLN were intraoperatively examined at three levels with HE-stained sections at a cutting interval of 150 μm. The remaining SLN tissue was fixed in formalin and embedded in paraffin for histologic analysis. The residual tissue was then examined by means of step sectioning at a cutting interval of 250 μm. Step sections were stained with HE. If no carcinoma cells were detected, immunohistochemistry with cytokeratin antibody Lu-5 or CK 22 using a standard immunoperoxidase method (ABC-Elite) was performed. Lu-5 (Bio Medicals, Augst, Switzerland) is a pan-cytokeratin monoclonal antibody that recognizes type I and II cytokeratin subfamilies of all epithelial and mesothelial cells.

Micrometastases are defined on the basis of a size of >0.2 mm and ≤2 mm in diameter according to the 2003 International Union Against Cancer (UICC) classification. Therefore, isolated tumor cells or tumor cell clusters measuring <0.2 mm in diameter did not meet the definition of micrometastases. Patients with submicrometastases (UICC, <0.2 mm; *n* = 3) were considered node negative for this investigation. Patients with SLN macrometastases immediately underwent ALND level I and II. Conversely, patients with negative SLN or SLN micrometastases (UICC, >0.2 to ≤2 mm) did not undergo further axillary surgery or radiation to the axilla.

Adjuvant therapy

After breast-conserving surgery, patients received adjuvant radiotherapy with 45 Gy over 5 weeks with a boost of 10 Gy to the tumor site, which was intraoperatively marked with clips. No radiation was provided to the axilla. Adjuvant therapy consisted of hormone treatment (tamoxifen for 5 years, 20 mg daily, no aromatase inhibitors) and/or chemotherapy (Adriamycin and cyclophosphamide or epirubicin and cyclophosphamide) every 3 weeks for a total of 12 weeks. In low-risk patients, elderly patients, and patients with contraindications for anthracyclines, six cycles of cyclophosphamide, meth-

otrexate, and 5-fluorouracil were provided. The indication for adjuvant therapy was based on the recommendation of the St. Gallen Consensus Conference.^{10,11} On the basis of these recommendations, patients with SLN micrometastases were considered node negative, and the decision to administer adjuvant therapy was based only on the characteristics of the primary tumor.

Postoperative follow-up

The follow-up diagnostic procedures were clinical examination of the breast and of the axillary lymph nodes every 4 months in the first 3 years after surgery, every 6 months in the next 2 years, and once a year thereafter. Mammography was performed annually. Additional ultrasound of the breast was indicated to clarify suspicious mammographic findings.

Statistical analyses

The Mann–Whitney *U*-test was used for comparisons of continuous outcomes; Fisher's exact test was used to compare dichotomous and categorical variables. The primary outcomes of this investigation were overall and disease-free survival. Disease-free survival was defined as the time from surgery to occurrence of a recurrence and was further classified into local, regional (axillary), and distant disease-free survival. Patients who did not experience relapse or death were censored at the last clinical visit. Survival probabilities for disease-free and overall survival were estimated by the Kaplan–Meier method. Between-group comparisons were carried out by the log rank test for disease-free and overall survival. The level of statistical significance was set below 0.05. All statistical tests were two sided. We used Microsoft Excel (Microsoft, Redmond, WA) to compile the data. Statistical analyses were performed by SPSS software (version 15.0.1, SPSS, Chicago, IL).

Results

Between April 1998 and September 2002, a total of 236 SLN biopsies were performed on 234 patients with early stage breast cancer (Fig. 1). The identification rate was 95% (224 of 236). A mean number of 2.1 ± 1.4 SLNs per patient were collected. The SLN were tumor-free in 123 (54.9%) of 224 patients and contained micrometastases in 27 (12.1%) of 224 patients. Among the 123 patients classified as node negative (pN0), there were 3 patients with isolated tumor cells (pN0+?, ≤ 0.2 mm) in the SLN. Micrometastases were detected by step sectioning with HE staining in 14 of 27 cases and by additional immunohistochemistry in 13 of 27 patients. The identi-

cation of micrometastases led to a formal upstaging in 18% (27 of 150) of patients. None of the node-negative patients ($n = 123$) and no patients with SLN micrometastases ($n = 27$) underwent formal completion level I and II ALND. The characteristics of the groups with negative SLN biopsy results and SLN micrometastases are listed in Table 1. Mean age was 59.6 ± 12.2 (SD) years and 61.7 ± 11.0 (SD) years, respectively. The patients were predominantly postmenopausal. Mean tumor size was 16.4 mm for the SLN-negative group and 16.9 mm for the SLN micrometastases group. There was no statistically significant difference between the subsets of negative SLN versus patients with SLN micrometastases for menopausal status, T stage, histological type and grading, localization of the primary tumor, estrogen and progesterone receptor status, the mean number of removed SLN, and use of adjuvant treatments (Table 2). A significantly higher percentage of patients with SLN micrometastases underwent mastectomy, whereas the fraction of patients undergoing breast-conserving treatment was higher in the SLN-negative group ($P = 0.005$; Table 1). Therefore, a lower fraction (14 of 27, 51.9%) of patients with SLN micrometastases received adjuvant radiotherapy compared with patients with negative SLN (104 of 123, 81.4%; Table 1). Three patients in the SLN-negative group had T4 tumors. This T4 stage was due to the invasion of the overlying skin (T4b) without exceeding the maximum tumor size (≤ 3 cm) as defined in the inclusion criteria.

Median follow-up times for the SLN-negative and SLN micrometastases group were 74 months (range, 1–105) and 77 months (range, 24–106), respectively. In the SLN-negative group ($n = 123$), local recurrence occurred in 7 (5.7%) of the 123 patients, axillary recurrence in 1 (.8%), and distant metastases in 7 (5.7%). Thirteen node-negative patients (13 of 123, 10.6%) died during follow-up; six deaths were related to metastatic breast cancer. In

Fig. 1 Study flow chart

Table 1. Patient and tumor characteristics

Characteristic	SLN negative (<i>n</i> = 123), <i>n</i> (%)	SLN micrometastases (<i>n</i> = 27), <i>n</i> (%)	SLN macrometastases (<i>n</i> = 74), <i>n</i> (%)	<i>P</i> value ^a
Age (y)				
Mean	59.6 ± 12.2	61.7 ± 11.0	63.5 ± 12.0	0.410
Range	32–88	40–82	40–93	
Menopausal status, <i>n</i> (%)				
Premenopausal	26 (21.1)	5 (18.5)	11 (14.9)	1.000
Postmenopausal	97 (78.9)	22 (81.5)	63 (85.1)	
Tumor size (mm)				
Mean	16.4 ± 8.0	16.9 ± 7.2	26.9 ± 11.7	0.554
Range	2–41	3–30	1–55	
T stage, <i>n</i> (%)				
T1a	6 (4.9)	2 (7.4)	1 (1.3)	0.301
T1b	23 (18.7)	1 (3.7)	2 (2.7)	
T1c	61 (49.6)	15 (55.6)	24 (32.4)	
T2	30 (24.4)	9 (33.3)	40 (54.1)	
T3	0 (0)	0 (0)	3 (4.1)	
T4	3 (2.4)	0 (0)	4 (5.4)	
Histology <i>n</i> (%)				
Ductal	98 (79.7)	21 (77.8)	58 (78.4)	0.783
Lobular	23 (18.7)	5 (18.5)	15 (20.3)	
Other	2 (1.6)	1 (3.7)	1 (1.3)	
Histological grading, <i>n</i> (%)				
G1	33 (26.8)	5 (18.5)	10 (13.5)	0.648
G2	59 (48.0)	15 (55.6)	43 (58.1)	
G3	31 (25.2)	7 (25.9)	21 (28.4)	
Primary tumor, <i>n</i> (%)				
Tumorectomy	104 (84.6)	14 (51.9)	37 (50.0)	0.0005
Mastectomy	19 (15.4)	13 (48.1)	37 (50.0)	
Quadrant, <i>n</i> (%)				
Upper outer	68 (55.3)	15 (55.6)	40 (54.1)	0.703
Upper inner	12 (9.8)	5 (18.5)	6 (8.1)	
Lower outer	23 (18.7)	4 (14.8)	8 (10.8)	
Lower inner	11 (8.9)	2 (7.4)	8 (10.8)	
Areolar	9 (7.3)	1 (3.7)	12 (16.2)	
Estrogen receptor status, <i>n</i> (%)				
Positive	103 (83.7)	22 (81.5)	61 (82.4)	0.778
Negative	20 (16.3)	5 (18.5)	13 (17.6)	
Progesterone receptor status, <i>n</i> (%)				
Positive	85 (69.1)	20 (74.1)	54 (73.0)	0.817
Negative	38 (30.7)	7 (25.9)	20 (27.0)	
No. of SLN per patient				
Mean	2.1 ± 1.5	1.9 ± 1.0	2.14 ± 1.4	0.877
Range	1–9	1–4	1–8	

SLN sentinel lymph node ^a*P* value between SLN negative and SLN micrometastases ± means SD

the subset of patients with SLN micrometastases, no local, axillary, or distant recurrences were observed during a median follow-up of 77 months. Two (7.4%) of 27 patients died; both deaths were unrelated to breast cancer (Table 2).

The 5-year overall survival was 93.1% in the SLN-negative group and 92.6% in patients with SLN micrometastases (Fig. 2). No statistically significant difference for overall survival was detected between patients with a

Table 2. Adjuvant therapy and follow-up

Characteristic	SLN negative (<i>n</i> = 123), <i>n</i> (%)	SLN micrometastases (<i>n</i> = 27), <i>n</i> (%)	<i>P</i> value
Adjuvant therapy, <i>n</i> (%)			
Hormone therapy	84 (68.3)	18 (66.7)	0.091 ^a
Chemotherapy	15 (12.2)	3 (11.1)	
Hormone therapy + chemotherapy	7 (5.7)	5 (18.5)	
None	17 (13.8)	1 (3.7)	
Median follow-up (mo) (range)	74.4 (1–105)	77.2 (24–106)	0.794 ^a
Recurrence of disease, <i>n</i> (%)			
Local recurrence	7 (5.7)	0 (0)	0.081 ^b
Regional recurrence 1	(0.8)	0 (0)	
Distant metastases	7 (5.7)	0 (0)	
Deaths, <i>n</i> (%)			
Tumor related	6 (4.9)	0 (0)	0.656 ^b
Not tumor related	7 (5.7)	2 (7.4)	

SLN sentinel lymph node; ^aFisher's exact test; ^bLog rank test **Fig. 2** Overall survival (OS), sentinel lymph node (SLN) negative vs SLN micrometastases

negative SLN and those with SLN micrometastases ($P = 0.66$). Furthermore, there was no statistically significant difference in the disease-free survival, with a 5-year survival of 90.7% in patients with a negative SLN and 100% in patients with SLN micrometastases ($P = 0.08$, Fig. 3). The 5-year locoregional (local and axillary) disease-free survival was 94.1% in the subset with negative SLN and 100% in patients with SLN micrometastases ($P = 0.17$; Fig. 4). Finally, there was no statistically significant difference in the axillary and distant disease-free survival between patients with negative SLN compared with those with SLN micrometastases ($P = 0.15$).

Fig. 3 Disease-free survival (DFS), sentinel lymph node (SLN) negative vs SLN micrometastases

Discussion

This prospective study has the longest follow-up in the literature regarding disease-free and overall survival for early-stage breast cancer patients with SLN micrometastases who did not undergo a level I and II completion ALND. Our investigation provides suggestive evidence that a completion ALND may be safely omitted in patients with SLN micrometastases. Therefore, patients with SLN micrometastases may be spared the considerable short- and long-term complications of a completion ALND.

The SLN biopsy has emerged as the standard staging method of the axillary lymph node status in early-stage breast cancer patients and has replaced level I and II ALND in many institutions.^{3,12,13} Many studies have proved the accuracy and the high negative predictive value of the SLN procedure.² However, the SLN procedure is associated with a false-negative rate of 8% to 10% when summarizing larger series.^{14–20} Krag et al. recently published the data of the National Surgical Adjuvant Breast and Bowel Project B-32 trial and cited a false-negative rate of 9.8%.¹⁴ Nevertheless, the rate of axillary recurrence remains low (0 to 2%) even during long-term follow-up, which was confirmed in the present study.^{8,17,21} Two randomized, controlled clinical trials reported no significant difference regarding axillary recurrences when comparing SLN biopsy only versus level I and II ALND in patients with node-negative disease.^{5,17} This implies that SLN biopsy not only provides accurate staging information, but also excellent regional control of clinically occult disease. Veronesi et al. proved in their study of 953 SLN-negative patients without completion ALND that a much lower than expected incidence of axillary recurrence occurred after a median follow-up of 38 months.¹²

It is clear that not all microscopic tumor foci in axillary lymph nodes will progress to clinically relevant local recurrences. Indeed, Al Hajj et al. found that only a minority of breast cancer cells had the ability to form new tumor cells.²² The hypothesis of breast cancer stem cells postulates the existence of two different cell populations spreading into lymph nodes. The true stem cells will have the capacity to progress to clinically detectable metastases, whereas the non-stem cells will not grow and will eventually disappear. Other experimental studies suggest that most isolated tumor cells are not viable and will not result in clinically relevant metastases.²³ Most interestingly, Colpaert et al. found a survival advantage for patients with lymph node micrometastases compared with node-negative patients; they hypothesized that this was a result of an enhanced host immune response that was the result of micrometastatic spread.²³ Finally, adjuvant therapy may also contribute to the locoregional control. Nodal tumor deposits were found to be chemosensitive, and the adjuvant treatment resulted in the ablation of residual microscopic axillary metastases.²⁴

Since the introduction of the SLN procedure into clinical practice, axillary lymph node micrometastases are more likely to be detected.^{1,25–30} This is because pathologists can focus their attention on a few lymph nodes, which can be analyzed more thoroughly by step sectioning and immunohistochemistry.²⁷ Conversely, the systematic use of step sectioning and immunohistochemistry is not feasible in the assessment of all nodes in ALND specimens because of time and financial constraints.⁷ The detection rate of micrometastases varies

according to different histopathological techniques and protocols. Current literature reports that 15 to 48% of all SLN metastases are micrometastases, leading to an upstaging of 9 to 25% of initially node-negative patients.^{25,27,30}

The prognostic significance and therapeutic implications of SLN micrometastases remain a matter of great debate. Unidentified micrometastases have been held responsible for the occurrence of up to 30% distant metastases of node-negative breast cancer patients.³¹ During the ALND era, various retrospective studies reported a significant disease-free and overall survival disadvantage in breast cancer patients with micrometastases; others, however, failed to find any association.^{32–34} Colleoni et al. analyzed retrospectively the impact of micrometastases and isolated tumor cells on survival in 1959 patients.³⁵ A SLN biopsy was performed in only 43% (847 of 1959) of the patients. After a median follow-up of 49.9 months, patients with micrometastases or isolated tumor cells had worse 4-year disease-free survival compared with node-negative patients. However, no significant overall survival difference was found. Similarly, Veronesi et al. compared outcomes in SLN-negative patients versus patients with SLN micrometastases with a completion ALND. No difference in the rate of breast cancer-related events was observed.³⁶ Chagpar et al. reviewed patients with negative SLN status determined by standard HE staining of bivalved sentinel nodes who did not undergo a completion ALND.³⁷ The specimens were reevaluated by step sections and immunohistochemistry. Twelve (14.3%) of 84 patients were found to have SLN micrometastases. After a median follow-up of 40

Fig. 4 Locoregional disease-free survival (DFS), sentinel lymph node (SLN) negative vs SLN micrometastases

Table 3. Recurrence after positive SLN biopsy without completion ALND

Study	Year	Type	<i>n</i>	Size of nodal infiltrate (mm)	Follow-up (months)	Axillary recurrence (<i>n</i>)	Patient sample
Liang ³⁹	2001	Retrospective	4	<2	14 ^a	0	Selected
Ganaraj ³⁸	2003	Prospective	17	<2	30 ^a	0	Selected
Guenther ⁴²	2003	Prospective	16	<2	32 ^b	0	Selected
Fant ⁴³	2003	Retrospective	27	<2	30 ^a	0	Selected
Fournier ⁴⁰	2004	Retrospective	6	≤ 2	12 ^a	0	Selected
Fan ⁴⁶	2005	Retrospective	27	≤ 2	29 ^b	1	Selected
Schrenk ⁴¹	2005	Prospective	16	>0.2 ≤ 2	48 ^b	0	Selected
Carlo ⁴⁷	2005	Prospective	21	<2	60 ^b	0	Selected
Chagpar ³⁷	2005	Retrospective	12	>0.2 ≤ 2	40 ^b	0	Unselected ^c
Haid ⁴⁸	2006	Prospective	6	>0.2 ≤ 2	47 ^b	0	Selected
Hwang ⁴⁹	2007	Retrospective	90	>0.2 ≤ 2	30 ^b	0	Selected
This study	2009	Prospective	27	>0.2 ≤ 2	77 ^b	0	Unselected

^aMean; ^bMedian; ^cHistopathological review of primarily negative SLN

months, no axillary recurrences or distant metastases were observed. There was no statistically significant difference in overall and distant metastasis-free survival compared with the SLN-negative group.

In our prospective study, 26.7% (27 of 101) of all SLN metastases were micrometastases. Because of their unknown prognostic significance, no formal completion ALND was performed in patients with SLN micrometastases. Only 2 of 27 SLN micrometastases were detected in frozen sections, whereas the remaining 25 were identified in permanent sections, and notably half of them exclusively with immunohistochemistry. After a median follow-up of 77 months, no local recurrence, axillary recurrence, or distant metastases were observed in patients with SLN micrometastases, so they were spared the considerable short- and long-term morbidity of a formal completion level I and II ALND.^{3,4} There were no significant differences in overall and axillary and distant disease-free survival between patients with negative SLN and SLN micrometastases without a completion ALND. The 5-year disease-free survival was even significantly higher in patients with SLN micrometastases compared with patients with negative SLN (100% vs 93.9%, $P = 0.039$; Fig. 3). This is because local recurrences occurred in 7 SLN-negative patients whereas no local recurrences were observed in patients with SLN micrometastases. To our knowledge this prospective study is the only one in the literature that reports the findings of an unselected group of patients with SLN micrometastases in whom a completion ALND was systematically omitted. Furthermore, our results are based on the longest follow-up in this specific group of patients (Table 3).

In nearly all other publications studying patients with SLN macrometastases, micrometastases, or isolated tumor cells in whom a completion ALND was omitted, the patients' selection was based on various criteria,

including patients refusing further surgery, elderly patients, patients with serious comorbid conditions, or patients who were thought to be at low risk for having residual axillary disease according to the nomogram developed at the Memorial Sloan-Kettering Cancer Center (Table 3).^{38–49} As a result of patient selection, which was based on the criteria described above, the results of these studies may be biased.

Regardless of the fact that most studies examined a selected patient group, only a few recurrences were observed after a follow-up time between 12 and 48 months for SLN micrometastases (Table 3).^{37,41–43,45–49} However, most of these patients were at low risk of having positive SLN according to the Memorial Sloan-Kettering Cancer Center nomogram; the follow-ups may not be sufficiently long for disease recurrence to occur, and patients may have benefited from adjuvant chemotherapy. In the present investigation, only 17.9% of SLN-negative patients and 29.6% of patients with SLN micrometastases underwent adjuvant chemotherapy. Despite these relatively low percentages of patients undergoing adjuvant chemotherapy, and despite a long-term follow-up, no axillary and distant recurrences occurred in our patient subset with SLN micrometastases. Ongoing prospective trials from the International Breast Cancer Study Group, National Surgical Adjuvant Breast and Bowel Project, and the American College of Surgeons Oncology Group will, we hope, provide definitive answers regarding the prognostic and therapeutic implications of micrometastases in breast cancer patients.

We would like to acknowledge the limitations of our study. First, the number of patients in the SLN micrometastases group is relatively small. However, this group of patients with SLN micrometastases is so far the best available sample of unselected patients in the literature in whom a completion ALND was systematically omitted.

Second, the median follow-up of 77 months in a group of early breast cancer patients might be too short to definitively answer the prognostic effect of SLN micrometastases on disease-free and overall survival, and longer observation periods may be required. Finally, although the patient characteristics were equally balanced between the SLN-negative group and the subset of patients with SLN micrometastases, there were significantly fewer patients undergoing mastectomy in the SLN-negative group. Therefore, a higher percentage of SLN-negative patients received adjuvant radiation to the breast compared with the SLN micrometastases group. This is important because even though no patients received specific axillary radiotherapy, it is well known that patients who undergo wholebreast radiation as part of their breast-

conserving therapy do have their level I and II axilla exposed to radiation. However, the fact that a much lower fraction of patients with SLN micrometastases received adjuvant radiotherapy further strengthens the main conclusion of our investigation.

In summary, the present analysis with the longest follow-up in the literature suggests that a completion ALND may be safely omitted in early-stage breast cancer patients with SLN micrometastases. In fact, no local, regional, or distant recurrence occurred in any of the 27 patients with SLN micrometastases during a median follow-up of 77 months. Therefore, patients with SLN micrometastases may be spared the substantial short- and long-term morbidity of a completion ALND.

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