

Axillary Recurrence After a Negative Sentinel Node Biopsy for Breast Cancer: Incidence and Clinical Significance

Marjolein L. Smidt, MD, Caroline M. M. Janssen, MD,
Deborah M. Kuster, MD, Erik D. M. Bruggink, MD, PhD, and
Luc J. A. Strobbe, MD, PhD

Department of Surgical Oncology, C22, Canisius Wilhelmina Hospital, PO Box 9015,
6500 GS Nijmegen, The Netherlands

Background: Sentinel lymph node biopsy (SLNB) carries the inherent risk of approximately 5% false-negative sampling. Undetected tumor-positive nodes of clinical importance are those that lead to axillary recurrence. This survey aims at clarifying the extent of this problem in current practice and literature.

Methods: In a regional teaching hospital, 696 consecutive breast cancer patients underwent SLNB between January 1998 and July 2003, and data were entered in a prospective database. PubMed and the Cochrane library were searched for a systematic review of the literature. Thirteen studies dealt with the follow-up of a cohort of sentinel lymph node (SLN)-negative patients or presented a case report.

Results: The SLN identification rate was 97.1%. The SLN was tumor free in 439 (65%) of the 676 patients. After a median follow-up of 26 months, axillary recurrence was detected in 2 of 439 patients 4 and 27 months after the SLNB. The incidence of clinically apparent false-negative SLNB is .46%. The systematic review resulted in 3184 SLNB-negative patients with a median follow-up of 25 months. Axillary recurrence occurred in eight patients after a median of 21 months. The axillary recurrence rate in the literature is .25%. One third of these patients present with synchronous systemic metastases.

Conclusions: Axillary recurrences after a negative SLNB occur, but at a much lower rate than would be expected on the basis of historical figures and the false-negative SLN findings. The natural history of axillary relapse after negative SLNB resembles the locoregional recurrence of breast cancer.

Key Words: Breast neoplasms—Sentinel lymph node biopsy—Neoplasm recurrence—False negative sampling.

The histological status of the axillary lymph nodes is the most important prognostic factor in patients with breast cancer.¹ The sentinel lymph node biopsy (SLNB) has proved to be a reliable alternative to the traditional axillary lymph node dissection (ALND) with regard to predicting the histological status of the

remaining axillary lymph nodes in clinical T1/2 N0 breast cancer.^{2–6} The SLNB has the advantage of reduced postoperative morbidity compared with ALND.⁷ In case of a positive sentinel lymph node (SLN), a complementary ALND is recommended to maximize regional control and complete axillary staging.

Several validation studies of SLN biopsies followed by ALND in breast cancer patients have been published. All these studies report the risk of false-negative sampling, with rates varying from 0% to

Received March 18, 2004; accepted August 25, 2004.

Address correspondence and reprint requests to: Marjolein L. Smidt, MD; E-mail: marjoleinsmidt@yahoo.com

Published by Springer Science+Business Media, Inc. © 2005 The Society of Surgical Oncology, Inc.

22%.^{2,6,8-12} A meta-analysis of 13 studies including 912 patients reported a false-negative rate of 5.1%.¹³ Once the validation phase is completed, an unknown number of patients with undetected tumor-positive nodes at SLNB do not undergo an ALND. Undetected tumor-positive nodes of clinical importance are those that lead to axillary recurrence.¹⁴

Several questions arise considering axillary relapse. In the setting of a negative SLNB, it would be interesting to identify prognostic factors for the incidence of axillary relapse, especially regarding prevention. The clinical consequences for the patient are unclear, and the nature of subsequent therapy is still open for debate.

The aim of this study was to identify the extent of this problem in current practice. The clinical consequences for patients with recurrent axillary disease were clarified. Furthermore, a systemic review of the literature was performed to determine incidence, patient and tumor characteristics, and subsequent therapy.

METHODS

Between January 1998 and December 2003, 696 consecutive patients had an SLNB for clinical T1/2 N0 breast cancer in a regional teaching hospital. After a validation phase, in which 20 patients underwent SLNB with an ALND in the same procedure, patients with a tumor-free SLN did not undergo an ALND. In any case of tumor involvement of the SLN, an ALND was performed. The follow-up consisted of a physical examination every 3 months during the first 2 years and subsequently every 6 months. All data were collected in a prospective database. The median age of these patients was 57 years. The median tumor size was 16 mm. The primary tumor was Tis in 22 patients (3%), T1 in 390 patients (56%), and T2 in 243 patients (35%). The histological tumor type was invasive ductal cancer in 73% and invasive lobular cancer in 13% of the patients (Table 1).

Lymphatic Mapping and Operative Procedures

The SLN procedure was performed with 60 MBq of ^{99m}Tc nanocolloid as a radioactive tracer and 2 mL of blue dye (Bleu Patente V; Guerbet, Aulnay-sous-Bois, France) for lymphatic mapping. The SLN was identified and harvested during surgery guided by lymphoscintigraphy, the blue lymphatic vessels, and detection of radioactivity by the gamma probe.

TABLE 1. Patient and tumor characteristics of 696 SLNB patients

Variable	Data
Median age, y (range)	57 (20–95)
Tumor size, mm (range)	16 (0–65)
Primary tumor	
T0	16 (2%)
Tis	22 (3%)
T1	390 (56%)
T2	243 (35%)
T3	19 (3%)
T4	6 (1%)
Histological type	
IDC	506 (73%)
ILC	90 (13%)
Other	100 (14%)
Grade ^a	
1	100 (17%)
2	282 (47%)
3	217 (36%)

SLNB, sentinel lymph node biopsy; IDC, invasive ductal cancer; ILC, invasive lobular cancer.

^a Nottingham combined histological grade.

Pathologic Examination of the SLN

The SLN was bisected, after which both halves were embedded in paraffin. Each part was step-sectioned at 500- μ m intervals at three levels and stained with hematoxylin and eosin. Immunohistochemical staining was performed with Cam 5.2 (Becton Dickinson, San Jose, CA).

Review of the Literature

To determine the axillary relapse rate after a negative SLNB for breast cancer, a systematic review of the literature was performed. PubMed and the Cochrane library were searched with the use of the Medical Subject Heading terms “breast neoplasms” and “sentinel lymph node biopsy.” This pair was linked to the terms “neoplasm recurrence,” “treatment outcome,” and “diagnostic errors.” This search strategy resulted in 221 titles. Only 11 studies dealt with follow-up of a cohort of SLN-negative patients or a case report on axillary relapse after negative SLNB in breast cancer patients. Two other studies were found through links and references.

RESULTS

At least 1 SLN could be identified in 676 (97.1%) of 696 patients. The median number of harvested SLNs was 2 (range, 0–9). In 237 (35%) of the 676 patients, the SLN contained metastatic disease. In 86 patients, this concerned micrometastases. In 6 of these 86 pa-

TABLE 2. Patient and tumor characteristics of all patients in the literature with recurrent axillary disease

Study	Age (y)	Primary tumor and therapy						Axillary recurrence and therapy		
		Primary tumor	Type	Grade	Hormonal receptor	Primary surgery	Adjuvant therapy	Axillary recurrence (mo)	Systemic recurrence (mo)	Systemic therapy
Salmon ²¹	47	T1a	Medullary	2	ER ⁻ PR ⁻	BCT	RT	19	No	RT + CT
Blanchard ²²	NS	NS	NS	NS	NS	MST	CT	41	No	NS
Loza ²³	41	T1a	IDC	2	ER ⁺ PR ⁻	BCT	RT + HT	28	No	RT + CT
Chung ²⁴	45	T1c	NS	NS	NS	NS	NS	4	No	NS
	51	T1c	NS	NS	NS	NS	NS	11	Yes	CT
	48	T1a	NS	NS	NS	BCT	CT	40	Yes	NS
Roumen ²⁵	46	T1b	IDC	2	NS	MST	No	14	Yes	RT + HT + ovariectomy
Estourgie ²⁶	44	T1c	IDC	2	NS	BCT	RT	21	No	RT + HT
Yen ²⁷	57	T1c	ILC	NA	ER ⁺ PR ⁻	MST	CT	24	No	CT
Smidt	75	T2	IDC	3	ER ⁺ PR ⁻	MST	HT	4	No	HT
	35	T1c	IDC	3	ER ⁺ PR ⁻	MST	No	27	No	Ovariectomy + HT

ER, estrogen receptor; PR, progesterone receptor; BCT, breast-conserving therapy; RT, radiotherapy; CT, chemotherapy; NS, not stated; MST, mastectomy; IDC, invasive ductal cancer; HT, hormonal therapy; ILC, invasive lobular cancer; NA, not applicable.

tients with micrometastatic disease, an ALND was omitted.

After a median follow-up of 26 months (range, 1–90 months), an axillary recurrence was detected in 2 patients out of 439 with a negative SLNB. The incidence of axillary relapse after tumor-negative SLNB was therefore .46%.

In one patient, physical examination revealed axillary lymph node recurrence 4 months after the SLNB. The ALND specimen contained two tumorous lymph nodes. The patient received an aromatase inhibitor. In a second patient, axillary relapse was detected by routine physical examination 27 months after the SLNB. She underwent an ALND and ovariectomy and received tamoxifen. The SLNs of these two patients were re-examined but did not reveal any metastasis. Patient and tumor characteristics concerning these two patients are listed in Table 2.

In a third patient with a .2-mm micrometastasis in the SLN, ALND was omitted. Axillary recurrence was resected 22 months after the SLNB. Tumor was found in the axillary fat and was not related to any preexisting lymph node structure. No technical problems were met during the ALND.

PubMed and the Cochrane library search resulted in 10 studies concerning the follow-up of a cohort of SLN-negative patients with breast cancer and in 3 case reports on axillary recurrence. The results of a total of 3184 patients (including the present series) with a median follow-up of 25 months (range, 16–46 months) were pooled. In eight patients, an axillary relapse was diagnosed. This resulted in an axillary recurrence rate of .25% (Table 3). Axillary relapse after negative SLNB of all 11 published cases oc-

curred after a median of 21 months. The data concerning these patients are listed in Table 2.

DISCUSSION

Axillary recurrence after a negative SLNB in breast cancer patients is, at .46%, rare in this group. The mean axillary relapse rate in comparable studies is equally low at .25%. These rates are far lower than would be expected if compared with the false-negative rates of the SLNB in the validation phase; a meta-analysis reported a false-negative rate of 5.1%.¹³

These results are supported by follow-up studies of clinically node-negative breast cancer patients in whom surgical axillary staging was omitted. A population-based study showed that 34% of the axillary lymph nodes of clinical stage I breast cancer patients contain metastases.¹⁵ In contrast with these findings, Greco et al.¹⁶ and Fisher et al.¹⁷ demonstrated that only 6.7% to 17.8% of the patients without ALND developed axillary recurrence after a follow-up period of 5 to 10 years. Axillary relapses were detected after a median period of 14.7 to 31 months. Hence, substantially fewer clinical recurrences were observed than would be expected on the basis of data reported in literature.

Several factors can explain the difference between the false-negative rate of the SLNB in the validation phase and the axillary relapse rates, as well as the lower than expected axillary recurrence rate after omitting ALND. According to the studies by Greco et al.¹⁶ and Fisher et al.,¹⁷ axillary relapse is to be expected, if it occurs, after a median of 14.7 to 31

TABLE 3. Incidence of axillary recurrence after negative sentinel lymph node biopsy in breast cancer patients

Study	Year of publication	No. patients	Study period	Follow-up (mo)	Axillary recurrence (% incidence)
Reitsamer ²⁸	2003	116	5/99–2/01	Mean 22 mo	0
Badgwell ²⁹	2003	159	4/98–10/99	Median 32 mo	0
Estourgie ²⁶	2003	353	1/97–11/01	Median 16 mo	1 at 21 mo (.3%)
Veronesi ⁷	2003	167	3/98–12/99	Median 46 mo	0
Schrenk ¹⁹	2001	83	6/96–9/00	Median 22 mo	0
Chung ²⁴	2002	206	1/98–12/01	Median 26 mo	3 at 4/11/31 mo (1.5%)
Giuliano ³⁰	2000	67	10/95–7/97	Median 39 mo	0
Roumen ²⁵	2001	100	12/97–6/00	Median 24 mo	1 at 14 mo (1%)
Dessureault ³¹	2000	809	4/94–4/99	Mean 20 mo	0
Blanchard ²²	2003	685	10/97–8/01	Median 29 mo	1 at 41 mo (.1%)
Present series	2004	439	5/97–12/03	Median 26 mo	2 at 4/27 mo (.5%)

months at a follow-up of 63 to 126 months. The follow-up period of the studies in the series in Table 3 amounted to a median length of only 16 to 46 months and might therefore be too short to lead to comparable results.

In contrast to earlier series, most patients currently receive adjuvant systemic treatment because of tumor and patient characteristics. Adjuvant chemotherapy has proved to destroy metastases in tumor-bearing axillary nodes and therefore can be expected to decrease axillary relapse rates.¹⁸

Another cause for the low relapse rate might be the decreasing incidence of failure to identify the SLN after the learning phase. A study with a longer validation phase showed an increase in identifying the SLN from 67% with 18 patients to 96% with 177 patients.¹⁹ The false-negative rates from the published studies always represent the validation phase. The studies reporting on the follow-up of SLN-negative patients have always passed this phase.

The young age of the patients with axillary recurrence is remarkable; almost all patients in literature are younger (median, 46 years) than the median age in this series (median, 57 years). This corresponds with the median age of 48 years of patients with axillary relapse after ALND.²⁰

The clinical consequences for patients with axillary relapse after a negative SLNB are yet unclear, but similarities to patients with axillary recurrence after ALND are hard to overlook. In both groups, approximately 30% of the patients with axillary recurrence present with simultaneous locoregional or systemic failure. Approximately 50% of the patients with axillary relapse after ALND develop distant metastatic disease. This suggests an ominous prognosis for patients with axillary relapse after a negative SLNB.²⁰

It is tempting to consider axillary relapse as a presentation of formal locoregional recurrence. A

patient with an axillary recurrence should therefore receive therapy for locoregional failure.

In conclusion, axillary recurrences after negative SLNB occur, but at a much lower rate than would be expected on the basis of historical figures and false-negative SLN findings. Considering the similarities to axillary relapse, subsequent therapy should be aimed at locoregional and systemic control.

REFERENCES

1. Fisher B, Bauer M, Wickerham DL, et al. Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. An NSABP update. *Cancer* 1983;52:1551–7.
2. Giuliano AE, Jones RC, Brennan M, Statman R. Sentinel lymphadenectomy in breast cancer. *J Clin Oncol* 1997;15:2345–50.
3. Giuliano AE, Dale PS, Turner RR, et al. Improved axillary staging of breast cancer with sentinel lymphadenectomy. *Ann Surg* 1995;222:394–9.
4. Turner RR, Ollila DW, Krasne DL, Giuliano AE. Histopathologic validation of the sentinel lymph node hypothesis for breast carcinoma. *Ann Surg* 1997;226:271–6.
5. Veronesi U. The sentinel node and breast cancer. *Br J Surg* 1999;86:1–2.
6. Veronesi U, Paganelli G, Galimberti V, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet* 1997;349:1864–7.
7. 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* 2003;349:546–53.
8. O’Hea BJ, Hill AD, El Shirbiny AM, et al. Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan-Kettering Cancer Center. *J Am Coll Surg* 1998;186:423–7.
9. Nano MT, Kollias J, Farshid G, Gill PG, Bochner M. Clinical impact of false-negative sentinel node biopsy in primary breast cancer. *Br J Surg* 2002;89:1430–4.
10. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer—a multicenter validation study. *N Engl J Med* 1998;339:941–6.
11. Chua B, Olivotto IA, Donald JC, et al. Outcomes of sentinel node biopsy for breast cancer in British Columbia, 1996 to 2001. *Am J Surg* 2003;185:118–26.

12. Bergkvist L, Frisell J, Liljegren G, et al. Multicentre study of detection and false-negative rates in sentinel node biopsy for breast cancer. *Br J Surg* 2001;88:1644–8.
13. Miltenburg DM, Miller C, Karamlou TB, Brunnicardi FC. Meta-analysis of sentinel lymph node biopsy in breast cancer. *J Surg Res* 1999;84:138–42.
14. Estourgie SH, Nieweg OE, Rutgers EJ, Kroon BB. What is a false-negative result for sentinel node procedures in breast cancer? *J Surg Oncol* 2003;82:141–2.
15. Voogd AC, Coebergh JW, Repelaer-van-Driel OJ, et al. The risk of nodal metastases in breast cancer patients with clinically negative lymph nodes: a population-based analysis. *Breast Cancer Res Treat* 2000;62:63–9.
16. Greco M, Agresti R, Cascinelli N, et al. Breast cancer patients treated without axillary surgery: clinical implications and biologic analysis. *Ann Surg* 2000;232:1–7.
17. Fisher B, Redmond C, Fisher ER, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. *N Engl J Med* 1985;312:674–81.
18. Rouzier R, Extra JM, Klijanienko J, et al. Incidence and prognostic significance of complete axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastatic lymph nodes. *J Clin Oncol* 2002;20:5–10.
19. Schrenk P, Hatzl-Griesenhofer M, Shamiyeh A, Waynad W. Follow-up of sentinel node negative breast cancer patients without axillary lymph node dissection. *J Surg Oncol* 2001;77:165–70.
20. Newman LA, Hunt KK, Buchholz T, et al. Presentation, management and outcome of axillary recurrence from breast cancer. *Am J Surg* 2000;180:252–6.
21. Salmon RJ, Bouillet TH, Lewis JS, Clough KB. Recurrence in the axilla after sentinel lymph node biopsy for breast cancer. *Eur J Surg Oncol* 2002;28:199.
22. Blanchard DK, Donohue JH, Reynolds C, Grant CS. Relapse and morbidity in patients undergoing sentinel lymph node biopsy alone or with axillary dissection for breast cancer. *Arch Surg* 2003;138:482–7.
23. Loza J, Colo F, Nadal J, Viniegra M, Chacon R. Axillary recurrence after sentinel node biopsy for operable breast cancer. *Eur J Surg Oncol* 2002;28:897–8.
24. Chung MA, Steinhoff MM, Cady B. Clinical axillary recurrence in breast cancer patients after a negative sentinel node biopsy. *Am J Surg* 2002;184:310–4.
25. Roumen RM, Kuijt GP, Liem IH, van Beek MW. Treatment of 100 patients with sentinel node-negative breast cancer without further axillary dissection. *Br J Surg* 2001;88:1639–43.
26. Estourgie SH, Nieweg OE, Valdes-Olmos RA, et al. Eight false negative sentinel node procedures in breast cancer: what went wrong? *Eur J Surg Oncol* 2003;29:336–40.
27. Yen TW, Mann GN, Lawton TJ, Livingston RB, Anderson BO. An axillary recurrence of breast cancer following a negative sentinel lymph node biopsy. *Breast J* 2003;9:234–6.
28. Reitsamer R, Peintinger F, Prokop E, et al. Sentinel lymph node biopsy alone without axillary lymph node dissection—follow up of sentinel lymph node negative breast cancer patients. *Eur J Surg Oncol* 2003;29:221–3.
29. Badgwell BD, Povoski SP, Abdessalam SF, et al. Patterns of recurrence after sentinel lymph node biopsy for breast cancer. *Ann Surg Oncol* 2003;10:376–80.
30. Giuliano AE, Haigh PI, Brennan MB, et al. Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer. *J Clin Oncol* 2000;18:2553–9.
31. Dessureault S, Dupont E, Shons A, et al. Early results of breast cancer lymphatic mapping from the H. Lee Moffit Cancer Center: no axillary recurrences in breast cancer patients after a negative sentinel lymph node biopsy. *Breast Cancer Res Treat* 2000;64:26.