Low risk of recurrence in breast cancer with negative sentinel node

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ABSTRACT

INTRODUCTION: The sentinel lymph node (SLN) procedure has emerged as a safe staging method with a low morbidity. The objective of the present study was to examine the recurrence rates including especially the axillary recurrence rate in SLN-negative patients after a long follow-up period.

MATERIAL AND METHODS: A total of 344 breast cancer patients were referred to SLN biopsy at our department from January 2000 to May 2005. Lymphoscintigraphy with ^{99m}Tc-nanocolloid was followed by same-day radioprobe-guided surgery. Among the 344 patients, 181 were SLN-negative. The group of SLN-negative patients was followed with regard to recurrence in general and axillary recurrence in particular by reviewing their respective medical files from control visits.

RESULTS: The identification rate (IR) was 99% (340/344). Extra-axillary SLNs were detected in seven patients (4%). One patient had an axillary recurrence 39 months after the primary operation, corresponding to an axillary recurrence rate of 0.6% after a median follow-up of 60 months (range 7-93).

CONCLUSION: With a high IR and an axillary recurrence rate of 0.6% after five years of follow-up, our data suggest that the SLN procedure is a valid and accurate method for the staging of breast cancer patients.

The axillary lymph node status is the most important prognostic factor in patients with invasive breast cancer [1]. Axillary lymph node dissection (ALND) has routinely been performed in order to determine whether cancer has spread to the regional lymph nodes or not. However, ALND (e.g. lymphoedema) is associated with significant morbidity [2].

Furthermore, with the growing use of mammography screening, a higher percentage of women presents with early stage breast cancer and, accordingly, more often with cancer-negative axillary lymph nodes. Thus, it has become essential to develop an alternative staging method that is associated with less morbidity.

In 1993, Krag et al issued the first publication of sentinel lymph node (SLN) biopsy in breast cancer patients. In a pilot study, they concluded that the SLN appeared to correctly predict the status of the remaining axilla [3]. Since then, the SLN method has gradually become the standard for staging of breast cancer patients. The main advantage lies in the reduction in the incidence of side effects with this method [4]; albeit we lack long-term clinical trials comparing survival after SLN biopsy with survival after ALND.

Extensive literature is available on the accuracy of the SLN procedure, and, accordingly, several reviews [5-7] have been published. The SLN procedure varies widely and, likewise, wide variation is found in the accuracy of the method (i.e., identification rates, false negative rates).

Follow-up studies on recurrence and survival after SLN biopsy show more consistent results with relatively low recurrence rates after long-term follow-up periods (two-three years) [8-12].

The aim of the present study was to describe the accuracy of the SLN procedure in SLN-negative patients by monitoring recurrence in general and the axillary recurrence rate (ARR) in particular after five years of follow-up.

MATERIAL AND METHODS

Patients

From January 2000 to May 2005, 344 consecutive patients were found suitable for the SLN biopsy procedure at Odense University Hospital. All patients except seven fulfilled the triple diagnostic criteria of breast cancer: positive palpation, positive mammography and positive histopathology (fine needle aspiration biopsy or needle core biopsy).

Seven patients with a non-palpable tumour had a positive ultrasound examination. Moreover, all patients presented with a unifocal primary tumour in clinical stage I (T1, N0, M0) or stage IIA (T2, N0, M0) according to the Cancer Staging Manual [13]. A Standards for Reporting of Diagnostic Accuracy flow diagram [14] of the study population is shown in **Figure 1**.

Among the 344 patients, 201 were SLN-negative. For various reasons (Figure 1), 20 of these patients either underwent ALND (n = 12) or were lost to follow-up

ORIGINAL ARTICLE

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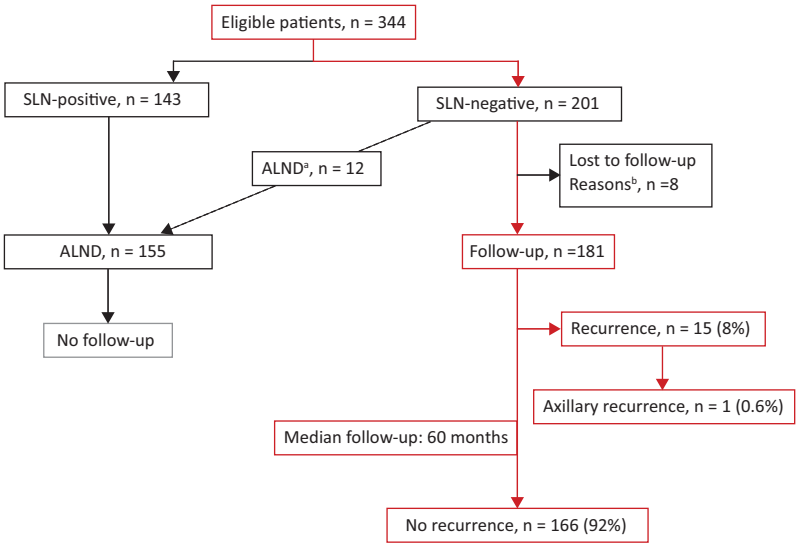
FIGURE 1

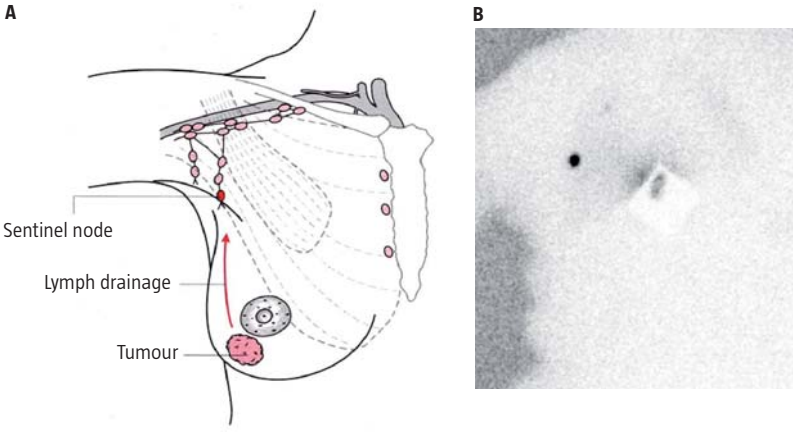
A Standards for Reporting of Diagnostic Accuracy diagram of eligible patients.



a) Reasons for performing ALND in 12 SLN-negative cases were: SLN not identified (n = 4), primary tumour histology benign, later histology malignant (n = 2), other lymph nodes clinically suspicious for malignancy (n = 2), hot spot in muscle (n = 1), number of hot spots in axilla > 9 (n = 1), tumour with multifocality, re-operation with ALND (n = 1), ALND due to tumour location close to the axilla (n = 1).
b) The reason for loss to of follow-up in eight patients was that they had moved to other areas and were being followed clinically at other hospitals.
ALND = axillary lymph node dissection; SLN = sentinel lymph node.

FIGURE 2

The sentinel lymph node biopsy procedure with the lymphatic network of the breast. **A**. The model illustrates the principle of the sentinel node being the first lymph node to receive lymph from the tumour area. **B**. An example of a lymphoscintigram. The scintigram shows the injection site in the right breast (covered by a small lead sheet) and a sentinel lymph node in the right axilla (anterior oblique projection with a flood source positioned behind the patient). Sparse activity is seen in a probably secondary lymph node cranially in the right axilla.



(n = 8). The remaining group comprising 181 SLN-negative patients was reviewed in the present analysis by using initial prospective recordings with retrospective follow-up data from succeeding clinical control visits. SLN-positive patients were not included in the study.

Sentinel lymph node biopsy

A same-day protocol was used in all patients. The protocol included radioisotope injection and scintigraphic imaging preoperatively on the day of surgery. Peritumoural and intradermal injections were made, the latter with periareolar localization in the quadrant of the tumour position. The radioisotope used was ^{99m}Tc-HSA (nanocolloid). A total dose of 18-20 MBq was given per procedure. Injection was followed by immediate dynamic gamma camera imaging (20 min) in relevant anterior oblique projections – an example is given in **Figure 2**. Two series (30 min and 2 h after injection) of static images were taken in three projections (anterior, lateral and anterior oblique). For clarity, the body contour was identified by means of a flood source positioned behind the patient and suitable landmarks were indicated. The scintigraphic findings were documented by images, reported in writing, and, if necessary, given orally.

Surgery

Surgery was performed in general anaesthesia and was typically completed within 3-4 hours after the injection of the radiopharmaceutical had been administered. The identification of hot nodes was guided by a handheld gamma probe, and a nuclear medicine physician was present when necessary during surgery.

A hot spot to background count ratio of > 10:1 defined a SLN to be removed. Patients with cancer-negative SLN biopsy had no further axillary dissection performed.

Histopathology

The SLNs were bisected. During the first four and a half years of the study period, frozen sections were cut at three levels for haematoxylin-eosin (HE) staining only. During the last year of the period, frozen sections were cut at three levels at 250-micrometre intervals for both HE and rapid immunohistochemistry (IHC) with a cytokratin antibody.

Permanent sections were also cut at 250 micrometre intervals for both HE and IHC (during the whole study period). All sections were scrutinized and a diagnosis of metastasis was made if either isolated tumour cells, micrometastases (0.2-2.0 mm) or macro-metastases were found. Lymph nodes from ALNDs were cut at two levels for HE only.

Treatment and follow-up

Mastectomy or breast-conserving therapy was performed according to existing recommendations. Radiotherapy was given against the residual breast following lumpectomy (48 Gy) and against regional nodes in node-positive disease (48 Gy). In all cases, 2 Gy were given in five fractions per week. Endocrine treatment and adju-

vant chemotherapy were administered according to current national guidelines.

Patients were followed at the Department of Oncology every six months for five years. At follow-up visits, all patients were examined clinically with regard to the breasts and axillae. When necessary, supplementary paraclinical examinations were performed (e.g., ultrasonography, X-ray, scintigraphy). A routine clinical mammography was performed every eighteen months or every second year.

RESULTS

Descriptive statistics

There were 180 female (99%) and one male patient (1%). Their median age was 58 years (range: 32-77). The median tumour size was 13 millimetres in the largest diameter (range: 1-48). In 96% of the patients (171/180), the tumour was palpable. See **Table 1** for further descriptive details.

Identification rate

The SLN could be identified in all 181 SLN-negative patients. However, in the total study population (including the SLN-positive patients), the SLN could be identified in 340 of 344 cases, revealing an identification rate (IR) of 99%. The median number of SLNs removed was three (range: one to eight).

Extra-axillary sentinel lymph nodes

Extra-axillary SLNs were detected by scintigraphy in seven patients (4%). In six of the patients, the extra-axillary location was in the internal mammary chain, and in one patient the SLN had a periclavicular location. The extraaxillary SLNs were not surgically removed by routine.

Follow-up

After a median follow-up period of 60 months (range: 7-93), we found an axillary recurrence in one patient 39 months after the primary operation, corresponding to an ARR of 0.6%. However, there was doubt whether the recurrence was located in a lymph node in the axilla or locally in the scar of the operated breast close to the axilla.

This patient was diagnosed with bone metastases at the same time and, therefore, no further operation of the axillary/local recurrence was performed.

Four patients (2%) had a local recurrence in the operated breast. Distant recurrence was observed in ten patients, which yielded a total recurrence rate (TRR) of 8% (15/181). Locations for distant recurrences are given in Table 1. Breast cancer-related death was observed in six SLN-negative patients, yielding a mortality rate (MR) of 3% (6/181) after five years of follow-up.

TABLE 1

Descriptive statistics and results of sentinel lymph node (SLN)-negative patients (n = 181).

Median age, years (range)	58 (32-77)
Gender, no. of patients (%)	
Female	180 (99)
Male	1 (1)
Median tumour size, mm (range)	13 (1-48)
Breast, no. of patients (%)	
Right	87 (48)
Left	94 (52)
Location in breast, no. of patients (%)	
Upper lateral	90 (50)
Lower lateral	16 (8)
Upper medial	50 (28)
Lower medial	20 (11)
Central	5 (3)
Type of tumour, no. of patients (%)	
Ductal carcinomas	145 (80)
Lobular carcinomas	21 (12)
Ductal carcinoma in situ	4 (2)
Other types	11 (6)
Median no. of SLNs removed (range)	3 (1-8)
Identification rate, % (n/N)	99 (340/344)
Axillary recurrence rate, % (n/N)	0.6 (1/181)
Total recurrence rate, % (n/N)	8 (15/181)
Mortality rate, % (n/N)	3 (6/181)
Locations for recurrences, no. of patients	
Ipsilateral axilla	1
Locally in breast	4
Bone	4
Liver	1
Lung	3
Contralateral breast	2

DISCUSSION

Follow-up

With a high IR of 99% and a low ARR of 0.6% after a median follow-up of 60 months, our results support the largely unanimous conclusion that SLN biopsy is a safe and reliable procedure for the staging of breast cancer patients [5-12]. Although we used same-day injection of radioisotope with pre-operative lymphoscintigraphy only (and no blue dye), our results do at least equal the results of comparable recent observational studies [5-12].

To date, a reasonable number of observational studies (**Table 2**) have provided follow-up data on SLN-negative breast cancer patients staged by the SLN procedure only [8-12]. In these studies, rather high IRs ranging from 92% to 100% have been reported with the most commonly used technique being the combination of radioisotope and blue dye with pre-operative lymphoscintigraphy. Despite follow-up periods varying from 16 to 47 months, consistently low ARRs ranging from 0% to

TABLE 2

Axillary recurrence in sentinel lymph node negative patients – results from other studies. Not all studies could be included in the reference list. A detailed reference list is available by request to the corresponding author.

Reference, first author, year	Patients, n[a]	Median follow-up, months	Technique used	Axillary recurrences, n	Axillary recurrence rate, %	Total recurrence rate, %	Mortality rate,%
Giuliano, 2000	67	39	B, L	0	0	1.5	1.5
Roumen, 2001	100	24	I + B, L	1	1.0	2.0	3.0
Schrenk, 2001	83	22	I + B, L	0	0	0	0
Veronesi, 2001	285	<24	I, L	0	0	0.7	0
Chung, 2002	208	26	I + B, L	3	1.4	2.9	n.a.
Hansen, 2002	238	39	B, I + B, L	0	0	1.7	1.3
Shivers, 2002	?	16	B, I + B	0	0	n.a.	n.a.
Badgwell, 2003	159	32	I + B	0	0	3.1	n.a.
Blanchard, 2003	685	29	I + B, L	1	0.1	n.a.	0.9
Ponzone, 2003	155	15	I, L	0	0	0	n.a.
Veronesi, 2003	167	46	I, L	0	0	n.a.	n.a.
Langer, 2004	122	42	I + B, L	1	0.8	3.3	n.a.
Naik, 2004	2,340	31	I + B, L	3	0.1	n.a.	n.a.
Reitsamer, 2004	200	36	I + B, L	0	0	n.a.	n.a.
Torrenga, 2004	104	57	I + B, L	1	1.0	3.8	1.9
Van der Vegt, 2004	106	35	I + B, L	1	1.0	n.a.	n.a.
Van Wessem, 2004	82	24	I + B, L	1	1.0	6.1	n.a.
Carcoforo, 2005	566	32	I + B, L	3	0.5	n.a.	n.a.
Jeruss, 2005	592	27	I, L	1	0.2	n.a.	n.a.
Kokke, 2005	113	38	I + B, L	2	1.8	1.8	n.a.
Smidt, 2005	439	26	I + B, L	2	0.5	n.a.	n.a.
Snoj, 2005	50	32	I + B, L	1	2.0	0	0
Zavagno, 2005	479	36	I, L	0	0	n.a.	n.a.
Haid, 2006	180	47	I + B, L	1	0.6	3.9	3.3
Rosing, 2006	89	16	I + B	1	1.0	1.0	0
Veronesi, 2006	167	79	I, L	1	0.6	n.a.	n.a.
Palesty, 2006	335	33	I + B, L	2	0.6	4.5	n.a.
De Kanter, 2006	149	65	I + B, L	4	2.7	7.4	n.a.
Van Rijk, 2007	299	22	I + B, L	1	0.3	n.a.	n.a.
Van der Ploeg, 2008	748	46	I + B, L	2	0.3	n.a	n.a.
Bergkvist, 2008	2,246	37	I + B, L	13	0.6	n.a.	n.a.
Kim, 2008	293	40	I, L	3	1.0	n.a	n.a.
Christiansen, 2008	4,061	21	I/I + B, (L)	21	0.5	4.8	n.a.
Poletti, 2008	804	39	I, L	4	0.5	1.9	3.4
Heuts. 2008	344	43	–	3	0.9	n.a.	n.a.
Kiluk, 2009	1,530	59	I + B	4	0.3	6	10
Sanli, 2009	121	44	I + B, L	3	2.5	6.6	n.a.
Imasato, 2010	261	39	I + B, L	2	0.8	3.1	0.6
Hildebrandt, present study	181	60	I, L	1	0.6	8.3	3.3

B = blue dye; I = isotope; L = lymphoscintigraphy; n.a. = not available.
a) Number of patients staged by sentinel lymph node biopsy only.

2% have been reported. One, at least partial, reason for the low ARRs may be the use of five years' endocrine treatment in high-risk patients. Thus, studies with follow-up periods exceeding five years seem to be warranted.

In the present study, we found a TRR of 8% and an MR of 3% after five years of follow-up. In other studies, TRRs range from 0% to 7% and MRs from 0% to 3%. Both measures have an expected increasing tendency with longer follow-up periods. Furthermore, most observational follow-up studies conclude that the SLN biopsy is a safe and reliable procedure for staging of breast cancer patients [15].

In a randomized controlled study comparing breast cancer patients undergoing the SLN biopsy procedure (n = 257) or the ALND procedure (n = 259), Veronesi et al found equally low recurrence rates (9.8 versus 11.5 recurrences per 1,000 women per year) and equally high five-year survival rates (98.4% versus 96.4%) with no statistically significant differences between the two

groups after a median follow-up period of 79 months [11]. They concluded that: "the SLN procedure can avoid ALND in patients with negative SLNs and that the removal of normal axillary lymph nodes in patients with breast cancer is no longer a justifiable procedure" – a statement that our data seem to fully support.

False negative rates

Extensive literature has been published on the accuracy of the SLN biopsy procedure [5-7]. The false negative rate is considered the most important measure of success for the procedure. However, large reviews display sizeable variation, i.e. IRs ranging from 40% to 100% and FNRs ranging from 0% to 29% [5-7]. A major reason for these considerable fluctuations may be diversity in the methods and techniques applied in the dozens of studies published on this subject [5-7]. A long list of factors may influence the accuracy of the procedure, e.g., the injection technique, the use of radiotracer, blue dye or a combination of both, the type and dose of radiotracer, the injection sites, time to operation after injection and the procedure for preoperative lymphoscintigraphy.

Unfortunately, no clear-cut comparative trials have been performed comparing one group of patients mapped by a single technique to another group mapped with a different technique.

Based on reviews of observational studies, there seem to be agreement that the use of a combined technique (radiotracer and blue dye) with a combination of injection sites (intra- or subdermal and interstitial) yields higher success rates [5-7].

Axillary recurrence rates

Despite the variation in FNRs, observational studies find rather consistently low ARRs as described above. Previously, in a learning series, we measured a FNR of 5.3% in 39 patients, and we therefore expected a higher ARR than the 0.6% actually observed during the following routine – a phenomenon which was also seen in other studies [9, 11, 16-18]. The repeated disparity between the FNRs and the ARRs may be explained by factors such as the possible existence of a learning curve, relatively short follow-up periods, a beneficial effect of adjuvant therapy and radiation, and the natural history of cancer including the possibility that occult metastatic foci in lymph nodes may never become clinically overt (i.e. the stem-cell hypothesis). Against the hypothesis of too short follow-up periods speak findings from earlier trials showing that most regional recurrences occur within the first two years after initial treatment [1]. The other factors mentioned above may mutually contribute to the disparity between the FNRs and the ARRs as seen in a number of observational studies [9, 11, 16-18].

With this in mind, and with the supporting results from the aforementioned long-term, comparative and randomized clinical trial [11], it seems safe to conclude that the SLN procedure alone is the method of choice for the staging of SLN-negative breast cancer patients. An upcoming topic is the issue of how to avoid ALND in SLN-positive patients with only sparse involvement of axillary lymph nodes, i.e. with only micrometastases in the SLN [19, 20].

Limitations

The present study was intended to serve as a prospective quality assessment of the SLN procedure in the daily routine with retrospective follow-up. A limited set of data was collected allowing no extensive characterization of the study population. The study population was defined by a positive triple test and referral to preoperative lymphoscintigraphy. This left no room for analysis of the group of patients who did not receive the SLN procedure. In general, the latter was characterized by either non-palpable tumour, large tumour size (> 5 cm), multifocality, referral (due to local capacity restrictions) to operation at other hospitals or "old age". Follow-up of the study patients was made retrospectively by means of their clinical files and without a comparable control group. In line with other studies, we did not collect follow-up data from the SLN-positive patients. Because of their differences in stage and prognosis, they were not considered comparable.

CONCLUSION

Our results suggest that the SLN biopsy method is a safe and reliable way of staging breast cancer patients. In line with the literature, our findings indicate that the SLN procedure alone is the procedure of choice in SLN-negative breast cancer patients.

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