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## Is the sentinel lymph node pathology protocol in breast cancer patients associated with the risk of regional recurrence?

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### Abstract

**Background:** Internationally, there is no consensus on the pathology protocol to be used to examine the sentinel lymph node (SN) in breast cancer patients. Previously, we reported that ultra-staging led to more axillary lymph node dissections (ALND). The question was, whether ultra-staging is effective in reducing the risk of regional relapse.

**Methods:** From January 2002 to July 2003, 541 patients from 4 hospitals were prospectively registered when they underwent a SN biopsy. In hospitals **A**, **B**, and **C**, 3 levels of the SN were examined pathologically, whereas in hospital **D** at least 7 additional levels were examined. Patients with a positive SN, including isolated tumor cells, underwent an ALND. This analysis focuses on the 341 patients with a negative SN. Primary endpoint was 5-year regional recurrence rate.

**Results:** In hospital **D** 34% of the patients had a negative SN as compared to 71% in hospitals **A**, **B**, and **C** combined ( $p < 0.001$ ). At 5 years follow-up, 9 (2.6%) patients had developed a regional lymph node relapse. In hospital **D** none of the patients had a regional recurrence, as compared to 9 (2.9%) cases of recurrence in hospitals **A**, **B**, and **C**.

**Conclusion:** The less intensified SN pathology protocol appeared to be associated with a slightly increased risk of regional recurrence. The absolute risk was still less than 3%, and does not seem to justify the intensified SN pathology protocol of hospital **D**.

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**Keywords:** Breast cancer; Sentinel lymph node; Pathology protocol; Local recurrence

### Introduction

The axillary lymph node status is one of the most important prognostic factors in breast cancer.<sup>1</sup> Nowadays, most patients do not have nodal involvement due to the

introduction of population-based breast cancer screening. With the risk of shoulder dysfunction and lymph edema of the arm, an ALND for axillary staging should be prevented whenever possible.<sup>2</sup>

Therefore, the sentinel lymph node (SN) procedure was introduced during the late 1990s.<sup>3</sup> Based on figures from the pre-SN era, it was assumed that a completion ALND could be avoided in approximately 60% of patients with operable breast cancer by carrying out a SN biopsy.<sup>4</sup>

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It is shown that in patients with a negative SN the risk of a positive non-SN varies from only 2%–9%. For instance, in the NSABP B-32 study the SN biopsy false-negative rate was 9.8%.<sup>5</sup> This seems to be an acceptable rate, if missed, especially when one considers that an increasing number of these patients are treated with adjuvant systemic therapy, reducing the risk that these undetected non-SN metastases will ever become clinically apparent.

Recently, the results from the ACOSOG Z0011 were reported, randomizing patients with 1 or 2 H&E-positive SN to observation or ALND.<sup>3</sup> Five-year regional recurrence rate was 0.9% for SN only compared to 0.5% for ALND ( $p = 0.11$ ). Adjuvant systemic therapy was used in the majority of patients (97%). In the IBCSG Trial 23-01, 931 patients were randomized between ALND and no ALND when patients had minimal SN involvement.<sup>6</sup> Minimal involvement was defined as metastases of  $\leq 2.0$  mm in size, including presence of isolated tumor cells. After 5 years follow-up less than 1% of patients had an axillary recurrence with no significant difference between both treated arms. Again of note, 92% of patients received breast conserving surgery with adjuvant radiotherapy, and 96% of patients received systemic therapy.

Internationally, it is recommended to examine the SN with hematoxylin-eosin (H&E) at, at least, 3 levels of the paraffin block, with immunohistochemistry (IHC) to be used in case of doubt. In the Netherlands, these minimal recommendations actually led to different local protocols. In some hospitals more than the minimally required number of levels is routinely investigated. In the eastern part of the Netherlands, 3 large teaching hospitals and 1 university hospital registered all their SN procedures prospectively during 18 months in the years 2002 and 2003. Based on this registry, we reported earlier that a very intensive pathology protocol in 1 hospital, led to a high detection frequency of isolated tumor cells in the SN. At the time, a completion ALND was recommended for all these patients. As a consequence more than twice as many patients underwent a completion ALND in the hospital with the intensified pathology protocol as compared with the hospitals who used the standard intensive pathology protocol (66% versus 29%;  $p < 0.0001$ ).<sup>7</sup>

In this present study we report the follow-up data of patients in these 4 hospitals who had a negative SN, and therefore did not undergo an additional ALND.

The obvious question was, whether ultra-staging, and thus more patients needing to undergo an additional ALND, is an effective way of reducing the risk of relapse.

## Methods

During eighteen months in the years 2002 and 2003 (January 2002–June 2003), consecutive patients from 4 hospitals (**A**, **B**, **C**, and **D**) were prospectively registered when they underwent a SN biopsy because of a cT1/T2N0Mx breast tumor. Patients were excluded from a SN

biopsy when there was presence of multifocality of the primary breast tumor, radiation therapy of the breast or axilla in the past, when patients had received neo-adjuvant systemic therapy, or when the SN was not detectable. The ethical committee approved the investigational protocol.

The prospectively collected data included the lymph node status with number of nodes examined, number of positive nodes, size of metastases, classification according to the tumor node metastasis (TNM) categories defined in the 6th edition of the TNM Classification of Malignant Tumors,<sup>8</sup> and the detection method (H&E/IHC). These items were separately registered for SNs and non-SNs. Also primary tumor characteristics (localization, tumor size, histology, histological grade, lymph and/or blood vessel invasion, hormone receptor status), patient characteristics (age), information on the surgical procedure (SN biopsy with or without ALND, lumpectomy or mastectomy, and various combinations), and information on adjuvant therapy (systemic and/or radiotherapy) were collected.

The surgical procedure was, in all 4 hospitals, in accordance to the Dutch guideline for treatment of breast cancer.<sup>9</sup> That is, SN localization was performed using the combined technique of blue dye and radioisotope in all patients. In the presence of isolated tumor cells, micro-, or macro-metastases in the SN, a completion ALND was recommended.

The Dutch guideline for treatment of breast cancer describes only the minimal criteria concerning the SN pathology protocol. It is advised to examine the SN with H&E at, at least, 3 levels of the paraffin block with IHC to be used in case of doubt. As a result, in hospitals **A**, **B**, and **C**, 3 levels of the SN were pathologically examined, whereas in hospital **D**, at least 7 additional levels were examined (at least 10 levels in total). In the absence of apparent metastases with H&E examination, IHC examination was performed in all 4 hospitals.

According to the international TNM-classification 2002, isolated tumor cells, micro-metastases, and macro-metastases were classified as follows: isolated tumor cells [pN0(i+)] are defined as solitary tumor cells or tumor cell clusters with a size of 0.2 mm or less. Micro-metastases [pN1mi] are more than 0.2 mm and maximally 2.0 mm in size. Macro-metastases are  $> 2.0$  mm in size. For the SN findings, 'sn' was added between brackets [pN(sn)].

This present analysis focuses on the SN negative patients in hospitals **A**, **B**, **C**, and **D**. These SN negative patients did not undergo a completion ALND.

For all patients still alive, follow-up data were collected up to July 1st 2008, guaranteeing a follow-up period of at least 5 years.

Follow-up of patients was done in line with the national guidelines.<sup>9</sup> In short: in the first year 3-monthly visit with physical examinations, in the second year 6-monthly, and thereafter yearly. All patients with remaining breast tissue underwent a yearly mammography and if indicated also an MRI scan. An ultrasound of the axilla was not routinely recommended. Axillary and infra- and supraclavicular lymph node recurrence was considered regional recurrence.

### Statistical analysis

The primary endpoint was the 5-year rate of regional recurrence, involving axillary and infra- and supraclavicular sites. The period to regional recurrence was defined as the interval from the date of diagnosis to regional recurrence. All regional recurrences were recorded, irrespective of presence of distant metastases. Patients who died before the end of follow-up were censored. Follow-up was censored at July 1st 2008.

To determine whether an association exists between the SN pathology protocol and regional recurrence rate, we compared the outcome for hospital **D** versus hospital **A**, **B**, and **C**.

The baseline characteristics of the 4 hospitals were compared with chi-square tests.

The hazard rate for regional recurrence for 5 years follow-up was determined using life-table analysis, reported with 95% confidence interval (CI). Differences between hospitals **D** versus **A**, **B**, and **C** were analyzed by using the logrank-test.

A  $p$ -value  $<0.05$  was considered statistically significant.

## Results

### Patient characteristics

We registered 198 eligible patients in hospital **A**, of which 134 (67.6%) patients had a negative SN. In hospital **B** 120 out of 153 (78.4%) patients had a negative SN, 59

out of 104 (56.7%) patients in hospital **C**, and 28 out of 86 (32.6%) patients in hospital **D**.

Patients in hospital **D** were more often diagnosed with isolated tumor cells (34.9% versus 5.3% in **A**, **B**, and **C**,  $p < 0.001$ ), which resulted in more completion ALNDs. Sixty-nine percent of patients in hospitals **A**, **B**, and **C**, as compared to 33% of patients in hospital **D** did not undergo a completion ALND, because of a negative SN ( $p < 0.0001$ ).

In total, 341 patients (63% of all registered patients) were SN negative, and did not undergo an additional ALND. Patient and primary tumor characteristics for the SN negative patients are shown in Table 1. There were overall no differences between hospital **D** versus hospitals **A**, **B**, and **C**.

### Risk of regional lymph node recurrence

At a follow-up of at least 5 years, 9 patients showed a regional lymph node relapse. Of these patients 5 patients underwent a mastectomy, and 4 patients underwent breast conserving surgery followed by radiotherapy. Only 4 out of 9 patients who had a recurrence received adjuvant systemic therapy (Table 3). Five (1.5%) patients had an axillary lymph node recurrence and 4 (1.2%) patients a supraclavicular recurrence (Table 2). There were no patients with combined relapse.

Based on actuarial cumulative risk analysis for regional recurrence, the 5-year regional recurrence rate was 2.4% (95% CI 0.8–4.0).

At this moment, none of the patients with a regional relapse had a distant relapse, and all patients with axillary lymph node recurrence underwent a delayed ALND.

Table 1  
Patient and primary tumor characteristics of SN negative patients per hospital.

Baseline characteristics	Hospital A	Hospital B	Hospital C	Hospital D	$p$ -value
	Number of patients $N = 131$ (%)	Number of patients $N = 113$ (%)	Number of patients $N = 59$ (%)	Number of patients $N = 28$ (%)	Hospital D versus A, B, and C
Age					0.799
<50	30 (22.9)	26 (23.0)	15 (25.4)	6 (21.4)	
50–<60	47 (35.9)	28 (24.8)	17 (28.8)	10 (35.7)	
60–<70	29 (22.1)	31 (27.4)	16 (27.1)	5 (17.9)	
≥70	25 (19.1)	28 (24.8)	11 (18.7)	7 (25.0)	
Tumor size (cm) <sup>a</sup>					0.158
≤1.0	22 (16.8)	42 (37.8)	16 (27.6)	12 (42.9)	
1.1–2.0	61 (46.6)	51 (46.0)	30 (51.7)	9 (32.1)	
2.1–3.0	38 (29.0)	13 (11.7)	8 (13.8)	4 (14.3)	
>3.0	10 (7.6)	5 (4.5)	4 (6.9)	3 (10.7)	
Histological grade <sup>b</sup>					0.979
I	30 (23.1)	49 (44.1)	20 (33.9)	9 (34.6)	
II	61 (46.9)	47 (42.3)	25 (42.4)	11 (42.3)	
III	39 (30.0)	15 (13.6)	14 (23.7)	6 (23.1)	
Hormone-receptor status <sup>c</sup>					0.339
ER and/or PgR +	120 (91.6)	88 (77.9)	47 (79.7)	20 (76.9)	
ER and PgR –	11 (8.4)	25 (22.1)	12 (20.3)	6 (23.1)	
Lymph and/or blood vessel invasion					0.129
No	124 (94.7)	109 (96.5)	57 (96.6)	25 (89.3)	
Yes	7 (5.3)	4 (3.5)	2 (3.4)	3 (10.7)	

<sup>a</sup> In 3 patients pathological tumor size was missing.

<sup>b</sup> In 5 patients histological grade was missing.

<sup>c</sup> In 2 patients hormone receptor status was missing; ER: estrogen receptor; PgR: progesterone receptor.

Table 2  
Recurrence pattern for SN negative patients per hospital and the total group.

	Hospital A	Hospital B	Hospital C	Hospital D	Total
	Number of patients <i>N</i> (%)	Number of patients <i>N</i> (%)	Number of patients <i>N</i> (%)	Number of patients <i>N</i> (%)	Number of patients <i>N</i> (%)
Total number SN procedures/patients	198	153	104	86	541
SN negative patients	134 (67.6)	120 (78.4)	59 (56.7)	28 (32.6)	341 (63.0)
Axillary recurrence	3 (2.2)	0	2 (3.4)	0	5 (1.5)
Supraclavicular recurrence	1 (0.7)	3 (2.5)	0	0	4 (1.2)
Local recurrence	0	4 (3.3)	1 (1.7)	0	5 (1.5)

Based on actuarial analysis, the 5-year regional recurrence rate for hospital **A** was 3.0% (95% CI 0.0–6.0), for hospital **B** 1.7% (95% CI 0.0–4.1), and 3.4% (95% CI 0.0–8.2) for hospital **C**. There were no regional recurrences in hospital **D** (Fig. 1). When taken hospitals **A**, **B**, and **C** together, the 5-year regional recurrence rate was 2.6% (95% CI 0.8–4.4), as compared to 0.0% in hospital **D** ( $p = 0.37$ ).

Table 3 shows patient and primary tumor characteristics, as well as the timeframe to nodal recurrence, of the 9 cases with regional lymph node recurrence.

All patients were 50 years of age or older and had an ER or PgR positive tumor. Five of 9 patients had not received adjuvant systemic therapy.

At a follow-up of 60–78 months, median time to recurrence was 27 months with a range of 4–66 months.

## Discussion

We reported before that further intensification of the SN pathology protocol, beyond the minimal recommendations, resulted in 37% more ALNDs because of higher detection frequency of SN isolated tumor cells.<sup>7</sup> Whether such a policy would reduce the number of recurrences, was the subject of this present study. In hospital **D**, using ultra-staging of the SN, no lymph node recurrences occurred during a follow-up of more than 5 years. In contrast, in the 3 hospitals (**A**, **B**, and **C**) using the ‘standard intensified’ pathology protocol, the 5-years regional recurrence risk was 2.6%.

Assuming that there is an absolute difference in the risk of regional recurrence of 3% between the hospitals with a ‘standard intensified’ pathology protocol and those which perform

ultra-staging of the SN, the question raises whether 37 extra ALNDs per 100 patients are worthwhile in order to prevent 3 regional recurrences. It gives a ratio for number needed to treat of approximately 1:13. In terms of morbidity of the surgical procedure and in terms of costs, a more than ‘standard intensified’ pathology protocol may thus not be of value.

Of note, during inclusion the national breast cancer guidelines of the Netherlands were quite conservative with respect to the recommendations for adjuvant systemic therapy. Only 4 out of 9 patients who had a recurrence had received adjuvant systemic therapy (Table 3). Nowadays, more patients with SN micrometastases are treated with more effective systemic therapy, such as anthracycline/taxane-containing regimens, which are considered the most effective chemotherapy in early breast cancer. If more patients would have had adjuvant systemic therapy, the risk of relapse might have been lower.<sup>10</sup> Further of note, 5 of 9 patients were treated with mastectomy without radiotherapy. The excellent results of the Z0011 study are thought to be related to the use of tangential radiotherapy to the axilla as part of the for inclusion requested breast conserving surgery, and the use of systemic therapy in nearly all patients.

In the years 2002 and 2003, it was within the Netherlands common practice that patients with isolated tumor cells in the SN underwent a completion ALND,<sup>9</sup> but during later years this policy changed, in agreement with ASCO guidelines. ASCO guidelines do not recommend a routine ALND if just isolated tumor cells are detected in the SN.<sup>11</sup>

In literature, many single center series and 4 randomized trials have been reported on axillary recurrence rates in patients with a negative SN.<sup>5,12–14</sup> The reported recurrence rates in these studies regarding SN negative patients seem

Table 3  
Patient characteristics of patients with regional lymph node recurrence.

Patient	Age-group	Tumor size (cm)	Histological grade	Hormone-receptor status	Systemic therapy	Radiotherapy	Time to lymph node recurrence (months)
1	≥ 70	1.4	I	ER and PgR +	–	+	23
2	50–59	1.5	II	PgR +	+	–	31
3	≥ 70	3.5	I	ER +	+	–	4
4	60–69	1.5	I	ER +	–	+	27
5	60–69	3.5	II	ER +	+	–	47
6	50–59	2.2	III	ER and PgR +	+	–	60
7	≥70	0.8	I	ER +	–	–	26
8	≥70	1.5	II	ER and PgR +	–	+	11
9	60–69	0.9	I	ER +	–	+	66

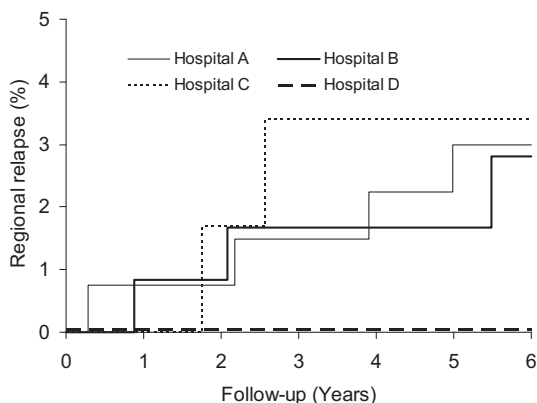


Figure 1. Cumulative risk for regional lymph node recurrence per hospital.

to be lower compared to our study. In most series the pathology protocol was not or only briefly mentioned as if this would not impact recurrence rate. In the first randomized trial on this topic, by Veronesi et al., it was reported that a very intensive SN pathology protocol was used.<sup>15</sup> In that particular study, approximately 15 pairs of sections were cut at 50  $\mu$ m intervals of each half of the SN, with approximately 60 sections per SN being examined. It is important to realize that the excellent follow-up results from this center cannot simply be translated to other hospitals if another pathology protocol is followed.

Also of note, in the aforementioned randomized Milan study only patients with a tumor of 2 cm or less were included, whereas currently in most centers the SN procedure is implemented for patients having a tumor size of 5 cm or less. This is of relevance, because, irrespective of SN findings, the primary tumor characteristics are also strongly associated with risk of non-SN metastases.<sup>16</sup>

In fact, breast cancer-specific survival is the most relevant endpoint to judge the clinical impact of the different SN pathology protocols. To this end, still too few deaths have occurred to draw conclusions with regard to differences in outcome between hospitals. We will continue to collect follow-up information from this cohort on disease-specific events, including breast cancer-related death.

In conclusion, we showed that hospital **D** performed 37% more completion ALNDs for no improvement in regional recurrence rate as compared to hospitals **A**, **B**, and **C** at 5 years follow-up. Whether the intensified SN pathology protocol of hospital **D** proves to be of value in 10 years, remains to be awaited. To this end, a SN pathology protocol as is used in most centers nowadays, with on average 3 levels per paraffin block, seems to be adequate.

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## Conflict of interest statement

The authors declare no conflict of interest.

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