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Regional Recurrence Risk Following a Negative Sentinel Node Procedure Does Not Approximate the False-Negative Rate of the Sentinel Node Procedure in Breast Cancer Patients Not Receiving Radiotherapy or Systemic Treatment

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ABSTRACT

Background. Although the false-negative rate of the sentinel lymph node biopsy (SLNB) in breast cancer patients is 5–7%, reported regional recurrence (RR) rates after negative SLNB are much lower. Adjuvant treatment modalities probably contribute to this discrepancy. This study assessed the 5-year RR risk after a negative SLNB in the subset of patients who underwent breast amputation without radiotherapy or any adjuvant treatment.

Methods. All patients operated for primary unilateral invasive breast cancer between 2005 and 2008 were identified in the Netherlands Cancer Registry. Patients with a negative SLNB who underwent breast amputation and who were not treated with axillary lymph node dissection, radiotherapy, or any adjuvant systemic treatment were selected. The cumulative 5-year RR rate was estimated by Kaplan–Meier analysis.

Results. A total of 13,452 patients were surgically treated for primary breast cancer and had a negative SLNB, and 2012 patients fulfilled the selection criteria. Thirty-eight RRs occurred during follow-up. Multifocal disease was associated with a higher risk of developing RR ($P = 0.04$). The median time to RR was 27 months and was significantly shorter in patients with estrogen receptor-negative (ER−) breast cancer (9.5 months; $P = 0.003$). The 5-year RR rate was 2.4% in the study population compared with 1.1% in the remainder of 11,440 SLNB-negative patients ($P = 0.0002$).

Conclusions. Excluding the effect of radiotherapy and systemic treatment resulted in a twofold 5-year RR risk in breast cancer patients with a tumor-free SLNB. This 5-year RR rate was still much lower than the reported false-negative rate of the SLNB procedure.

Sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) as a minimally invasive staging procedure for patients with invasive breast cancer. While meta-analyses documented a false-negative rate (FNR) of the SLNB of 5–7%, the incidence of regional (axillary) recurrence after a negative SLNB in literature is much lower; recently conducted systematic reviews reported an incidence of axillary recurrence after a negative SLNB of 0.3–0.6%.[1–5]

Additional treatment modalities contribute to the discrepancy between the FNR of the SLNB and the reported regional recurrence (RR) rates. Randomized, controlled trials have shown a favorable effect of adjuvant systemic

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therapy on the risk of locoregional recurrence.[6–9] In a previous population-based study, a lower risk of RR was observed following breast conserving surgery (BCS) than after amputation of the breast, suggesting a positive effect of radiotherapy to the breast on the RR rate.[10]

It is conceivable that patients with negative SLNB outcomes who are not treated with adjuvant systemic therapy and who do not undergo radiotherapy of the breast or thoracic wall will develop clinically manifest regional disease more often. For this group, the risk of developing a RR might shift towards the reported FNR of the SLN procedure over time.

To eliminate the contribution of the additional nonsurgical treatments, we evaluated in a population-based cohort the 5-year risk of developing a RR after a negative SLNB in the subset of breast cancer patients who were surgically treated with breast amputation and who did not undergo ALND, were not treated with radiotherapy, and did not receive adjuvant systemic therapy.

METHODS

Study Design and Patients

All patients operated for primary unilateral invasive breast cancer between January 1, 2005 and December 31, 2008 were identified in the Netherlands Cancer Registry (NCR). The NCR is a nationwide, population-based cancer registry containing information on patient, tumor, and treatment characteristics. The registration of data from patients' medical records is performed by registration employees. For the primary endpoint of the present study, we selected patients who were treated with breast amputation and who had a tumor-negative SLNB (pN0). In addition, patients did not have an additional ALND, no treatment with radiotherapy, and no adjuvant or neoadjuvant systemic therapy (chemotherapy, endocrine therapy, or trastuzumab). Exclusion criteria yielded a history of previous breast cancer, a synchronous contralateral breast cancer, and incomplete follow-up data (e.g., no information, missing event date). For comparison of the endpoint of interest, the aforementioned study group was compared to the remaining group of surgically treated breast cancer patients with a tumor-free SLNB. The latter group consisted of patients who received radiotherapy as part of breast-conserving therapy, patients who received radiotherapy following amputation, and the patients who received adjuvant systemic chemotherapy or endocrine therapy.

The following items were extracted from the NCR: age, gender, histologic type (ductal, lobular, mixed ductal/lobular or other), pathologic tumor size (pT), histologic grade (Bloom–Richardson), multifocality (yes/no), hormone receptor status (ER/PR), HER2 status, intrinsic subtype (HR+/HER2−, HR+/HER2+, HR−/HER2+, HR−/HER2−), operative treatment (breast amputation/BCS), resection margin status (positive/negative), ALND (yes/no), radiotherapy (yes/no), chemotherapy (yes/no), endocrine therapy (yes/no), and trastuzumab (yes/no). Standard assessment of HER2-status was implemented in the Netherlands mid-2005.

Outcomes

Frequencies of clinicopathological characteristics were compared between patients who developed RR versus patients who remained free of RR during 5-years of follow-up. In patients who developed RR, the time to RR with respect to the baseline characteristics was evaluated. Five-year follow-up data on RR (and local recurrence) were collected for all patients treated during the study period through active surveillance by NCR registrars (in addition to routine annual surveillance to detect any disease recurrence).[11] Incomplete data on follow up were mainly applicable for the years 2007 and 2008 in which 47% (n = 43) of the hospitals provided follow-up data since data collection for those years was only performed on request.

The 5-year RR rate for patients with a negative SLNB treated with breast amputation without ALND, radiotherapy, or adjuvant systemic therapy was extracted and compared with the 5-year RR rate of the remainder of all patients with a negative SLNB, irrespective of their adjuvant treatment. In patients who developed a RR, simultaneous occurrence of a local recurrence (LR) was assessed and defined as the establishment of a LR within 3 months of the occurrence of a RR.

Definitions of Endpoints

Regional recurrence (RR) was defined as recurrence of breast cancer in ipsilateral regional lymph nodes (e.g., axillary, infra/supraclavicular, or in the internal mammary chain). Local recurrence (LR) was defined as the occurrence of breast cancer or ductal carcinoma in situ in the ipsilateral breast or in the skin or subcutaneous tissue of the ipsilateral chest wall. Follow-up commenced at the date of final surgery and ended with any type of recurrence (event), death (censored), or the date of last follow-up (censored).

Statistical Analysis

The distribution of clinicopathologic characteristics is presented in percentages. Frequencies of baseline characteristics were compared between patients who developed RR versus patients who remained free of RR during 5 years

of follow up, using a χ^2 test for differences in categorical data. For the normally distributed continuous variable, age and means were calculated, and a *t*-test was performed. In patients who had developed a regional recurrence, the difference in median time to recurrence in relation to the baseline characteristics was evaluated performing a Kruskal–Wallis test. Cumulative 5-year RR rates were calculated through Kaplan–Meier estimates. The RR rate in the study group was compared to the rate in the remainder of SLNB-negative patients by means of a log-rank test. Statistical analysis was performed using STATA (version 13.1 2013, Texas).

RESULTS

During the study period, 34,734 patients underwent surgery for breast cancer, of whom 22,416 underwent the SLNB procedure. In total, 13,452 of these patients had a tumor-negative SLNB (pN0). Of the latter group, 3731 patients had undergone breast amputation (Fig. 1). The study population consisted of 2012 SLNB-negative patients who underwent breast amputation without ALND and who did not receive radiotherapy to the breast or adjuvant systemic treatment (Table 1). The mean age of the study population was 64 years [standard deviation (SD) 12.5 years]. Pathologic tumor size was classified as T1-2 in 98.0% of patients.

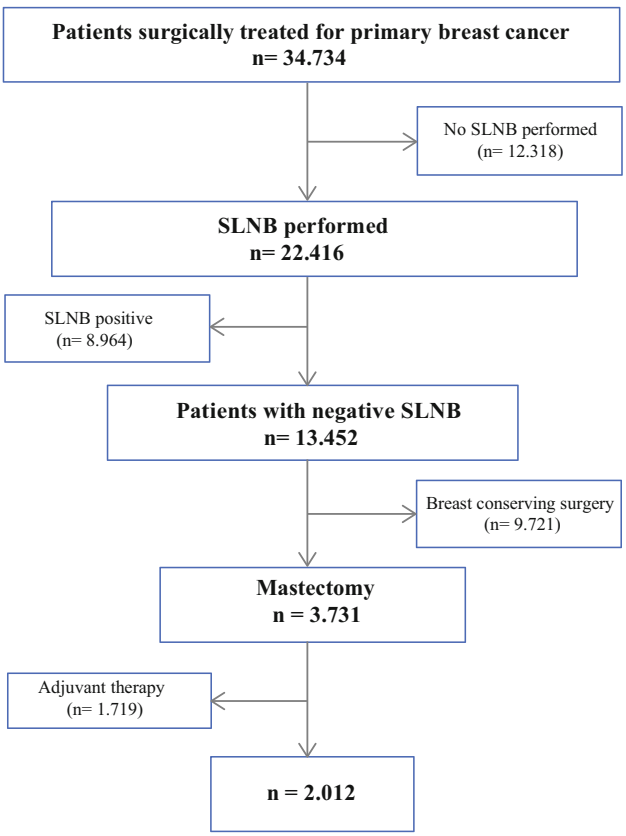

FIG. 1 *SLNB* sentinel lymph node biopsy, *BCS* breast-conserving surgery, *ALND* axillary lymph node dissection

In the 2012 SLNB-negative patients who underwent breast amputation without ALND and who did not receive radiotherapy to the breast or adjuvant systemic treatment, a total of 38 RRs occurred during the follow-up period. In 10 of these patients (26.3%), a LR was detected simultaneously. Patients who developed RR were younger ($P = 0.008$) and suffered more often from multifocal disease ($P = 0.04$) compared with the group of patients who remained free of RR (Table 1). In the 38 patients who developed a RR, the median time to recurrence was 27 (interquartile range [IQR] 13–44) months. ER-negative breast cancers were not associated with a higher risk of developing RR, but the median time to recurrence was significantly shorter in patients with a RR of an ER-negative breast cancer (9.5 months; Table 2).

The cumulative 5-year risk of developing a RR in the study population was 2.4% (95% confidence interval [CI] 1.7–3.4%; Fig. 2). A total of 38 RRs occurred with a median time to recurrence of 27 (IQR 13–44) months. No flattening of the slope of the curve was observed throughout the 5-year follow-up. The cumulative 5-year RR of the SLNB-negative patients who did receive radiotherapy or systemic therapy as part of their treatment ($n = 11{,}440$) was 1.1% (117 events; 95% CI 1.0–1.4%; $P = 0.0002$) with a median time to recurrence of 29 months (IQR 16–44 months).

DISCUSSION

In this study, a significantly higher risk of developing a RR was observed in SLNB-negative patients who had been treated with breast amputation and who did not receive radiotherapy or systemic therapy as part of their routine treatment, implying that nonsurgical treatments contribute significantly to the risk of developing a RR. Recurrence events were evenly distributed over the study period of 5 years. Tumor characteristics other than multifocality were not associated with a risk of developing RR.

The 5-year RR rate in the selected group of patients was 2.4% and was higher than the RR rate of SLNB-negative patients who did receive additional nonsurgical therapies as part of routine treatment (1.1%). A multicenter analysis on axillary recurrences after a negative sentinel lymph node biopsy in 929 patients with cT1-3N0 breast cancer reported a 5-year estimated axillary recurrence rate of 1.6%.[12] The observed difference between the RR rates of our study population and the remainder of all SLNB-negative patients confirms the beneficial effect of nonsurgical treatment modalities. A risk-reducing effect of adjuvant

TABLE 1 Baseline characteristics of all patients who underwent breast amputation and sentinel lymph node biopsy (pN0) who did not undergo ALND, and did not receive radiotherapy or adjuvant systemic therapy (n = 2012) and of the patients who developed a regional recurrence during 5-year follow-up (n = 38)

Characteristics	All patients n = 2012 (%)	Patients developing regional recurrence n = 38 (%)	P*
Age, year (mean, SD)	65 (54–73)	59 (14.2)	0.008**
Age (categories)			
< 35	3 (0.10%)	0 (0%)	0.20
35–50	292 (14.5%)	10 (26.3%)	
50–70	953 (47.4%)	17 (44.7%)	
> 70	764 (38%)	11 (29%)	
Histological type			
Ductal	1570 (78%)	33 (86.9%)	0.39
Lobular	230 (11.4%)	4 (10.5%)	
Mixed	100 (5%)	1 (2.6%)	
Other	112 (5.6%)	–	
Tumor size (T-stage)			
T1a/1M	223 (11.1%)	2 (5.2%)	0.80
T1b	463 (23%)	9 (23.7%)	
T1c	1010 (50.2%)	21 (55.3%)	
T2	277 (13.8%)	6 (15.8%)	
T3	9 (0.5%)	–	
T4	0	–	
X	30 (1.5%)	–	
Bloom–Richardson Histologic grade			
I	707 (35.1%)	10 (26.3%)	0.32
II	899 (44.7%)	22 (57.9%)	
III	253 (12.6%)	6 (15.8%)	
Unknown	153 (7.6%)	–	
Multifocality			
No	1594 (79.2%)	25 (68%)	0.04
Yes	377 (18.8%)	12 (32%)	
Unknown	41 (2%)	1	
Estrogen receptor status			
Negative	367 (18.2%)	9 (24%)	0.22
Positive	1623 (80.7%)	29 (76%)	
Unknown	22 (1.1%)	–	
Progesterone receptor status			
Negative	733 (36.4%)	13 (37%)	0.54
Positive	1244 (61.8%)	22 (63%)	
Unknown	35 (1.8%)	3	
HER2 receptor status			
Negative	154 (76.6%)	26 (87%)	0.84
Positive	202 (10%)	4 (13%)	
Unknown	270 (13.4%)	8	

TABLE 1 continued

Characteristics	All patients $n = 2012$ (%)	Patients developing regional recurrence $n = 38$ (%)	P*
Intrinsic subtype			
HR+/HER2−	1297 (64.5%)	22 (73.3%)	0.67
HR+/HER2+	99 (4.9%)	1 (3.3%)	
HR−/HER2+	102 (5%)	3 (10%)	
HR−/HER2−	163 (8.1%)	4 (13.3%)	
Unknown	351 (17%)	8	

Categorical variables are displayed as *n* (%)

ALND axillary lymph node dissection, *HR* hormone receptor status, *RR* regional recurrence, *SD* standard deviation

*χ^2 test was used to compare frequencies in clinicopathological characteristics between patients who developed RR ($n = 38$) versus patients who remained free of RR during 5 years of follow-up ($n = 1974$)

**Refers to the *t*-test to assess the difference in mean age (continuous variable)

treatment on RR has been reported previously. Van Wely et al.[13] reported an axillary recurrence rate of 2.8% in a prospective institutional study. RRs were detected in 11 patients after a median of 27 months. Ten of these patients had been primarily treated with mastectomy, and only three of these patients had received adjuvant systemic treatment. The patients had been surgically treated between 1998 and 2004, in a period when adjuvant systemic treatment guidelines were more lenient than after 2004. The same author also conducted a meta-analysis demonstrating a significant risk reducing effect on RR of external beam radiotherapy to the breast.[5] Bulte et al.[14] retrospectively analyzed 54 patients who had developed axillary metastases after a tumor-negative SLNB procedure: 36 patients had been treated with mastectomy, and 37% had received adjuvant systemic treatment.

While the absence of nonsurgical therapy contributed to a higher risk of RR, the observed RR rate of the study population was still two to three times lower than the previously reported FNR of the SLNB procedure, i.e., 5–7% in literature. The duration of the follow-up period of the present study may be one explanation for the discrepancy between the RR rate and the FNR of the SLNB, because RR rates are likely to be higher after a longer follow-up. Primary tumor characteristics, such as tumor size, malignancy grade, and molecular subtype, did not affect the risk of developing RR, albeit that the time to recurrence was significantly shorter in patients with E− breast cancer.

Because our study population mainly comprised ER+ breast cancer patients, a follow-up period beyond 5 years may reveal more RRs. The latter theory is supported by the slope of the RR curves in the present study: RR occurred evenly throughout the study period. In a study by Matsen et al.[15], the incidence of late axillary recurrence in 1529 SLNB-negative patients increased from 0.6% after 5 years to 0.9% after 10 years of follow-up. The 10-year follow-up results of the Z0011 also support the theory that RRs will develop after the 5-year follow-up period, because the 10-year RR increased from 0.9 to 1.5% in the SLNB-arm of the study.[16] On the other hand, it also may be possible that not all positive axillary lymph nodes will eventually evolve into a clinically detectable RR.

Support for the latter is paradoxically found in the Z0011 trial as well.[17] In the study arm that received completion ALND, 27% additional tumor-containing lymph nodes were found while the reported rate of patients who developed overt metastases in the SLNB alone arm (0.9%) is in sharp contrast with this. Even though radiotherapy and adjuvant systemic treatments will have played a substantial role in lowering the recurrence rate in the study, it is unlikely that these treatments can account for the whole difference.

A strength of the present study is the nationwide study design in a large population with complete 5-year follow-up, although one may argue that the 5-year follow-up period is too short for a definitive answer. Another limitation of this study is that we do not have additional data on how the SLNB procedure was conducted in the different centres and cannot assess whether RRs possibly occurred more when a particular approach was applied. Also, in the 38 patients who developed a RR in 5 years of follow-up, approximately a quarter of patients developed a simultaneous local recurrence. In these patients, it remains unclear whether the SLNB procedure may have been false negative or if the detected RR developed from their local recurrence with a true negative initial SLNB.

In the present study, we explored the discrepancy between the FNR of the SLNB procedure and the rare occurrence risk of regional recurrence by studying SLNB-negative patients who received no additional nonsurgical treatment. In this particular subset of patients, the clinical

TABLE 2 The cumulative regional recurrence rate in patients who underwent breast amputation and sentinel lymph node biopsy (pN0) and did not undergo ALND, radiotherapy, or adjuvant systemic therapy (n = 2012) and the time to recurrence for patients developing regional recurrence during 5-year follow-up (n = 38)

Characteristics	5 years regional recurrence rate (%)*	Median time to regional recurrence (months)	P**
Age (categories)			
< 35	–	–	0.90
35–50	3.7	26.7	
50–70	2.4	26	
>70	1.8	36.9	
Histological type			
Ductal	2.7	22.1	0.62
Lobular	2.0	37.6	
Mixed	1.1	36.9	
Other	–	–	
Tumor size (T-stage)			
T1a/1M	1.0	20	0.10
T1b	2.5	39.4	
T1c	2.7	32	
T2	2.4	10.7	
T3	–	–	
T4	–	–	
X	–	–	
Bloom–Richardson histologic grade			
I	1.6	29.5	0.11
II	3.3	31.6	
III	2.6	10.7	
Unknown	–	–	
Multifocality			
No	2.1	28.9	0.95
Yes	3.6	26.7	
Unknown	2.6	–	
Estrogen receptor status			
Negative	2.6	9.5	0.003
Positive	2.3	35	
Unknown	–	–	
Progesterone receptor status			
Negative	2.4	13.4	0.001
Positive	2.4	39.8	
Unknown	–	–	
HER2 receptor status			
Negative	2.4	22	0.67
Positive	3.0	18.9	
Unknown	1.8	–	
Intrinsic subtype			
HR +/HER2−	2.2	30.1	0.05
HR +/HER2+	2.7	60	
HR −/HER2+	3.2	11.8	
HR −/HER2−	2.7	9.1	
Unknown	2.7	–	

ALND axillary lymph node dissection, *HR* hormone receptor status, *RR* regional recurrence

*5-Year cumulative regional recurrence rate using Kaplan–Meier estimates

**P values refer to the Kruskal–Wallis test to assess differences in time to recurrence

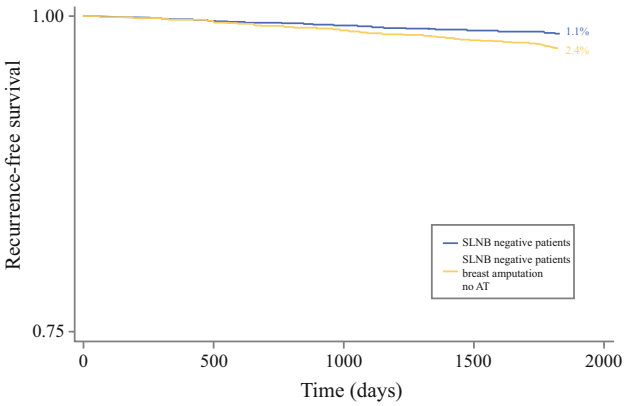

FIG. 2 *SLNB* sentinel lymph node biopsy

implications in terms of additional treatment adjustment are limited. Then again, the unselected group of all SLNB-negative patients also may serve as a model to evaluate the effects of whole breast radiotherapy and systemic therapies on the risk that additional metastases become overt. We will study these effects as part of a future project. Together with the results of the present study, the latter data may be extrapolated to patients with tumor-positive SLNBs to better grasp the even larger discrepancy between the rate of additional nonsentinel lymph node metastases (25–30%) and the observed regional recurrence rate when axillary clearance is omitted (1%).[17,18]

In this study, a higher risk of developing a RR was observed in SLNB-negative patients who had been treated with breast amputation without radiotherapy or systemic therapy. The risk of developing a RR remains lower than what would be expected based on the known FNR of the SLNB procedure, and even after a longer period of follow-up, it remains questionable whether the 5–7% of all patients who undergo breast cancer surgery and who have a false-negative SLNB procedure will eventually develop overt lymph node metastases.

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