

Introduction of sentinel node biopsy and stage migration of breast cancer[☆]

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Abstract

Aim: The purpose of this study was to examine in a large population based group of breast cancer patients treated in a regular care setting whether the introduction of the Sentinel Node Biopsy (SNB) led to detection of a higher percentage of patients with positive regional lymph nodes.

Methods: The study includes 3665 early breast cancer patients, aged 30–85 years, diagnosed in the period 1997–2002 and registered at the Regional Cancer Registry of the Comprehensive Cancer Centre Middle Netherlands. During this period the SNB was introduced. The outcome of staging was compared for groups staged with or without SNB. A logistic regression model was used to adjust for age, calendar period and tumour size.

Results: Overall a quarter of all patients over the period 1997–2002 underwent a SNB as method of lymphatic staging. The use of SNB clearly increased over time: from 2% in 1998 to 65% in 2002. The percentage node positive patients also rose significantly; before introduction of the SNB 30% of all patients were diagnosed with positive lymph nodes, and after SNB introduction this percentage was 40%. The increase is largely explained by the increase of patients diagnosed with only micrometastases. Adjustment did not change the results.

Conclusion: In conclusion, introduction of the SNB in early breast cancer led to significant upstaging of breast cancer patients treated in a regular care setting, due to the detection of more micrometastases. Since the relevance of micrometastases for long term survival is not yet known, this upstaging potentially led to over treatment of patients. On the other side, for some patients axillary lymph node dissection was prevented by the SNB procedure, preventing comorbidity.

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Introduction

In the Netherlands over 11,000 women are newly diagnosed with breast cancer every year (Netherlands Cancer Registry; data at www.iKCnet.nl). About 90% is diagnosed with a small tumour (<5 cm). An important prognostic factor for these patients is the tumour status of the regional lymph nodes, which is the main determinant of adjuvant

therapy. To establish the regional lymph node status, patients formerly underwent an axillary lymph node dissection (ALND) after (local) tumour resection. Removal of the axillary lymph nodes often causes negative side effects, such as neuropathy (63–78%), functional restriction of the shoulder (1–21%) and oedema (2–20%).¹

In the 1990's a new technique for intra operative lymphatic mapping was developed, the sentinel node biopsy (SNB).^{2–5} This procedure identifies the first lymph node(s) draining the site of the primary tumour. This is the most likely first site of metastasis and therefore only the SN(s) is (are) initially removed and examined for the presence of tumour tissue. Several reviews have concluded that the

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SNB is a valid method of lymphatic staging.^{6–8} As a result of the development and introduction of the SNB, patients with a tumour negative sentinel node no longer undergo standard ALND. For these patients the new procedure means they undergo a less aggressive staging procedure with considerable reduction of morbidity. In the Netherlands, guidelines for the application of SNB for staging of breast cancer patients were published in 1999.⁹

It has been hypothesised that the introduction of the SNB leads to a shift in staging of early breast cancer. The more thorough pathological examination of the lymph nodes due to the use of serial sectioning and immunohistochemistry, leads to the more frequent detection of (micro) metastases.¹⁰ This increase could have an important effect on the treatment of patients.^{11,12} Based on the Dutch treatment guidelines, most patients with small tumours and negative nodes will not be treated with adjuvant therapy, while patients staged with metastases will receive adjuvant treatment. It is not yet clear whether patients with micrometastases should be treated as node positive or negative.¹³

Aim of this study was to investigate in a large, population based patient group treated within a regular clinical setting, whether the introduction of the SNB indeed led to upstaging of breast cancer patients.

Patients and methods

Data were collected from the Regional Cancer Registry (RCR) of the Comprehensive Cancer Centre Middle Netherlands (CCCMN), which collects data on all new cancer cases in the central part of The Netherlands. The region has over 1.3 million inhabitants. It comprehends 7 hospitals, 3 of which are community hospitals, 1 is a university hospital and 3 are teaching hospitals. The latter four have their own nuclear medicine department and pathology laboratory. The community hospitals use the facilities of these hospitals. Almost all early breast cancer patients living in the central part of The Netherlands are diagnosed and treated at these 7 hospitals. After being notified by pathologists and medical registration offices, specially trained registration clerks from the RCR collect data from the hospital files.

We retrospectively identified all patients with breast carcinoma stage T1/T2, aged 30–85 years, diagnosed from 1997–2002 and registered at the RCR ($n = 4319$). Patients with clinically diagnosed metastases in regional lymph nodes or distant metastases were excluded, as well as patients who did not undergo surgical treatment or lymphatic staging ($n = 654$).

For the remaining patients ($n = 3665$) we extracted information from the cancer registry concerning the method of lymphatic staging and the clinical and pathological TNM stage (including the outcome of lymphatic staging).

We describe the introduction of the SNB over time by comparing percentage of lymph node involvement in three

groups of patients: patients who underwent only an ALND, a SNB and an ALND or only a SNB. Also the outcome of lymphatic staging over time is described in three groups: patients with negative nodes, micrometastasis and macrometastases (coded according to the TNM classification of the UICC^{14,15}). To determine whether a stage migration occurred, we compared the outcome of the lymphatic staging before and after the introduction of the SNB. Therefore we compared patients who underwent staging through only ALND with patients staged through SNB. In this last group we joined the groups SNB only and SNB in combination with ALND.

In further analyses we constructed a logistic regression model with lymphatic stage (negative versus positive) as outcome of the method of staging (ALND versus SNB). In this model we adjusted for three possible confounders: year of diagnosis, age at diagnosis and tumour size (defined as T1–T2). Analyses were conducted with the Statistical Package for Social Sciences (SPSS 12.0.1).

Results

Table 1 shows the characteristics of included patients. Almost three quarter of all patients were diagnosed with a tumour smaller than 2 centimetres. Women in the age 50–70 were more often diagnosed with a smaller tumour than women in the age groups 30–50 and 70–85 (77% vs. 69% and 64%, χ^2 -test, $df = 2$; $P < 0.001$).

Over the whole period more than a quarter of all included patients underwent a SNB for lymphatic staging. Half of this group received only a SNB, the other half underwent a SNB in combination with an ALND. SNB was more frequent in younger patients. The percentage decreases from 29% within patients aged 30–50 to 26% in patients aged 50–70 and 21% in patients aged 70–85

Table 1
Characteristics of early breast cancer patients from a cancer registry

	Number of patients ($n = 3665$)
Age (median – range)	57 (30–84)
–30–50	1159
–50–70	1760
–70–85	746
Tumour stage	
–T1	2639
–T2	1026
Method of lymphatic staging	
–only ALND	2721
–SNB and ALND	502
–only SNB	442
Outcome of lymphatic staging	
–Negative lymph node(s)	2473
–Positive lymph node(s), only micrometastases	113
–Positive lymph node(s), macrometastases	1079

Table 2
Method of lymphatic staging over the period 1997–2002 in 3665 breast cancer patients from a cancer registry

	1997	1998	1999	2000	2001	2002	Total
Only ALND	545	518	566	515	364	213	2721
	100%	99%	88%	79%	52%	35%	74%
ALND and SNB	0	5	69	113	145	170	502
	0%	1%	11%	17%	21%	28%	14%
Only SNB	0	3	7	25	184	223	442
	0%	1%	1%	4%	27%	37%	12%
Total	545	526	642	653	693	606	3665

(χ^2 -test, $df = 2$; $P < 0.001$). Younger patients were more frequently diagnosed with positive nodes than older patients (40% vs. 30% and 29%, χ^2 -test, $df = 2$; $P < 0.001$). The use of a SNB for staging patients was not determined by the size of the tumour, defined as T1 versus T2 (26% vs. 25%, χ^2 -test, $df = 1$; $P = 0.658$).

In Table 2 the method of lymphatic staging is presented according to year. In 1997 SNB was not yet used as method of staging in the region Middle Netherlands. The introduction started in 1998, and its use increased from 2% in 1998 to 21% in 2000 and 65% in 2002. Most patients who underwent a SNB in the period 1998–2000 also received an ALND. The number of patients with only SNB rose quickly after 2000 and in 2002 37% of all patients were staged by a SNB only.

Table 3 shows the outcome of lymphatic staging according to the year of incidence. Over time the percentage of lymph node positive patients rose significantly from 28% in 1997 to 38% in 2002 (χ^2 -test for trend; $P < 0.001$).

Table 4 shows the outcome of lymphatic staging according to staging method dichotomised as ALND and SNB (with or without additional ALND). Data show that 30% of patients staged through ALND were found lymph node positive versus 40% of patients staged through SNB. This is a significant increase in detection of positive nodes after the introduction of the SNB (χ^2 -test, $df = 1$; $P < 0.001$). The increase in positive lymph nodes found when diagnosed through a SNB is largely explained by the increase in the detection of micrometastases. The increase of micrometastases was significant (1% to 8%, χ^2 -test, $df = 1$; $P < 0.001$), the increase of macrometastases was not significant (29% to 32%, χ^2 -test, $df = 1$; $P = 0.08$).

Table 3
Percentage of lymph node involvement in 3665 breast cancer patients from a cancer registry over the period 1997–2002

	1997	1998	1999	2000	2001	2002	Total
Negative	389	360	452	440	457	375	2473
	72%	68%	70%	67%	66%	62%	68%
Micrometastases	2	5	3	12	31	60	113
	0%	1%	1%	2%	5%	10%	3%
Macrometastases	154	161	187	201	205	171	1079
	28%	31%	29%	31%	29%	28%	29%
Total	545	526	642	653	693	606	3665

Table 4
Percentage of lymph node involvement in 3665 breast cancer patients from a cancer registry according to method of staging

	ALND	SNB*	Total
Negative	1906	567	2473
	70%	60%	68%
Micrometastases	35	78	113
	1%	8%	3%
Macrometastases	780	299	1079
	29%	32%	29%
Total	2721	944	3665
	100%	100%	100%

*Including all patients with SNB, with or without a following ALND.

To adjust for possible confounders, we estimated the odds having positive lymph nodes by the method of staging (ALND versus SNB). In our logistic regression model the crude odds ratio was 1.5 (95% CI: 1.3–1.8). Adjusted for age at diagnosis, tumour size and year of incidence, the odds ratio decreased to 1.4 (95% CI: 1.1–1.7), which was still significant.

Discussion

Our analyses using data from the RCR of the central region of the Netherlands showed that the introduction of the SNB for staging of early breast cancer patients increased the percentage of patients who were diagnosed with positive lymph nodes. The proportion of patients with positive nodes increased from 30% before introduction to 40% after introduction of the SNB. This increase is for the larger part explained by the increase of patients diagnosed with only micrometastases.

The advantage of using data from a cancer registry is that this represents a geographical population and it therefore produces non-selected, population based data. The region of the CCCMN includes 3 community hospitals, as well as 3 teaching hospitals and a university hospital. It represents the actual situation in diagnosing and staging breast cancer patients in The Netherlands.

In our analyses we used data collected during the period of introduction of the SNB in the region (1997–2002). In 2002 65% of selected patients underwent a SNB as method of lymphatic staging. We expect this percentage to rise in later years. Furthermore, we expect the percentage of patients who undergo an ALND after the SNB to drop. During the introduction of the new treatment protocol, hospitals were advised to validate the technique in their local setting. During this learning curve (almost) all SNB's were followed by an ALND in order to confirm an acceptable percentage false-negative rate (under 5%).^{9,16} Now that the procedure has become standard, a larger group of patients will be saved an ALND and the possible negative side effects such as neuropathy, functional restriction and oedema that go with it.

In 1995 Giuliano estimated the possible stage shift in a prospective study with 296 patients. It was shown that

29% of the ALND group was node positive and 42% of the SNB group. The percentage of micrometastasis was 3% of the ALND group and 16% of the SNB group.¹⁰ A study by Cserni et al reported the increase in lymph node positive patients to be 9–47% higher after diagnosing through immunohistochemistry, depending on the exact technique used.¹⁷ The increase of lymph node positive patients in our study from 30 to 40% is in line with these reported earlier findings. The percentage of micrometastases found however is on the low end of the spectrum described by Cserni et al. This might be explained by the fact that our study describes the implementation of the procedure in the regular care setting. Our data also suggest that over time sentinel node biopsies are more extensively examined, resulting over time in an increase of the percentage of patients with micrometastasis of all patients undergoing a SNB: the percentage of micrometastasis of all SNB was 4% in 1999, 9% in 2000 and 15% in 2002. The reason for this increase is not clear.

The status of the regional lymph nodes is still one of the most important prognostic factors for breast cancer patients. However, the importance of micrometastases is more and more discussed. One important question is whether patients with only micrometastases in a SN need ALND. Several studies have tried to predict the outcome of the ALND after SNB.^{5,18–22} Determinants of the outcome of the ALND are the number of positive SNs, the size of the metastasis in the SN, the size of the primary tumour and the receptor status of the primary tumour. Based on a combination of these characteristics subgroups have been described in which the chances of further metastases in the ALND is under 10%. However, none of the authors of these studies advised to replace the ALND by axillary surveillance. They all refer to ongoing randomised trials with large groups of patients, like trial Z0011 of the American College of Surgeons Oncology Group, in which patients with a small tumour-positive SN are randomized to ALND or no additional axillary therapy. A second relevant question is whether patients with only micrometastasis need adjuvant treatment, such as chemotherapy. The current Dutch treatment guideline states that it is not clear whether patients with only micrometastasis (and no other indications for metastasis) should be considered for chemotherapy.¹³ In our study patients with only micrometastasis were often treated with adjuvant chemotherapy: 13% of node negative patients, 58% of patients with only micrometastasis and 63% of patients with macro-metastasis received chemotherapy.

Our study shows that the introduction of SNB in the regular treatment setting of patients with early breast cancer has led to an increase in patients with (micro) metastases in regional lymph nodes. These findings emphasize the importance of gaining knowledge on the relevance of micrometastases found through immunohistochemistry for the long term survival of patients. These data are expected to come from large ongoing randomised trials. Meanwhile, the debate on optimal staging and treatment of this

group of patients will continue. Based on cancer registry data, it is possible to examine over time the treatment of patients with only micrometastases. Also, differences in treatment between hospitals can be studied. This would give more insight in the actual impact of the introduction of the SNB on the regular treatment of early breast cancer patients.

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