# The sentinel lymph node in breast cancer, a re-appraisal

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Voor mijn ouders

COLOFON



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# The sentinel lymph node in breast cancer, a re-appraisal

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**Marieke Johanna Bolster**
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**Promotoren**
Prof. dr. V.C.G. Tjan-Heijnen (Maastricht Universitair Medisch Centrum)
Prof. dr. Th. Wobbes

**Copromotor**
Dr. P. Bult

**Manuscriptcommissie**
Prof. dr. J.H.W. de Wilt (voorzitter)
Prof. dr. H.J.M. van Krieken
Prof. dr. E.J.Th. Rutgers (Universiteit van Amsterdam)

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Chapter 1

# General Introduction

## GENERAL INTRODUCTION

Breast cancer is a major health care problem, with still a rising incidence[1]. The most important prognostic factor in primary breast cancer is the axillary lymph node status[2], also in the era of molecular prognostic tools such as the Oncotype DX®[3] and the MammaPrint® test[4]. The recent St Gallen International Breast Cancer Conference Expert Panel agreed that factors arguing for the inclusion of adjuvant chemotherapy were node positivity (in case of involvement of more than 3 lymph nodes), and high risk primary tumor characteristics (high histological grade, low hormone receptor status, positive Human Epidermal growth factor Receptor 2 (HER2) status, 'Triple negative' status) in case of a negative axillary lymph node status[5]. To provide information about the lymph node status, axillary lymph node dissection (ALND) has long been considered as the gold standard. However, because of the substantial morbidity associated with ALND and a reduced incidence of nodal involvement over time due to the introduction of population-based breast cancer screening, the role of ALND as part of a proper diagnostic work-up has been questioned[6]. Therefore, the sentinel lymph node (SN) procedure was introduced during the late 1990s, and was shown to be a reliable strategy to replace ALND in selected patients with primary breast cancer[7,8].

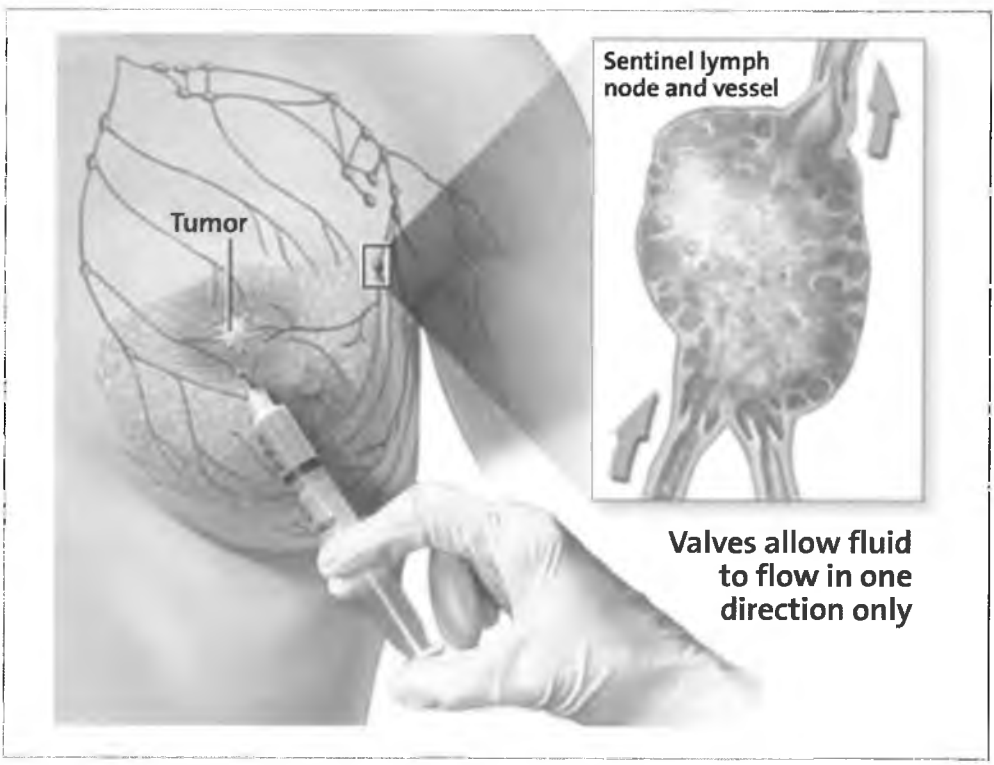


*Figure 1. Lymphatic drainage of the breast and technique of the SN procedure (illustration @ A. D. A. M.)*

The SN is the first lymph node(s) upon which the primary tumor drains (figure 1). In case of a negative SN, completion ALND can be avoided, as in that situation the incidence of non-SN metastases is very low[9]. 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[10]. At the time of execution of the study presented in this thesis, a completion ALND was performed in case the SN showed tumor involvement, including isolated tumor cells and micrometastases.

Obviously, a reliable examination of the SN by the pathologist is crucial, as a false-negative finding may result in undertreatment, both locally and systemically. Consequently, pathologists have intensified the examination of the SN by using serial sectioning (SS) and immunohistochemistry (IHC), whereas previously, the axillary lymph nodes were examined by haematoxylineosin (H&E) in one or two slides only. However, intensified examination of the SN may result in increased detection of isolated tumor cells (solitary tumor cells or tumor cell clusters with a size of ≤0.2mm) and micrometastases (>0.2mm-≤2.0mm)[11], of which the clinical significance is unclear[12]. If, upon the detection of isolated tumor cells and micrometastases a completion ALND is performed this could partially offset the expected reduction in the rate of ALND, while it is uncertain whether isolated tumor cells or micrometastases in the SN are clinically significant, and thus justify a completion ALND. In addition, the increased detection of isolated tumor cells and micrometastases may result in an increased administration of adjuvant systemic therapy.

In this thesis we questioned whether part of the advantages associated with the introduction of the SN procedure, might be lost due to the intensified pathological examination of the SN. In addition, we questioned whether a completion ALND is necessary in case of isolated tumor cells or micrometastases in the SN.

We hypothesized in **Chapter 2** that the prevalence of non-sentinel lymph node (non-SN) metastases, obtained after a completion ALND, would be lower in patients with isolated tumor cells or micrometastases in the SN versus macrometastases (>2.0mm) in the SN[11]. In case the incidence of non-SN metastases would be 5% or less in specific subgroups of patients, we postulated that a completion ALND is likely not justified.

Intensified pathological examination of the SN may result in increased detection of tumor-affected lymph nodes. Therefore, we hypothesized in **Chapter 3** that the introduction of the SN procedure has led to stage migration due to the intensified work-up of the SN by the pathologist.

Internationally, there is no consensus on the SN pathology protocol to be used[13,14]. Therefore, various hospitals use different SN pathology protocols. We prospectively collected clinical and pathological data on breast cancer patients who underwent a SN biopsy in four different hospitals. In the four involved hospitals, different SN pathology protocols existed. In hospitals A, B, and C, 3

levels of the paraffin block of the SN were pathologically examined (minimal recommendations according to the Dutch breast cancer guideline), whereas in hospital D, at least 7 additional levels were examined (at least 10 levels in total). In **Chapter 4** we tested the hypothesis that differences in SN pathology protocols between hospitals leads to different numbers of completion ALNDs performed, of which the relevance was aimed to be determined.

We reported the follow-up data of patients who had a negative SN, and therefore did not undergo an additional ALND, in **Chapter 5**. The obvious question was, whether ultrastaging, and thus more patients needing to undergo an additional ALND, is effective in reducing the risk of regional relapse.

Breast cancer is not only a substantial health care problem in terms of burden of disease, but also in terms of health care costs[15]. In chapters 6 and 7 we presented cost-effectiveness studies. The primary aim of our study in **Chapter 6** was to evaluate cost-effectiveness from a hospital perspective of three axillary staging scenarios: a conventional ALND versus a SN procedure in day care surgery prior to breast surgery versus a SN procedure performed during surgery of the breast. In **Chapter 7** we evaluated the potential impact of new national guidelines for adjuvant systemic therapy in breast cancer patients, introduced in the Netherlands in 1998 and 2001[16]. The change in number of patients eligible for adjuvant systemic therapy after the introduction of these new guidelines, as well as the cost-effectiveness of treatment of patients with breast cancer was analyzed.

Finally, in **Chapter 8** we discuss our findings in the light of current developments in the diagnosis and treatment of breast cancer.

## REFERENCES


1 *DeSantis C, Howlader N, Cronin KA, et al. Breast cancer incidence rates in U.S. wo-men are no longer declining. Cancer Epidemiol Biomarkers Prev 2011;20:733-739.*

2 *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;52:1551-1557.*

3 *Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006; 24:3726-3734.*

4 *Knauer M, Mook S, Rutgers EJ, et al. The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer. Breast Cancer Res Treat 2010;120: 655-661.*

5 *Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes-dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 2011;22: 1736-1747.*

6 *Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst 2006;98:599-609.*

7 *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: 2553-2559.*

8 *Miltenburg DM, Miller C, Karamlou TB, et al. Meta-analysis of sentinel lymph node biopsy in breast cancer. J Surg Res 1999;84: 138-142.*

9 *Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010;11:927-933.*

10 *van Dijck JA, Coebergh JW, Siesling S, et al. Breast cancer in women. In: Trends of cancer in the Netherlands 1989-1998 (ed). Utrecht, the Netherlands: Association of comprehensive cancer centers/Netherlands Cancer Registry, 2002:31-32.*

11 *Sobin LH, Wittekind C. International union against cancer. TNM classification of malignant tumors, Sixth Edition. New York: Wiley-Liss, 2002.*

12 *Cserni G, Gregori D, Merletti F, et. al. Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer. Br J Surg 2004;91: 1245-1252.*

13 *European Working Group of Breast Screening Pathology: Cserni G, Amendoeira I, Apostolikas N, et al. Pathological work-up of sentinel lymph nodes in breast cancer. Review of current data to be considered for the formulation of guidelines. Eur J Cancer 2003;39:1654-1667.*

14 *Cserni G, Amendoeira I, Apostolikas N, et al. Discrepancies in current practice of pathological evaluation of sentinel lymph nodes in breast cancer. Results of a questionnaire based survey by the European Working Group of Breast Screening Pathology. J Clin Pathol 2004;57:695-701.*

15 *Koopmanschap MA, van Roijen L, Bonneux L, et al. Current and future costs of cancer. Eur J Cancer 1994;30:60-65.*

16 *Bontenbal M, Nortier JW, Beex LV et al. Adjuvant systemic therapy for patients with resectable breast cancer: guideline from the Dutch National Breast Cancer Platform and the Dutch Society for Medical Oncology. Ned Tijdschr Geneeskd 2000;144:984-989.*

# CHAPTER 2

Chapter 2

# Risk factors for non-sentinel lymph node metastases in patients with breast cancer. The outcome of a multi-institutional study

*Marieke J. Bolster, Petronella G.M. Peer, Peter Bult, Frederik B.J.M. Thunnissen, René F.M. Schapers, Jos W.R. Meijer, Luc J.A. Strobbe, Charles L.H. van Berlo, Jean H.G. Klinkenbijl, Louk V.A.M. Beex, Theo Wobbes, Vivianne C.G. Tjan-Heijnen*

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## ABSTRACT

### Background

In this multi-institutional prospective study, we evaluated whether we could identify risk factors predictive for non-sentinel lymph node (non-SN) metastases in breast cancer patients with a positive sentinel lymph node (SN).

### Methods

In this multi-institutional study, 541 eligible breast cancer patients were included prospectively.

### Results

The occurrence of non-SN metastases was related to the size of the SN metastasis (P = 0.02), primary tumor size (P = 0.001), and lymphovascular invasion (P = 0.07). The adjusted odds ratio was 3.1 for SN micro-metastasis compared to SN isolated tumor cells, 4.0 for SN macro-metastasis versus SN isolated tumor cells, 3.1 for tumor size (> 3.0 cm compared with ≤ 3.0 cm), and 2.0 for lymphovascular invasion (yes versus no). There were no positive non-SNs when the primary tumor size was ≤ 1.0 cm (N = 24) (95% confidence interval (95% CI) 0% - 14.0%). The proportion of positive non-SNs ranged in a prognostic logistic regression model from 9.7% (95% CI 4.0% - 23.0%) for patients with SN isolated tumor cells, tumor size of 1.1 - 3.0 cm, and without vessel invasion, to 72.6% (95% CI 47.0% - 89.0%) for patients with SN macro-metastasis, tumor size > 3.0 cm, and with vessel invasion.

### Conclusion

We identified three predictive factors for non-SN metastases in breast cancer patients with a positive SN: size of the SN metastasis; primary tumor size; and vessel invasion. We were not able to identify a specific group of patients with a positive SN in whom the risk for non-SN metastases was less than 5%.

## INTRODUCTION

The most important prognostic factor in primary breast cancer is the axillary lymph node status. To provide information about the lymph node status, axillary lymph node dissection (ALND) has long been considered as the gold standard. However, because of the substantial morbidity associated with ALND and a reduced incidence of nodal involvement over time, the role of ALND as part of a proper diagnostic work-up has been questioned. For this reason, ALND has now largely been replaced by the sentinel lymph node (SN) biopsy.

The SN is the first lymph node(s) upon which the primary tumor drains. Cases where the SN shows tumor involvement, a completion ALND will still be performed. However, in patients with a negative SN, completion ALND can be avoided, as in that situation the incidence of non-SN metastases is very low[1]. According to the Netherlands Cancer Registry, approximately 60% of breast cancer patients had node-negative disease before the introduction of the SN biopsy[2]. Hence, it was expected that in these 60% of patients with resectable breast cancer, a completion ALND could be avoided by carrying out a SN biopsy.

Obviously, a reliable examination of the SN by the pathologist is crucial, as a false-negative finding may result in under-treatment. Consequently, pathologists have intensified the examination of the SN by using serial sectioning (SS) and immunohistochemistry (IHC), whereas previously, the axillary lymph nodes were examined by haematoxylin-eosin (H&E) in one or two slides only. However, intensified examination of the SN may result in increased detection of isolated tumor cells and micrometastases, the clinical significance of which is unclear[3].

We postulated that the SN biopsy leads to an increased detection of isolated tumor cells and micro-metastases due to the intensified work-up of the SN by the pathologist. If, upon the detection of isolated tumor cells and micro-metastases a completion ALND is performed this could partially offset the expected reduction in the rate of ALND, while in fact, it is uncertain whether a SN with isolated tumor cells or micrometastases justifies a completion ALND.

In summary then, we hypothesized that the incidence of non-sentinel lymph node (non-SN) metastases would be lower in patients with isolated tumor cells or micro-metastases in the SN versus those with macrometastases and, that in case the incidence of non-SN metastases would be 5% or less in specific subgroups of patients, a completion ALND would not likely justified.

## PATIENTS AND METHODS

During eighteen months in the years 2002 and 2003, patients from four hospitals (Canisius-Wilhelmia Hospital, Nijmegen, Viecuri Medical Center, Venlo, Rijnstate Hospital, Arnhem, Radboud University Nijmegen Medical Center) were prospectively included for a SN biopsy when a cytological or histological proven invasive breast cancer was present with a clinical tumor size of 5 cm or

less. Patients were excluded when there was clinical proof of axillary lymph node metastases, presence of multifocality if they had undergone radiotherapy of the breast or axilla in the past, if they had received neo-adjuvant systemic therapy, and when the SNs were not detectable.

The prospectively collected data included the lymph node status and number of nodes examined, number of positive nodes, size of metastases, classification according to the tumor node metastasis (TNM) categories defined in the sixth edition of the TNM Classification of Malignant Tumors[4], and the detection method (H&E/IHC). These items were separately registered for SNs and non-SNs. Also details of primary tumor characteristics (localization, tumor size, histology, histological grade, lymph and/or blood vessel invasion, hormone receptor status), patient characteristics (age) and information on the surgical procedure (SN biopsy with or without ALND, lumpectomy or mastectomy and various combinations) were collected.

The surgical procedure and the pathological examination were in accordance to the Dutch guideline for treatment of breast cancer[5]. SN localization was performed using the combined technique of blue dye and radioisotope in all patients. At least three levels at, at least 150 micron interval were examined with H&E. In the absence of apparent metastases with H&E examination, IHC examination was performed. In the presence of isolated tumor cells, micro-, or macro-metastases in the SN, a completion ALND was recommended. The nodes in the ALND specimen were examined at one to two levels with H&E staining.

According to the international TNM-classification 2002, isolated tumor cells, micro-metastases, and macro-metastases were classified as follows: isolated tumor cells (pNo(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)). In this present paper we added: pN1+, which refers to pN1a and higher pN positive stages. Further, we added the term 'pNtotal', which refers to the final pTNM stage including both the SN and, if applicable, the non-SNs findings.

***Statistical analyses***

We tried to identify a subgroup of breast cancer patients in whom the incidence of metastatic disease in the non-SNs (obtained after completion ALND) had to be reliably predicted to be 5% or less. In such a group we considered omitting completion ALND justified.

The following variables were explored for prognostic significance with respect to occurrence of non-SN metastases in patients in whom non-SNs were removed: age (≥ 50 years versus < 50 years), SN-findings (isolated tumor cells versus micro-metastases versus macro-metastases), tumor size (≤ 1 cm, 1.1 - 2 cm, etc up to > 5 cm), histological grade (I versus II versus III), hormone-receptor status (ER-positive and/or PgR-positive versus both negative) and lymph

| Patient/tumor characteristics | Number of patients N = 541 (%) | |
|---|---|---|
| **Age (years)** | | |
| < 36 | 15 | (2.8) |
| 36 - < 50 | 117 | (21.6) |
| 50 - < 60 | 173 | (32.0) |
| 60 - < 70 | 127 | (23.5) |
| ≥ 70 | 109 | (20.1 |
| **Tumor size (cm)[a]** | | |
| ≤ 1.0 | 119 | (22 3) |
| 1 1 - 2.0 | 241 | (45.1) |
| 2.1 - 3.0 | 122 | (22 8) |
| 3.1 - 4.0 | 34 | (6 4) |
| 4.1 - 5.0 | 11 | (2.1) |
| > 5.0 | 7 | (1 3) |
| **Histological grade[b]** | | |
| I | 158 | (29.6) |
| II | 242 | (45.3) |
| III | 134 | (25.1) |
| **Hormone-receptor status[c]** | | |
| ER and/or PgR + | 467 | (86 8) |
| ER and PgR - | 71 | (13.2) |
| **Lymph and/or blood vessel invasion** | | |
| No | 463 | (85.6) |
| Yes | 78 | (14.4) |
| **Final nodal status** | | |
| pN0 | 335 | (61.9) |
| pN0(i+) | 47 | (8.7) |
| pN1mi | 49 | (9.1) |
| pN1+ | 110 | (20.3) |

***Table 1. Patient and tumor characteristics***

a: In 7 patients pathological tumor size was missing. b: In 7 patients histological grade was missing. c: In 3 patients hormone receptor status was missing. Tumor size: pathological tumor size; ER: estrogen receptor; PgR: progesterone receptor; pN1+: pN1a and higher pN positive stages.

and/or blood vessel invasion (yes or no). Those variables yielding a P-value of less than 0.10 for the chi-square test were incorporated in a multiple logistic regression model. Subgroups were formed based on combinations of these variables. For each subgroup the model-based predicted probability for non-SN metastases was compared with the proportion of women who actually had positive non-SN nodes. Goodness of fit was assessed by the deviance statistic. The discrimination of the model was measured by the area under the receiver operating characteristic (ROC) curve.

The strength of a risk factor for non-SN metastases was expressed by the odds ratio. The relation between pathological tumor size and nodal status was also assessed with a logistic regression model.

## RESULTS

### *Patient inclusion*

Five hundred eighty-seven patients were included prospectively. In 28 (4.7%) patients there was no invasive tumor-component, in thirteen (2.2%) patients the SN was not detectable, four (0.7%) patients received neo-adjuvant systemic therapy, and one (0.2%) patient already had a pre-operatively proven pathological axillary lymph node. These 46 patients were excluded leaving 541 patients in our prospective database. Patient characteristics are shown in table 1.

### *Positive versus negative SN and non-SNs*

Of the 541 eligible patients, 338 (62.5%) patients had a negative SN and 203 (37.5%) a positive SN (figure 1).

Among SN-positive patients (N = 203), 186 patients underwent a completion ALND. From these 186 patients, 56 patients had positive non-SNs. Seventeen patients who had tumor involvement in the SN did not undergo a completion ALND. In three of these seventeen patients there was no completion ALND done, but there were non-SNs removed during the SN procedure, classified by the surgeon or pathologist as non-SNs. These three patients had negative non-SNs (figure 2).

SN-negative patients did not undergo a completion ALND, with the exception of

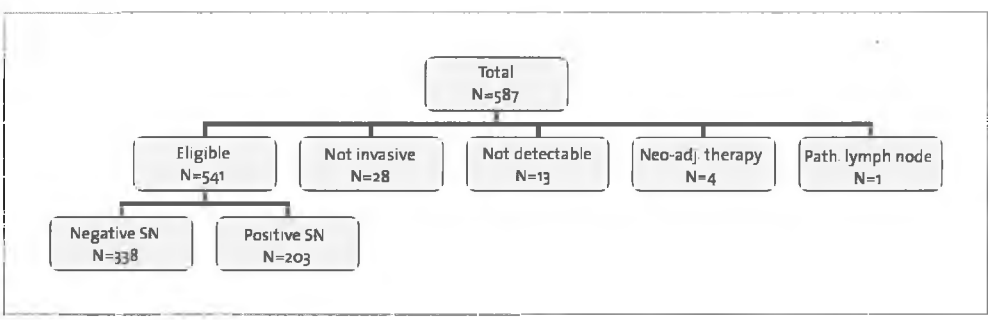


*Figure 1. Prospective study population*
Reasons for, and numbers of exclusion; SN status among eligible patients. Neo-adj.: neo-adjuvant; Path.: pathological; SN: sentinel lymph node.

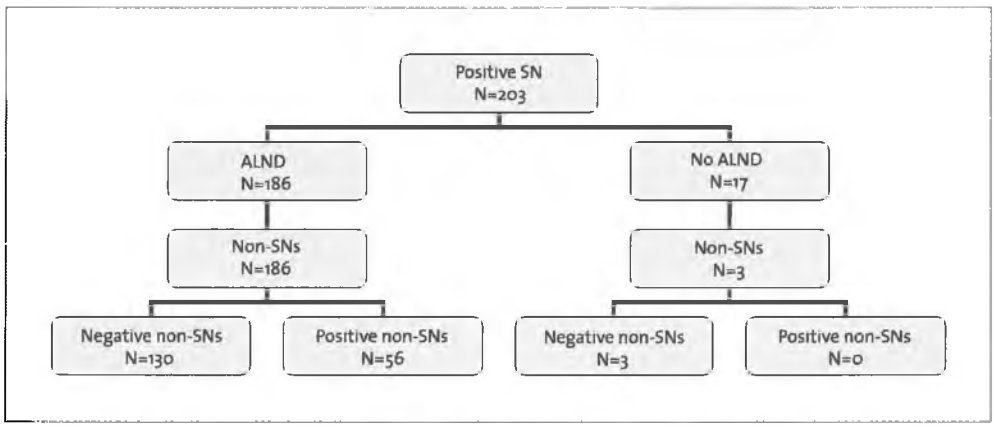


***Figure 2. Positive SNs: non-SN status when non-SNs were removed***
SN: sentinel lymph node; ALND: axillary lymph node dissection.

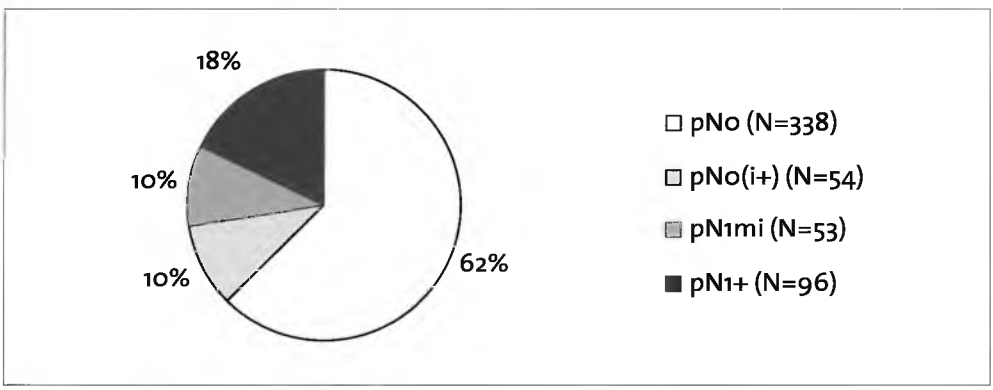


***Figure 3. Sentinel lymph node status: pN(sn)***

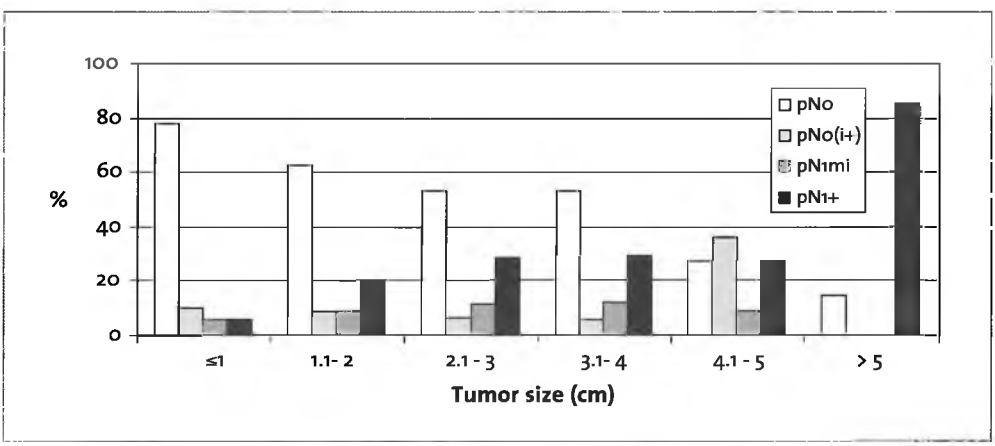


***Figure 4. The final nodal status (pNtotal) in relation to pathological tumor size***

three patients in whom positive non-SNs were removed during the SN procedure.

### *SN and final nodal classification according to TNM*

In 54 out of 541 (10.0%) patients the SN contained isolated tumor cells (pNo(i+)(sn)), in 53 (9.8%) patients the SN contained micro-metastases (pN1mi(sn)), and in 96 (17.7%) patients macro-metastases (pN1+(sn)) (figure 3).

Thirteen patients with a positive SN shifted into a higher nodal stage when non-SNs were taken into account (pNtotal) (table 2). The final nodal stage was classified as node-negative in 335 (61.9%) patients. Forty-seven (8.7%) patients had isolated tumor cells, 49 (9.1%) patients had micro-metastases, and 110 (20.3%) patients had macro-metastases (table 2).

The incidence of macro-metastases increased with increasing tumor size (5.9% for tumors ≤ 1 cm, 19.9% for tumors 1.1 - 2 cm, 28.7% for tumors 2.1 - 3 cm, 29.4% for tumors 3.1 - 4 cm, 27.3% for tumors 4.1 - 5 cm, and 85.7% for tumors > 5 cm) (P for trend < 0.0001). The incidence of negative final nodal stages decreased with increasing tumor size (P for trend < 0.0001) (figure 4).

### *Impact of SN and primary tumor characteristics on occurrence of non-SN metastases*

The incidence of non-SN metastases was significantly related to the size of the SN metastases. Non-SN metastases occurred in 14.6% of patients with isolated tumor cells in the SN, in 28.6% of patients with micro-metastases in the SN and in 38.0% of patients with macro-metastases in the SN, in whom non-SNs were removed (chi-square test, P = 0.02). Of 7 patients with isolated tumor cells in the SN and positive non-SNs, 2 had micro-metastases, and 5 had macro-metastases in the non-SNs. Of 14 patients with micro-metastases in the SN and positive non-SNs, 4 had isolated tumor cells,

| | pNtotal after inclusion of non-SNs | | | |
|---|---|---|---|---|
| pN(sn) | pNo<br>N | pNo(i+)<br>N | pN1mi<br>N | pN1+<br>N |
| pNo(sn) N=338 | 335 | 0 | 0 | 3[a] |
| pNo(i+)(sn) N=54 | | 47 | 2 | 5 |
| pN1mi(sn) N=53 | | | 47 | 6 |
| pN1+(sn) N=96 | | | | 96 |

***Table 2. Sentinel lymph node status and final nodal status***

a: SN-negative patients did not undergo a completion ALND, with the exception of 3 patients in whom positive non-SNs were removed during the SN procedure. SN: sentinel lymph node; pNtotal: final pTNM stage including both the SN and, if applicable, the non-SNs findings; pN1+: pN1a and higher pN positive stages.

| Tumor characteristics | Non-SNs removed[a] (N) | Positive non-SNs (%) | P-value univariate | P-value multivariate |
|---|---|---|---|---|
| **Age (years)** | | | 0.97 | |
| ≥ 50 | 138 | 29.7 | | |
| < 50 | 51 | 29.4 | | |
| **pN(sn)** | | | 0.02 | 0.03 |
| pNo(i+) | 48 | 14.6 | | |
| pN1mi | 49 | 28.6 | | |
| pN1+ | 92 | 38.0 | | |
| **Tumor size (cm)** | | | 0.001 | 0.001 |
| ≤ 1.0 | 24 | 0.0 | | |
| 1.1 - 2.0 | 77 | 27.3 | | |
| 2.1 - 3.0 | 56 | 30.4 | | |
| 3.1 - 4.0 | 16 | 56.2 | | |
| 4.1 - 5.0 | 7 | 42.9 | | |
| > 5.0 | 6 | 66.7 | | |
| **Histological grade** | | | 0.59 | |
| I | 42 | 28.6 | | |
| II | 90 | 33.3 | | |
| III | 55 | 25.5 | | |
| **Hormone-receptor status** | | | 0.48 | |
| ER and/or PgR + | 174 | 30.5 | | |
| ER and PgR - | 14 | 21.4 | | |
| **Lymph and/or blood vessel invasion** | | | 0.07 | 0.17 |
| No | 129 | 25.6 | | |
| Yes | 60 | 38.3 | | |

***Table 3. Incidence of positive non-SNs in relation to patient and primary tumor characteristics and by SN classification***
a: Non-SNs were not removed in all patients. SN: sentinel lymph node; pN1+: pN1a and higher pN positive stages; ER: estrogen receptor; PgR: progesterone receptor

4 had micro-metastases, and 6 had macro-metastases in the non-SNs. Of 35 patients with macro-metastases in the SN and positive non-SNs, 5 had micro-metastases and 30 patients had macro-metastases in the non-SNs.

Tumor size was also significantly associated with the incidence of positive non-SNs. None of 24 patients with a tumor size of 1.0 cm or smaller had non-SN metastases. Twenty-seven percent (27.3%) of patients with a tumor size 1.1 - 2 cm had a positive non-SN compared to 30.4% with a tumor size 2.1 - 3 cm, compared to 56.2% with a tumor size 3.1 - 4 cm, compared to 42.9% with a tumor size 4.1 - 5 cm, and compared to 66.7% with a tumor size > 5 cm (chi-square test, P = 0.001). In addition, patients without lymph and/or blood vessel invasion had an incidence of 25.6% of positive non-SNs compared with an incidence of 38.3% in patients with vessel invasion (chi-square test, P = 0.07) (table 3).

*Multivariate analysis on risk factors*

In the multivariate analysis, the P-value for lymph and/or blood vessel invasion increased mainly because of the association between tumor size and lymph and/or blood vessel invasion (likelihood ratio test, pN(sn): P = 0.03, tumor size: P = 0.001, and vessel invasion: P = 0.17) (table 3).

*Probabilities for non-SN metastases*

There were no positive non-SNs when the primary tumor size was ≤ 1.0 cm (N = 24). However, because of the small number of observations, the confidence interval (CI) was quite large and included the predefined upper tolerable limit of 5% (95% CI 0% - 14%). Of these 24 patients, twelve patients had solely isolated tumor cells in the SN of whom eleven had no lymph and/or blood vessel invasion. Six patients had micro-metastasis in the SN and six patients had macro-metastasis in the SN.

For tumors > 1 cm the probability for positive non-SNs was determined with a prognostic logistic regression model including pN(sn), tumor size and lymph and/or blood vessel invasion. Subgroups were formed based on the combinations of these variables. The categories for tumor size 1.1 - 2 cm and 2.1 - 3 cm were joined, because there was hardly any difference in predicted probability of positive non-SNs (less than 0.8%) between these two categories for tumor size. Tumors > 5 cm (N = 6) were excluded because the fit of the model improved considerably from P = 0.05 to P = 0.18 for the deviance statistic. The discrimination of the model, measured by the area under the ROC curve, was 0.67. For each subgroup the model-based predicted probability for non-SN metastases was compared with the proportion of patients who actually had positive non-SNs.

In patients with tumor size 1.1 - 3 cm and no lymph and/or blood vessel invasion, the incidence of positive non-SNs was 7.1% in case of isolated tumor cells in the SN, 29.6% in case of micro-metastasis in the SN and 30.0% in case of macro-metastasis in the SN. The predicted probability of positive non-SNs according to our model of these three groups was for isolated tumor cells in the SN 9.7% (95% CI 4% - 23%), for micro-metastasis in the SN 25.0% (95% CI 14% - 41%), and for macro-metastasis in the SN 30.0%

(95% CI: 20% - 42%). See table 4 and figures 5a and 5b for further incidences.

The strength of a risk factor for non-SN metastases was expressed by the odds ratio (OR). The OR for pN1mi(sn) compared to pN0(i+)(sn) was 3.1 (95% CI 0.99 - 9.8), and for pN1+(sn) versus pN0(i+)(sn) 4.0 (95% CI 1.4 - 11.5). The OR for tumor size (> 3.0 cm compared to ≤ 3.0 cm) was 3.1 (95% CI 1.2 - 8.1), and the OR for lymph and/or blood vessel invasion (yes versus no) 2.0 (95% CI 0.9 - 4.2).

## DISCUSSION

The axillary lymph node status is still the most important prognostic factor in primary breast cancer and, therefore, important for making adjuvant therapy decisions. For patients who have a negative SN, enough prognostic information has been obtained and a completion ALND is not recommended anymore.[1] However, the role of ALND as a therapeutic procedure remains controversial for patients with a tumor-positive SN, especially for those who only have isolated tumor cells or micro-metastasis in the SN. The aim of this present study was to identify

| pN(sn) | Lymph and/or blood vessel invasion | Tumor size (cm) | Patients (N) | Positive non-SNs (N) | Observed proportion of positive non-SNs (%) | 95% CI | Predicted proportion of positive non-SNs (%) | 95% CI |
|---|---|---|---|---|---|---|---|---|
| | | ≤ 1.0 | 24 | 0 | 0.0 | 0-14 | | |
| pN0(i+) | No | 1.1 - 3.0 | 14 | 1 | 7.1 | | 9.7 | 4-23 |
| | | 3.1 - 5.0 | 4 | 0 | 0.0 | | 24.9 | 9-53 |
| | Yes | 1.1 - 3.0 | 14 | 3 | 21.4 | | 17.6 | 7-37 |
| | | 3.1 - 5.0 | 3 | 2 | 66.7 | | 39.8 | 17-68 |
| pN1mi | No | 1.1 - 3.0 | 27 | 8 | 29.6 | | 25.0 | 14-41 |
| | | 3.1 - 5.0 | 4 | 1 | 25.0 | | 50.8 | 27-75 |
| | Yes | 1.1 - 3.0 | 8 | 2 | 25.0 | | 39.9 | 22-61 |
| | | 3.1 - 5.0 | 3 | 3 | 100.0 | | 67.3 | 40-87 |
| pN1+ | No | 1.1 - 3.0 | 50 | 15 | 30.0 | | 30.0 | 20-42 |
| | | 3.1 - 5.0 | 5 | 4 | 80.0 | | 57.1 | 33-79 |
| | Yes | 1.1 - 3.0 | 20 | 9 | 45.0 | | 46.1 | 30-63 |
| | | 3.1 - 5.0 | 4 | 2 | 50.0 | | 72.6 | 47-89 |

***Table 4. Observed and predicted proportion of positive non-SNs in relation to primary tumor and SN characteristics***
SN: sentinel lymph node; 95% CI: 95% confidence interval; pN1+: pN1a and higher pN positive stages.

primary tumor and SN characteristics that would allow the prediction of non-SN metastases, and to identify a subgroup of patients that may not require completion ALND.

In this prospective study, 541 patients with primary breast cancer who successfully underwent a SN biopsy were included. In agreement with others, we demonstrated that the SN biopsy is an excellent tool to make a first selection for the omission of a completion ALND, with 62.5% of patients having a negative SN. These were all patients with clinically T1 or T2 tumors. Of interest, of 186 patients with a positive SN who subsequently underwent a completion ALND, only 30% of patients had one or more positive non-SN. According to a prior meta-analysis approximately 50% of patients who had a positive SN would be expected to have residual disease in the axilla.[1] This striking difference may be explained by the currently accepted intensified pathology protocol with the detection of more and smaller metastases in the SN. Indeed, in nearly 50% of our patients with a positive SN, the SN contained only low-volume metastasis, i.e., isolated tumor cells or micro-metastasis. This may support our initial hypothesis, that some of the patients having small SN metastasis may not benefit from a completion ALND.

In a recent meta-analysis on twenty-five publications, it was concluded that the risk of non-SN metastases with low-volume

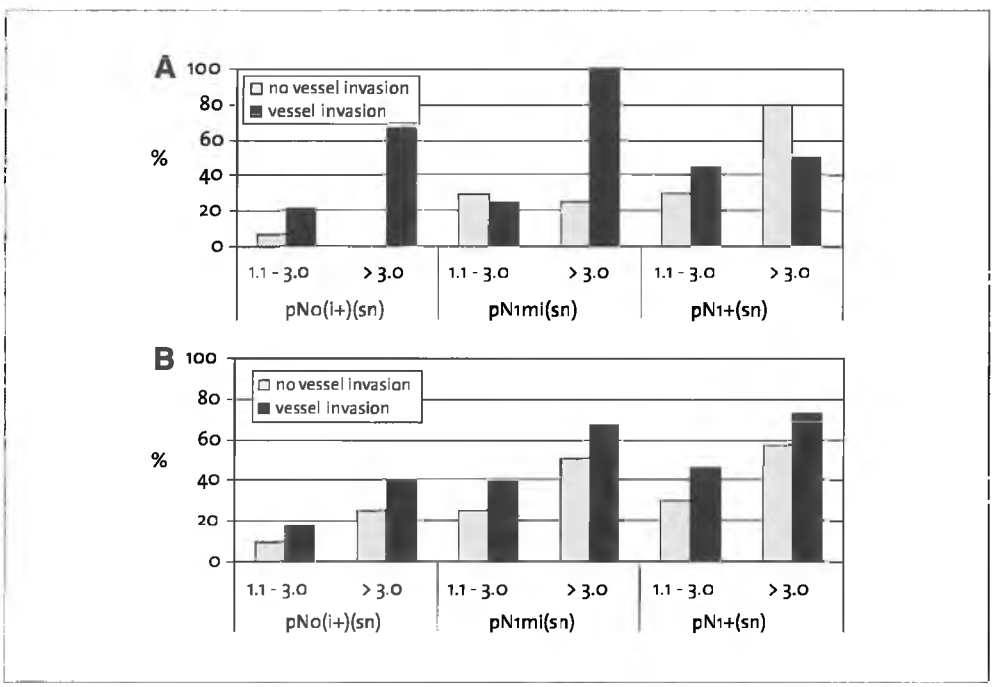


*Figure 5a. Observed proportion (%) of positive non-SNs in relation to primary tumor size, pN(sn) and lymph and/or blood vessel invasion. Figure 5b. Model-based predicted proportion (%) of positive non-SNs in relation to primary tumor size, pN(sn) and lymph and/or blood vessel invasion.*

metastasis in the SN is around 10 - 15 percent.[3] This meta-analysis was not based on individual patient data and therefore, as not all studies contained details of the subgroup categorization, the investigators were not able to perform any other quantitative analyses that might have predicted the occurrence or absence of metastases in the non-SNs.

In our study, we observed that 14.6% of patients with isolated tumor cells in the SN did have non-SN involvement and 28.6% of patients with micro-metastasis, compared to 38.0% of patients with macro-metastasis in the SN. Obviously, patient selection (T1 versus T1/2 tumors) and differences in pathology protocols may account for some of the differences between reported detection rates.

In this present study, we demonstrated that apart from the size of SN metastasis, the primary tumor size and the presence or absence of lymph and/or blood vessel invasion were also associated with the occurrence of metastases in the non-SNs. However, no single variable predicted non-SN metastases with sufficient accuracy that ALND might safely be omitted. Others also reported similar associations, but only few performed additional analyses on whether a combination of factors would better distinguish between high-risk and low-risk categories[6-10].

In two small studies the combination of two risk factors was analyzed, showing that none of the patients who had small SN metastasis (≤ 2 mm including isolated tumor cells) in combination with a small primary tumor size (≤ 2 cm in diameter) did have non-SN metastases[11,12]. In a large study by Weiser et al., none of 24 patients with three predictive factors (tumor size ≤ 1 cm, SN with isolated tumor cells or micrometastasis, and absence of lymphovascular invasion) had non-SN metastases, whereas 58% of patients with none of the favorable factors had disease in the non-SN[13]. Unfortunately, 95% Cis were not reported, so it remains unclear whether upfront decision making based on these three factors is fully reliable. In this latter study, they reported that selection by the two aforementioned variables only was not possible, as 26% of patients with favorable SN metastasis and tumor size had non-SN metastases.

As shown in table 4 and figures 5, one extra risk factor multiplied the percentage of the observed as well as the model-based predicted proportion of positive non- SNs on average by three times. The OR for SN micrometastases compared to SN isolated tumor cells was 3.1, and for SN macro-metastases versus SN isolated tumor cells was 4.0. The OR for tumors larger than 3 cm compared to tumors smaller than 3 cm was 3.1, and the OR for lymph and/or blood vessel invasion (presence versus absence) was 2.0.

However, despite a significant association between the presence of non-SN metastases and size of SN metastases, primary tumor size and lymph and/or blood vessel invasion, we were not able to identify a specific group of patients with a 'positive' SN in whom the incidence of positive non-SNs could be reliably predicted to be less than 5%. So although we observed that the risk of positive non-SNs decreased with reduced number

of risk factors, the predicted proportion of patients with positive non-SNs was still 9.7% for patients who had as the only risk factor the presence of isolated tumor cells. It can be hypothesized, that with a larger study population, the confidence intervals may become smaller, supporting in due time the concept that completion ALND may safely be omitted in patients with isolated tumor cells in the SN who have small primary tumors (possibly < 1.0 cm) without lymph and/or blood vessel invasion, but, definite proof could not be given in this present study including 541 eligible patients. Of note, the number of patients who might theoretically be a good candidate for omitting completion ALND was estimated to be 5.0% (11 out of 203) of patients with a positive SN.

In our study, we hypothesized that an expected detection-frequency of non-SN metastases of 5% or less would not justify a completion ALND. The limit of 5% is arbitrary, and, in fact, based on a consensus among Dutch physicians that the benefit of treatment should ideally involve at least 5% of patients[5]. However, a 5% risk assessment may be too conservative, and something closer to 10% might be more reasonable for some patients. With that in mind, the data presented in this paper suggest that patients with tumors < 1 cm, and patients with 1.1 - 3.0 cm tumors, no lymph and/or blood vessel invasion, and only isolated tumor cells in the SN could be considered for the ommission of completion ALND, since the predicted risk of non-SN involvement is 9.7% and the observed risk was 7.1%. However, as the confidence interval is still a little wide (4% - 23%) due to the small sample size, further data are eagerly awaited before definite recommendations can be made. Obviously, the proof of principle is made on axillary relapse rates and on overall survival values. In breast cancer it may require considerable time before small metastases left behind become clinically manifest as regional recurrences or the source of distant metastases. A study of SN in 243 melanoma patients had previously shown that early nodal recurrence after negative SN findings could be explained by micrometastases being overlooked at first analysis[14].

An ongoing Milanese trial (IBCSG 2301) randomly allocates breast cancer patients with micro-metastatic SNs to completion ALND or surveillance. An American study (NSABP-32) compares SN resection with conventional ALND in clinically node-negative breast cancer patients. These trials may provide greater clinical evidence for the formulation of policies on axillary sparing after a positive SN biopsy.

To this end, we conclude that completion ALND should still be recommended to all patients with a 'positive' SN, i.e. with isolated tumor cells, micro-metastases or macro-metastases, as we were not able to identify a specific group of patients with favorable primary tumor and SN characteristics in whom the incidence of positive non-SNs would reliably be predicted to be less than 5%.

## REFERENCES


1 *Miltenburg DM, Miller C, Karamlou TB, Brunicardi FC. Meta-analysis of sentinel lymph node biopsy in breast cancer. J Surg Res 1999; 84:138-142.*

2 *Van Dijck JA, Coebergh JW, Siesling S, et. al. Breast cancer in women. In: Trends of cancer in the Netherlands 1989-1998 (ed). Utrecht, the Netherlands: Association of comprehensive cancer centers/Netherlands cancer registry, 2002:31-32.*

3 *Cserni G, Gregori D, Merletti F, et. al. Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer. BJS 2004; 91:1245-1252.*

4 *Sobin LH, Wittekind C. International union against cancer. TNM classification of malignant tumors, Sixth Edition. New York: Wiley-Liss, 2002.*

5 *National Breast Cancer Organization Netherlands (2004). Guideline treatment of patients with breast cancer. Available: http://www.oncoline.nl.*

6 *Teng S, Dupont EL, McCann C, et. al. Do cytokeratin-positive-only sentinel lymph nodes warrant complete axillary lymph node dissection in patients with invasive breast cancer? Am Surg 2000; 66:574-578.*

7 *Rahusen FD, Torrenga H, van Diest PJ, Pijpers R, van der Wall E, Licht J, Meijer S. Predictive factors for metastatic involvement of non-sentinel nodes in patients with breast cancer. Arch Surg 2001; 136:1059-1063.*

8 *Chua B, Ung O, Taylor R, Bilous M, Salisbury E, Boyages J. Treatment implications of a positive sentinel lymph node biopsy for patients with early-stage breast carcinoma. Cancer 2001; 92:1769-1774.*

9 *Jakub JW, Diaz NM, Ebert MD, et. al. Completion axillary lymph node dissection minimizes the likelihood of false negatives for patients with invasive breast carcinoma and cytokeratin positive only sentinel lymph nodes. Am J Surg 2002; 184:302-306.*

10 *Leers MP, Schoffelen RH, Hoop JG, et. al. Multiparameter flow cytometry as a tool for the detection of micrometastatic tumour cells in the sentinel lymph node procedure of patients with breast cancer. J Clin Pathol 2002; 55:359-366.*

11 *Reynolds C, Mick R, Donohue JH, et. al. Sentinel lymph node biopsy with meta-stasis: can axillary dissection be avoided in some patients with breast cancer? J Clin Oncol 1999; 17:1720-1726.*

12 *Chu KU, Turner RR, Hansen NM, Brennan MB, Bilchik A, Giuliano AE. Do all patients with sentinel node metastasis from breast carcinoma need complete axillary node dissection? Ann Surg 1999; 229:536-541.*

13 *Weiser MR, Montgomery LL, Tan LK, et. al. Lymphovascular invasion enhances the prediction of non-sentinel node metastases in breast cancer patients with positive sentinel nodes. Ann Surg Oncol 2001; 8:145-149.*

14 *Gershenwald JE, Colome MI, Lee JE, et. al. Patterns of recurrence following a negative sentinel lymph node biopsy in 243 patients with stage I or II melanoma. J Clin Oncol 1998; 16:2253-2260.*

# CHAPTER 3

Chapter 3

# More tumor-affected lymph nodes because of the sentinel lymph node procedure but no stage migration, because the 2002 TNM classifies small tumor deposits as pathological No breast cancer

*Marieke J. Bolster, Peter Bult, Carla A.P. Wauters, Luc J.A. Strobbe, Petronella G.M. Peer, Theo Wobbes, Vivianne C.G. Tjan-Heijnen*

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## ABSTRACT

### Background

Intensified examination of the sentinel lymph node (SN) may result in increased detection of tumor-affected lymph nodes. The authors of this report hypothesized that the introduction of the SN procedure has led to a stage migration because of the intensified work-up of the SNs by the pathologists.

### Methods

After the introduction of the SN procedure, 360 patients with operable breast cancer were included prospectively from 2 large hospitals (A and B). The prospectively included patients ('SN era') were compared with 88 historical controls from the year 1994, who were diagnosed with primary breast cancer before the introduction of the SN procedure.

### Results

After correction for classical clinical and pathologic prognostic factors in a multiple logistic regression analysis, the detection frequency of lymph node involvement was significantly higher in the SN era group compared with the historical controls ($P = 0.04$). However, when using the 2002 TNM classification, in which isolated tumor cells (≤ 0.2 mm) were categorized as node-negative disease, no stage migration was observed ($P = 0.98$). Also, when analyzing both hospitals (hospital A versus hospital B) separately with respect to lymph node involvement, there was no difference, between the SN era and the historical controls ($P = 0.79$ and 0.69, respectively). This remained non significant after the analysis was corrected for patient and primary tumor characteristics ($P = 0.85$ and 0.66, respectively).

### Conclusion

Introduction of the SN procedure has led to the detection of more tumor-affected lymph nodes because of the intensified workup of the SNs by the pathologists. However, stage migration did not occur when tumor deposits of ≤ 0.2 mm were categorized as lymph node-negative disease, according to the 2002 TNM classification.

## INTRODUCTION

The axillary lymph node status is still considered to be the most important prognostic factor in primary breast cancer. During recent years the sentinel lymph node (SN) procedure was shown to be a reliable strategy to replace axillary lymph node dissection (ALND) in selected patients with primary breast cancer[1].

Approximately 60 - 70% of breast cancer patients had node-negative disease before the introduction of the SN biopsy[2]. Hence, it was assumed that a completion ALND could be avoided in these 60 - 70% of patients with early breast cancer.

Obviously, a reliable examination of the SN is crucial, as a false-negative finding may result in under-treatment both locally and systemically. Consequently, pathologists have intensified the examination of the SN by using serial sectioning (SS) and immunohistochemistry (IHC), whereas previously, the axillary lymph nodes were examined by haematoxylin-eosin (H&E) in 1 or 2 slides only. However, intensified examination of the SN may result in increased detection of tumor-affected lymph nodes. Therefore, we decided to test the hypothesis that the introduction of the SN procedure has led to a stage migration due to the intensified work-up of the SN by the pathologist.

## PATIENTS AND METHODS

After the introduction of the SN procedure, patients with operable breast cancer were included prospectively during 18 months in the years 2002 and 2003 from 2 large hospitals; a university and a community teaching hospital. A SN biopsy was performed in cases with a clinical tumor size of 5 cm or less, with no clinical proof of axillary lymph node metastases, no evidence of multifocality of the primary breast tumor, no radiotherapy of the breast or axilla in the past, and no use of neo-adjuvant systemic therapy. The remaining patients underwent an immediate ALND.

The prospectively included patients ('SN era'), that is, patients with a SN biopsy with or without a completion ALND or with an immediate ALND were compared with historical controls, who were diagnosed with primary breast cancer before the SN introduction, and who had undergone an immediate ALND. In the 2 hospitals, SN biopsies have been performed since 1997. Therefore, patients who had surgery in the year 1994 were selected as historical controls, to prevent misinterpretations from gradually introduced changes in pathology procedures. For both groups, patients who had an ipsilateral breast carcinoma in the past (prior ALND) or who were classified as having M1- or T4-disease[3] were excluded.

The surgical procedure was in accordance to the Dutch guideline for treatment of breast cancer[4]. 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 pathology processing technique of the

SN was according to the Dutch guideline for treatment of breast cancer[4], that is, at least 3 levels at, at least 150 micron interval had to be examined with H&E. In hospital A, the minimal recommendation was met as 3 levels of the SN were routinely examined, whereas in hospital B 7 additional levels (10 in total) were routinely examined in all patients. In the absence of apparent metastases with H&E examination, IHC examination (CAM5.2) was performed in both hospitals on all levels, again in agreement with the national guideline.

The nodes in the immediate ALND and in the completion ALND specimen were totally embedded when 0.5 centimeter or smaller, bisected when between 0.5 and 1.0 centimeter, or sliced in 3 or more slices when larger than 1.0 centimeter. The paraffin block was examined at 1 (hospital A) or 2 levels (hospital B) with H&E staining. IHC examination was not routine used. The nodes in the ALND specimen in the pre-SN period were per hospital examined similarly as the ALND specimen in the SN era.

The prospectively and retrospectively collected data included the lymph node status with number of nodes examined, number of positive nodes, size of nodal metastases, and the detection method (H&E/IHC). The slides of the lymph nodes from the historical controls and the first part of the cases from the SN-era were revised in both hospitals (P.B. and C.W.). In 2002 the 6th edition of the TNM classification was introduced and there was a slight change in the classification of lymph node involvement with the previous version, necessitating review of cases which were classified according to the 5th TNM classification. That is, solitary tumor cells or tumor cell clusters with a size of 0.2 mm or less are classified as isolated tumor cells (pNo(i+)), metastases more than 0.2 mm and maximally 2.0 mm in size as micro-metastases (pN1mi), and metastases > 2.0 mm in size as macro-metastases. Further, final nodal stage refers to the final pTNM stage including both the SN and, if applicable, the non-SNs findings[3]. Also primary tumor characteristics (localization, tumor size, histology, histological grade, lymph and/or blood vessel invasion, hormone receptor status), patient characteristics (age) and information on the surgical procedure (SN biopsy with or without a completion ALND, immediate ALND, lumpectomy or mastectomy and various combinations) were collected. As there appeared to be a difference in hormonal receptor status and presence of vessel invasion between the 2 time cohorts, we revised the slides of the primary tumor of all historical controls prevent a classification bias over time (for example changes in cut-off values for defining ER/PgR status). The revision did not reveal significant changes (data not shown). In the tables, only revised data are shown.

***Statistical analyses***

The final nodal stage was dichotomized into node-negative disease and node-positive disease. The difference in the occurrence of node-negative disease in the SN era and among historical controls was tested with a chi-square test. With multiple logistic regression analysis this difference was corrected for age and the tumor characteristics tumor size, histological grade, hormone-

receptor status, and lymph and/or blood vessel invasion. To determine whether a difference in lymph node involvement was caused by variation in the individual hospitals, the registered data of each hospital were also analyzed separately. Two options were considered for isolated tumor cells: in one option isolated tumor cells were considered as node-negative disease, in the other option as node-positive disease. A P-value < 0.05 was considered statistically significant.

## RESULTS

### *Patient inclusion*

In total, 360 patients were prospectively included from the 2 hospitals A and B. Of these, 284 patients underwent a SN biopsy

| Patient/tumor characteristics | SN era n = 360 (%) | Historical controls n = 88 (%) | P-value |
|---|---|---|---|
| **Age median (range) (years):** | 57 (28-96) | 55 5 (35-82) | 0.30 |
| **Tumor size (cm)#** | | | 0.36 |
| ≤ 1.0 | 62 (17.4) | 10 (11.4) | |
| 1 1 - 2.0 | 131 (36.8) | 37 (42 0) | |
| 2.1 - 3.0 | 94 (26.4) | 26 (29.5) | |
| 3.1 - 4.0 | 31 (8.7) | 10 (11 4) | |
| 4.1 - 5.0 | 17 (4.8) | 1 (1.1) | |
| > 5.0 | 21 (5.9) | 4 (4.6) | |
| **Histological grade##** | | | 0.36 |
| I | 68 (19.3) | 16 (18.2) | |
| II | 164 (46 6) | 35 (39 8) | |
| III | 120 (34.1) | 37 (42.0) | |
| **Hormone-receptor status###** | | | < 0.0001 |
| ER and/or PgR + | 318 (89.8) | 62 (73.8) | |
| ER and PgR - | 36 (10.2) | 22 (26.2) | |
| **Lymph and/or blood vessel invasion####** | | | 0.01 |
| No | 246 (70.7) | 48 (56.5) | |
| Yes | 102 (29.3) | 37 (43 5) | |

***Table 1. Patient and primary tumor characteristics***

# In 4 patients pathological tumor size was missing, ## In 8 patients histological grade was missing, ### In 10 patients hormone receptor status was missing; ER: estrogen receptor; PgR: progesterone receptor, #### In 15 patients lymph and/or blood vessel invasion was missing.

(with or without a completion ALND), while 76 patients had an immediate ALND because of contraindications for a SN biopsy. Eighty eight patients were retrospectively included with an immediate ALND from the same 2 hospitals, as historical controls. These were 88 consecutive patients who underwent surgery in the year 1994.

***Patient and primary tumor characteristics***

There were no differences in age, tumor size, or histological grade between the cohort of the SN era compared to the cohort of the historical controls. However, in the SN era more patients had a hormone receptor positive tumor, and patients had less often lymph and/or blood vessel invasion compared to the historical controls (table 1).

***Axillary lymph node involvement***

First, we analyzed the rates of having no axillary lymph node involvement, defined as having no macro-metastasis, no micro-metastasis, nor isolated tumor cells in either the SN or/and ALND, actually, according to the previous TNM classification[5]. In the SN era, 175 (49%) patients, of the total of 360 patients, had no lymph node involvement, compared to 49 (56%) of the 88 historical controls (P = 0.23). However, after correction for age, tumor size, histological grade, hormone receptor status, and lymph and/or blood vessel invasion, we observed that the 2 cohorts now showed a significant difference in lymph node involvement (P = 0.04), which was more often seen in the patients from the SN era (figure 1).

***Individual hospitals***

To determine whether the observed difference in lymph node involvement was caused by variation in one of the individual hospitals, the registered data of each hospital were analyzed separately. For hospital A, the rates of lymph node involvement were quite comparable for the SN era and the historical controls (P = 0.62). On the contrary, in hospital B, 32% of patients had no lymph node involvement in the SN era, compared to 49% of patients in the historical cohort (P = 0.04).

When looking at patient and primary tumor characteristics, hospital A showed a significant difference in hormone receptor status and lymph and/or blood vessel invasion, when comparing patients from the SN era with the historical controls. In the SN era more patients had a hormone receptor positive tumor, and tumors showed less lymph and/or blood vessel invasion. Tumor size and histological grade were not significantly different. Hospital B showed a significant difference in tumor size and hormone receptor status. In the SN era more patients had a hormone receptor positive tumor and more patients had a tumor with a small tumor size (≤ 1.0 cm and 1.0 - 2.0 cm) compared to the historical controls. Histological grade and lymph and/or blood vessel invasion were not significantly different. After correction for patient and primary tumor characteristics, the difference between the 2 cohorts in having no lymph node involvement remained not significant in hospital A (P = 0.49) (figure 2), whereas the difference in hospital B remained significant (P = 0.005) (figure 3).

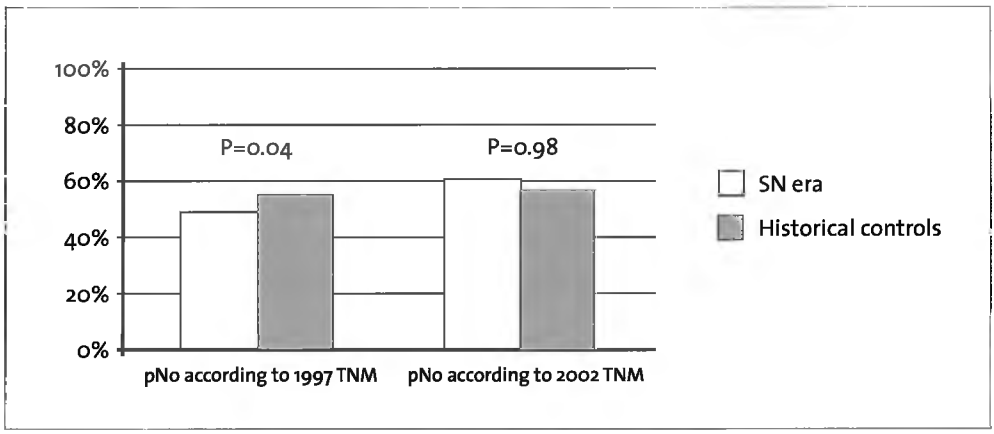


*Figure 1. Node negative rate according to 1997 TNM and 2002 TNM classification (Multivariate analyses)*

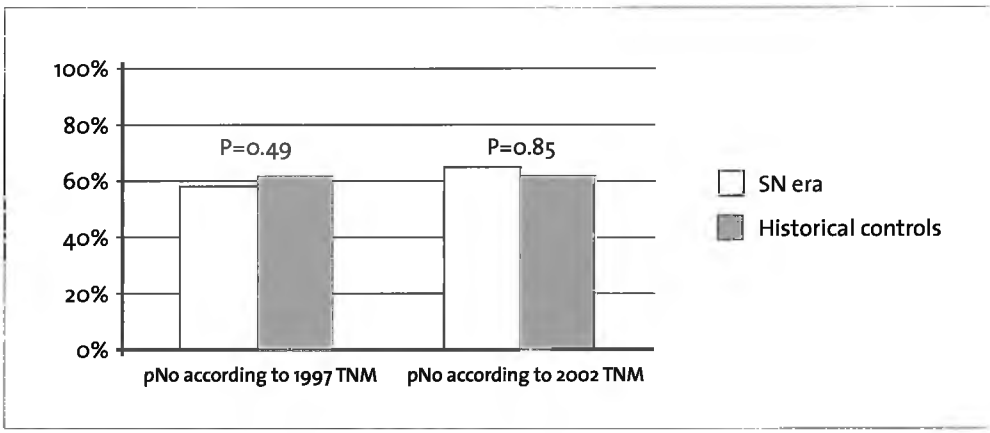


*Figure 2. Hospital A: node negative rate according to 1997 TNM and 2002 TNM classification (Multivariate analyses)*

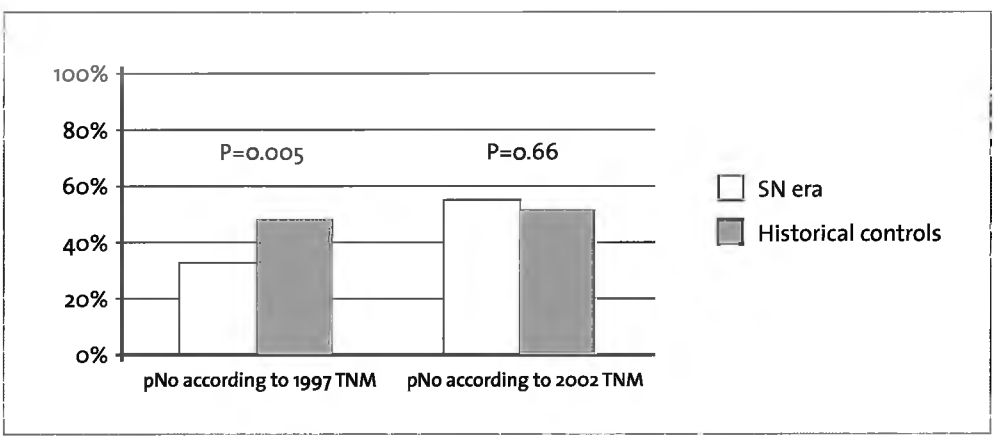


*Figure 3. Hospital B: node negative rate according to 1997 TNM and 2002 TNM classification (Multivariate analyses)*

### *Isolated tumor cells considered as node-negative disease*

Since the clinical relevance of isolated tumor cells is subject of debate, the above analyses were again performed now with isolated tumor cells considered as node-negative disease (N0), whereas only micro- or macro-metastasis as node positive (N1 and higher) disease, as has been introduced by the 2002 TNM classification[3]. When looking at the axillary lymph node status, there was hardly any difference now between the SN era and the historical controls. Two hundred nineteen (61%), out of 360, patients had no lymph node involvement in the SN era, compared to 50 (57%), out of 88, patients in the historical cohort (P = 0.49). After correction for patient and primary tumor characteristics, it remained a not significant difference (P = 0.98) (figure 1).

As shown in figures 2 and 3, there was also no difference, between the SN era and the historical controls, in having no lymph node involvement in hospital A, as well in hospital B (P = 0.79 and 0.69, respectively). Also after correction for patient and primary tumor characteristics, there was no difference in hospital A, nor in hospital B (P = 0.85 and 0.66, respectively).

## DISCUSSION

In this study we examined whether the introduction of the SN procedure has led to a stage migration due to the intensified work-up of the SN by the pathologist, when compared to patients who had underwent an immediate ALND.

In our cohort study, including 360 patients from the SN era and 88 historical controls, it was shown that after correction for classical clinical and pathologic prognostic factors, the detection frequency of lymph node involvement was significantly higher in the SN era compared to the historical controls (P = 0.04). However, when using the 2002 TNM classification, with isolated tumor cells being categorized as node-negative disease, there was no stage migration observed (P = 0.98).

The data of both hospitals were also analyzed separately to determine whether the observed difference in having no lymph node involvement was caused by variation in the individual hospitals. We concluded in a previous paper that there are differences in SN pathology protocols between the hospitals, which do lead to differences in SN findings[6]. In hospital A 3 levels of the SN were examined pathologically, whereas in hospital B at least 7 additional levels were examined. In hospital B, more patients were diagnosed with a positive SN (P < 0.001) as compared to hospital A, but mainly due to increased detection of isolated tumor cells.

Many authors hypothesized that due to a more complete and intensified pathologic examination of the SN, more tumor-affected lymph node cases would be detected, with improved staging accuracy and stage migration as a consequence[7-12]. But, of importance, these publications refer to the period before the TNM classification was revised. As it was foreseen that due to the introduction of the SN procedure there would be mainly an increased detection of isolated tumor cells,

the TNM classification was revised in 2002[3]. Before revision, isolated tumor cells were not distinguished from micro-metastases; both were being classified as 'pN1a'. But, as the prognostic significance of isolated tumor cells was debated and to enable comparisons of treatment results, it was then agreed to classify isolated tumor cells as node-negative disease, whereas micro-metastases still as node-positive disease[13]. We previously discussed this dilemma of classification versus clinical relevance[14].

So, in this present study we made a difference between isolated tumor cells and micro-metastasis. We analyzed isolated tumor cells as 'node-positive' disease, according to the 1997 TNM classification and because all these patients underwent a completion ALND, and we considered isolated tumor cells as 'node-negative' disease according to the 2002 TNM classification. Stage migration was seen when classifying according to 1997 TNM, but was prevented by classifying according to 2002 TNM, when determining the axillary lymph node status.

The occurrence of SN and non-SN metastases is associated with the primary tumor size and with lymphovascular invasion. These are the most powerful variables that are independently predictive of positive SN and non-SN results[15-17]. There was no difference in tumor size between our 2 study cohorts. However, we observed that in the SN era more patients had a hormone receptor positive tumor (90% versus 74%), and patients from the SN era had less often lymph and/or blood vessel invasion (29% versus 44%) compared to the historical controls. It is unclear, whether this change is a true change or would reflect in part changes in pathology protocols over time. To prevent bias from the latter possibility, we revised the slides of the primary tumor of all historical controls. This revealed no major differences. In part, the lower rate of hormone receptor positivity in the historical controls, compared to the SN era patients, might be explained by a higher rate of grade III tumors (42% versus 34%, respectively). Of note, the results were corrected for these differences in the multivariate analysis.

Of course, many questions remain yet unsolved. Most importantly: is the presence of isolated tumor cells in axillary lymph nodes of independent prognostic relevance? So far, data are lacking or contradicting. For that reason, we are now conducting a very large cohort study in several thousands of breast cancer patients to address this major question: 'Micro-metastasis or isolated tumor cells: relevant and robust or rubbish?' in the Dutch MIRROR study.

To this end, this is the first study assessing stage migration by the introduction of the SN procedure, while using the new 2002 TNM classification. We conclude that the introduction of the SN procedure has led to the detection of more tumor-affected lymph nodes due to the intensified work-up of the SN by the pathologist. However, as these were mainly isolated tumor cells, no stage migration occurred, because TNM classification has been changed since the introduction of the SN procedure (2002), now classifying isolated tumor cells as node-negative disease with a cut-off value of 0.2 millimeters.

## REFERENCES


1 *Miltenburg DM, Miller C, Karamlou TB, et al. Meta-analysis of sentinel lymph node biopsy in breast cancer. J Surg Res. 1999; 84:138-142.*

2 *van Dijck JA, Coebergh JW, Siesling S, et al. Breast cancer in women. In: Trends of cancer in the Netherlands 1989-1998 (ed). Utrecht, the Netherlands: Association of comprehensive cancer centers/Netherlands Cancer Registry, 2002:31-32.*

3 *Sobin LH, Wittekind C. International Union Against Cancer. TNM classification of malignant tumors. 6th ed. New York: Wiley-Liss, 2002.*

4 *National Breast Cancer Organization Netherlands Guideline treatment of patients with breast cancer, 2004. Available via http://www.oncoline.nl*

5 *Sobin LH, Wittekind C. International Union Against Cancer. TNM classification of malignant tumors. 5th ed. New York: Wiley-Liss, 1997.*

6 *Bolster MJ, Bult P, Schapers RF, et al. Differences in sentinel lymph node pathology protocols lead to differences in surgical strategy in breast cancer patients. Ann Surg Oncol. 2006;13:1466-1473.*

7 *Giuliano AE, Dale PS, Turner RR, et al. Improved axillary staging of breast cancer with sentinel lymphadenectomy. Ann Surg. 1995;222:394-401.*

8 *Jansen L, Nieweg OE, Valdes Olmos RA, et al. Improved staging of breast cancer through lymphatic mapping and sentinel node biopsy. Eur J Surg Oncol. 1998;24: 445-446.*

9 *DiFronzo LA, Hansen NM, Stern SL, et al. Does sentinel lymphadenectomy improve staging and alter therapy in elderly women with breast cancer? Ann Surg Oncol. 2000;7:406-410.*

10 *de Widt-Levert LM, Tjan-Heijnen VC, Bult P, et al. Stage migration in breast cancer: surgical decisions concerning isolated tumour cells and micro-metastases in the sentinel lymph node. Eur J Surg Oncol. 2003;29: 216-220.*

11 *Galimberti V, Veronesi P, Arnone P, et al. Stage migration after biopsy of internal mammary chain lymph nodes in breast cancer patients. Ann Surg Oncol. 2002;9: 924-928.*

12 *van der Heiden-van der Loo M, Bezemer PD, Hennipman A, et al. Introduction of sentinel node biopsy and stage migration of breast cancer. Eur J Surg Oncol. 2006; 32:710-714*

13 *Hermanek P, Hutter RV, Sobin LH, et al. International Union Against Cancer. Classification of isolated tumor cells and micrometastasis. Cancer. 1999;86:2668-2673.*

14 *Tjan-Heijnen VC, Bult P, de Widt-Levert LM, et al. Micrometastases in the sentinel lymph node; a classification and treatment dilemma in breast cancer. Breast Cancer Res Tr. 2001; 70:81-88.*

15 *Chen M, Palleschi S, Khoynezhad A, et al. Role of primary breast cancer characteristics in predicting positive sentinel lymph node biopsy results: a multivariate analysis. Arch Surg. 2002;137:606-610.*

16 *Tan YY, Wu CT, Fan YG, et al. Primary tumor characteristics predict sentinel lymph node macrometastasis in breast cancer. Breast J. 2005;11:338-343.*

17 *Bolster MJ, Peer PG, Bult P, et al. Risk factors for non-sentinel lymph node metastases in patients with breast cancer. The outcome of a multi-institutional study. Ann Surg Oncol. 2007;14:181-189.*

# CHAPTER 4

Chapter 4

# Differences in sentinel lymph node pathology protocols lead to differences in surgical strategy in breast cancer patients

*Marieke J. Bolster, Peter Bult, René F.M. Schapers, Jos W.R. Meijer, Luc J.A. Strobbe, Charles L.H. van Berlo, Jean H.G. Klinkenbijl, Petronella G.M. Peer, Theo Wobbes, Vivianne C.G. Tjan-Heijnen*

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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). At present, therefore, various hospitals use different SN pathology protocols of which the effect has not been fully elucidated. We hypothesized that differences between hospitals in SN pathology protocols affect on subsequent surgical treatment strategies.

### Methods

Patients from 4 hospitals (A-D) 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. In the absence of apparent metastases with Hematoxylin and Eosin examination, immunohistochemical examination was performed in all 4 hospitals.

### Results

In total, 541 eligible patients were included. In hospital D, more patients were diagnosed with a positive SN ($P < 0.001$) as compared to hospitals A, B, and C, mainly due to increased detection of isolated tumor cells. This led to more completion axillary lymph node dissections (ALND) in hospital D (66.3% of patients, ($P < 0.0001$), compared to 29.0% in hospitals A, B, and C combined. Positive non-SNs were detected in 13.9% of patients in hospital D compared with 9.7% in hospitals A, B, and C ($P = 0.70$). That is, in 52.4% of patients in hospital D a negative completion ALND was performed compared with in 19.3% of patients in hospitals A, B, and C combined.

### Conclusion

Differences in SN pathology protocols between hospitals do have a substantial effect on SN findings and subsequent surgical treatment strategies. Whether ultra-staging and, thus, additional surgery can offer better survival remains to be determined.

## INTRODUCTION

The axillary lymph node status is still the most important prognostic factor in primary breast cancer. During recent years, the sentinel lymph node (SN) procedure was shown to be a reliable strategy to replace axillary lymph node dissection (ALND) in selected patients with primary breast cancer[1]. On the basis of 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[2].

Obviously, a reliable examination of the SN by the pathologist is crucial, because a false-negative finding may result in under-treatment both locally and systemically. Consequently, pathologists have intensified the examination of the SN by using serial sectioning (SS) and immunohistochemistry (IHC), whereas previously, the axillary lymph nodes were examined by haematoxylin-eosin (H&E) in 1 or 2 slides only. In the past decade a lot of research focused on this topic and this was summarized in an excellent review. It was shown that an intensified examination of the SN results in a significant increased detection of isolated tumor cells and micrometastases[3]. Unfortunately, internationally, there is no consensus on the SN pathology protocol to be used[4-5]. At present, therefore, various hospitals use different SN pathology protocols.

So far, there are no data on whether differences in SN pathology protocols have an impact on subsequent surgical treatment strategies. In our region, we prospectively collected clinical and pathological data on breast cancer patients who underwent a SN procedure. In the 4 involved hospitals, different pathology protocols existed. Therefore, we decided to test the hypothesis that differences in SN pathology protocols between hospitals would lead to different numbers of completion ALND performed, of which the relevance was aimed to be determined.

## PATIENTS AND METHODS

Patients from 4 hospitals (A, B, C, and D) were prospectively registered when they underwent an SN biopsy because of a cytological or histological proven invasive breast cancer with a clinical tumor size of 5 cm or less. Patients were excluded from a SN biopsy when there was clinical proof of axillary lymph node metastases, multifocality in the primary breast tumor or radiotherapy 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[6], 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 and hormone receptor status),

patient characteristics (age) and information on the surgical procedure (SN biopsy with or without ALND, lumpectomy or mastectomy, and various combinations) were collected.

The surgical procedure was, in all 4 hospitals, in accordance to the Dutch guideline for treatment of breast cancer[7]. SN localization was performed by 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 pathology procedure for the SN examination is also described in the Dutch guideline for treatment of breast cancer. However, in this guideline only the minimal criteria are described. Pathologists are 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. These minimal recommendations actually led to quite different local pathology protocols. In hospitals A, B, and C, 3 levels of the SN were pathologically examined. 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.

All lymph nodes in the ALND specimen were examined. In hospital B at least 3 levels were examined with H&E and IHC. In hospital D the nodes were examined at least at 2 levels with H&E, and in hospitals A and C at 1 level. In hospitals A, C, and D IHC examination was used only when H&E examination was not conclusive.

According to the international TNM-classification 2002, isolated tumor cells, micro-metastases, and macro-metastases were classified as follows: isolated tumor cells [pNo(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)]. In this article we added: pN1+, which refers to pN1a and higher pN positive stages.

### *Statistical analyses*

The results of the 4 hospitals concerning SN findings, performance of completion ALND, and non-SN findings after a positive SN were compared by using chi-square tests. The differences in detecting a positive SN between the 4 hospitals were corrected for patient and primary tumor characteristics with a logistic regression analysis. A P-value < 0.05 was considered statistically significant.

## RESULTS

### *Patient characteristics*

Five hundred eighty seven patients were prospectively included. In 28 patients there was no invasive tumor-component, in 13 patients the SN was not detectable, 4 patients received neo-adjuvant systemic therapy, and 1 patient had already a proven axillary lymph node metastasis. These 46 (7.8%) patients were excluded, leaving 541 patients in our prospective database. Of the 541 eligible patients, 198 patients had surgery in hospital A, 153 patients in hospital B, 104 patients in hospital C, and 86 patients in hospital D.

| Patient/tumor characteristics | Hospital A Number of patients N = 198 (%) | Hospital B Number of patients N = 153 (%) | Hospital C Number of patients N = 104 (%) | Hospital D Number of patients N = 86 (%) |
|---|---|---|---|---|
| **Age (years)** | | | | |
| < 36 | 7 (3.6) | 5 (3 3) | 2 (1.9) | 1 (1.2) |
| 36 - < 50 | 43 (21.7) | 29 (19.0) | 27 (26 0) | 18 (20.9) |
| 50 - < 60 | 67 (33.8) | 39 (25 5) | 34 (32 7) | 33 (38 4) |
| 60 - < 70 | 43 (21.7) | 40 (26.1) | 26 (25 0) | 18 (20 9) |
| ≥ 70 | 38 (19.2) | 40 (26.1) | 15 (14 4) | 16 (18.6) |
| **Tumor size (cm)*** | | | | |
| ≤ 1.0 | 29 (14.9) | 46 (30.5) | 19 (18.6) | 25 (29.1) |
| 1 1 – 2 0 | 84 (43.1) | 70 (46 4) | 54 (52 9) | 33 (38.4) |
| 2.1 – 3 0 | 58 (29 7) | 25 (16.6) | 23 (22 6) | 16 (18 6) |
| 3.1 – 4 0 | 15 (7.7) | 8 (5 3) | 4 (3.9) | 7 (8 1) |
| 4 1 – 5.0 | 6 (3.1) | 1 (0.6) | 1 (1.0) | 3 (3.5) |
| > 5.0 | 3 (1.5) | 1 (0.6) | 1 (1.0) | 2 (2 3) |
| **Histological grade**** | | | | |
| I | 35 (17 9) | 66 (43.7) | 31 (29.8) | 26 (31.3) |
| II | 100 (51 0) | 63 (41.7) | 45 (43 3) | 34 (41.0) |
| III | 61 (31.1) | 22 (14.6) | 28 (26 9) | 23 (27.7) |
| **Hormone-receptor status***** | | | | |
| ER and/or PgR + | 182 (91.9) | 126 (82 4) | 85 (81.7) | 74 (89.2) |
| ER and PgR - | 16 (8.1) | 27 (17.6) | 19 (18.3) | 9 (10.8) |
| **Lymph and/or blood vessel invasion** | | | | |
| No | 177 (89.4) | 144 (94.1) | 92 (88 5) | 50 (58 1) |
| Yes | 21 (10.6) | 9 (5.9) | 12 (11.5) | 36 (41.9) |

***Table 1. Patient and primary tumor characteristics per hospital***

* In 7 patients pathological tumor size was missing, ** In 7 patients histological grade was missing, *** In 3 patients hormone receptor status was missing; ER: estrogen receptor; PgR: progesterone receptor.

Patient and primary tumor characteristics per hospital are listed in table 1.

### *Differences in SN findings between the 4 hospitals*

Three hundred thirty eight (62.5%) patients of the total of 541 eligible patients had a negative SN, and 203 (37.5%) a positive SN. In 54 out of 541 (10.0%) patients the SN contained isolated tumor cells, in 53 (9.8%) patients micro-metastases, and in 96 (17.7%) patients macro-metastases.

There was a significant difference in detecting a positive SN among the 4 hospitals ($P < 0.0001$). In hospital D, more patients were diagnosed with a positive SN as compared to hospitals A, B, and C ($P < 0.001$).

Of note, when looking at patient and primary tumor characteristics there were overall no large differences among the 4 hospitals that might have contributed to the difference in SN findings (table 1). However, there was a remarkable difference in documented presence of lymph and/or blood vessel invasion. Lymph and/or blood vessel invasion was seen more frequently in hospital D.

The higher incidence of a positive SN in hospital D compared with hospital A remained significant ($P < 0.001$) when corrected, with a logistic regression analysis, for patient and primary tumor characteristics. Similarly, with correction for patient and primary tumor characteristics, the higher incidence of a positive SN in hospital D compared to hospital B remained significant ($P < 0.001$), whereas the higher incidence of a positive SN in hospital D compared with hospital C could be partly explained by the presence of lymph and/or blood vessel invasion, now resulting in borderline significance for the difference in detecting a positive SN between these 2 hospitals ($P = 0.06$).

The higher incidence of a positive SN in hospital D was mainly the result of isolated tumor cells being far more often documented in patients in this hospital ($P < 0.0001$) (table 2). The detection rate of micro- and

| pN(sn) | Hospital A N = 198 (%) | Hospital B N = 153 (%) | Hospital C N = 104 (%) | Hospital D N = 86 (%) |
|---|---|---|---|---|
| pNo(sn) | 134 (677) | 117 (76.5) | 59 (56.7) | 28 (32.5) |
| pNo(i+)(sn) | 16 (8.1) | 4 (2 6) | 4 (3 9) | 30 (34.9) |
| pN1mi(sn) | 16 (8.1) | 13 (8 5) | 10 (9 6) | 14 (16 3) |
| pN1+(sn)# | 32 (16.1) | 19 (12 4) | 31 (29 8) | 14 (16.3) |

***Table 2. Sentinel lymph node (SN) status distributed per hospital*** * pN1+: pN1a and higher pN positive stages.

macro-metastases in hospital D (32.6%) was not significantly different from the detection rate in hospitals A and C (24.2% and 39.4%) and was only slightly higher than in hospital B (20.9%) (P = 0.05).

### *Completion ALND in the 4 hospitals*

Differences in SN findings led to large differences in the numbers of completion ALND performed. In hospital D, a completion ALND after a positive SN was performed in 66.3% of patients versus, in 31.8% of patients in hospital A, 21.6% of patients in hospital B, and in 34.6% of patients in hospital C (P < 0.0001). One patient in hospital A, 3 (3/0) patients in hospital B, 5 patients in hospital C and 1 patient in hospital D did not undergo a completion ALND despite documented isolated tumor cells or micro-metastasis in the SN. In 3 patients there was no full completion ALND done, but there were non-SNs re-moved during the SN procedure, which all were negative.

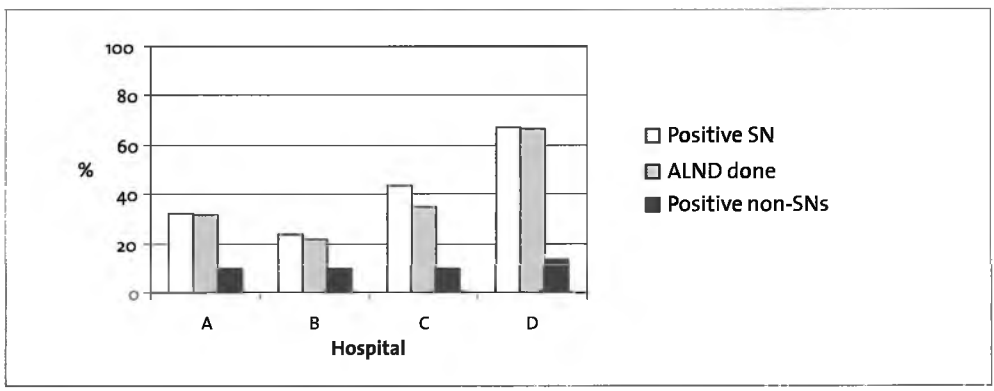


*Figure 1. Results of patients who underwent a sentinel lymph node (SN) biopsy and completion axillary lymph node dissection (ALND) per hospital.*

| Hospital | Positive SN | SNs## | ALND done | Positive non-SNs | Non-SNs## | Positive non-SNs N* (% of ALND) |
|---|---|---|---|---|---|---|
| A (N = 198) | 64 (32.3) | 1.6 | 63 (31.8) | 19 (9.6) | 9.6 | 19 (30.2) |
| B (N = 153) | 36 (23.5) | 1.7 | 33 (21.6) | 15 (9.8) | 8.6 | 15 (45.5) |
| C (N = 104) | 45 (43.3) | 1.9 | 36 (34.6) | 10 (9.6) | 11.4 | 10 (27.8) |
| D (N = 86) | 58 (67.4) | 1.9 | 57 (66.3) | 12 (13.9) | 18.0 | 12 (21.1) |

*Table 3. Number of patients who underwent a sentinel lymph node (SN) biopsy and completion axillary lymph node dissection (ALND) per hospital* * Number of patients, ## Mean number of lymph nodes removed per patient.

*Non-SN findings in the 4 hospitals*

The number of patients with positive non-SNs after a positive SN per hospital is shown in table 3 and figure 1. In hospital D, positive non-SNs were detected in 13.9% of all patients who underwent a SN biopsy, compared to 9.6% in hospital A, 9.8% in hospital B, and 9.6% in hospital C (P = 0.70).

When analyzing the number of patients with positive non-SNs after completion ALND done in case of a positive SN, we found a trend for fewer positive non-SNs in hospital D (12 out of 57 (21.1%)), compared to 19 out of 63 (30.2%) in hospital A, 15 out of 33 (45.5%) in hospital B, and 10 out of 36 (27.8%) in hospital C (P = 0.11).

The incidence of non-SN metastases was related to the size of the SN metastasis. For instance, in hospital A the SN contained isolated tumor cells in 16 patients. All 16 underwent a completion ALND and of these 16 patients, 2 (12.5%) patients had positive non-SNs. Non-SN metastases occurred in 4 (26.7%) of the 15 patients with micro-metastases in the SN. Of the 32 patients with macro-metastases in the SN, non-SN metastases occurred in 13 (40.6%) patients. In hospital D, the SN contained isolated tumor cells in 30 patients. All 30 patients underwent a completion ALND and of these 30 patients, 4 (13.3%) patients had positive non-SNs. Non-SN metastases occurred in 4 (30.8%) of the 13 patients with micro-metastases in the SN. Of the 14 patients with macro-metastases in the SN, 4 (28.6%) patients had positive non-SNs in hospital D. This indicates also for this hospital, that the incidence of non-SN metastases was related to the size of the SN metastasis, although less strong related compared to hospital A. See for more detailed information per hospital figures 2-4.

## DISCUSSION

This is the first study ever reporting that analyzed the effect of different SN pathology protocols on decision making for a completion ALND in breast cancer patients. We prospectively compared the policies in 4 large hospitals in the eastern part of the Netherlands. In agreement with recommendations of the European Organization for Research and Treatment of Cancer (EORTC)[8], the guidelines in the Netherlands advise to examine the paraffin block of the SN at, at least, 3 levels. We observed that these minimal recommendations actually led to substantial differences between the hospitals. In 1 hospital (D) the SN was routinely examined at, at least, 10 levels, whereas the other 3 hospitals routinely examined the SN at 3 levels. With similar eligibility criteria for a SN biopsy, the detection frequency of isolated tumor cells was 34.9% in hospital D compared to 8.1% in hospital A, 2.6% in hospital B, and 3.9% in hospital C. The detection frequency of micro-metastasis was 16.3% in hospital D compared to 8.1% in hospital A, 8.5% in hospital B, and 9.6% in hospital C. Other authors have found, on the basis of a study of 1959 patients, a detection frequency of isolated tumor cells of 2.9%, and a detection frequency of micro-metastasis of 8.9%[9]. Viale et al. found a detection frequency of micro-metastasis of 12.9%, on the basis of a study of 4351 patients, but no distinction was made between isolated tumor cells and micro-metastasis[10].

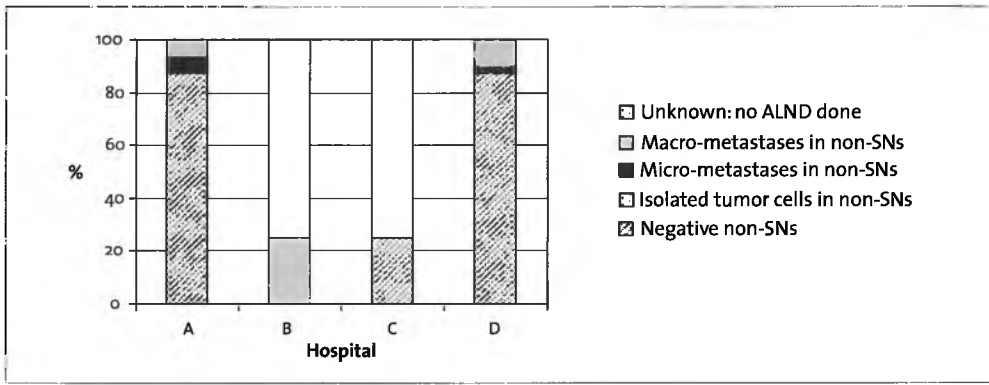


*Figure 2. Status of non-sentinel lymph nodes (non-SNs), removed during completion axillary lymph node dissection (ALND), in cases with isolated tumor cells in the sentinel lymph node (SN). In hospital A 16 of 16, in B 1 of 4, in C 1 of 4, and in D 30 of 30 cases with isolated tumor cells underwent a completion ALND.*

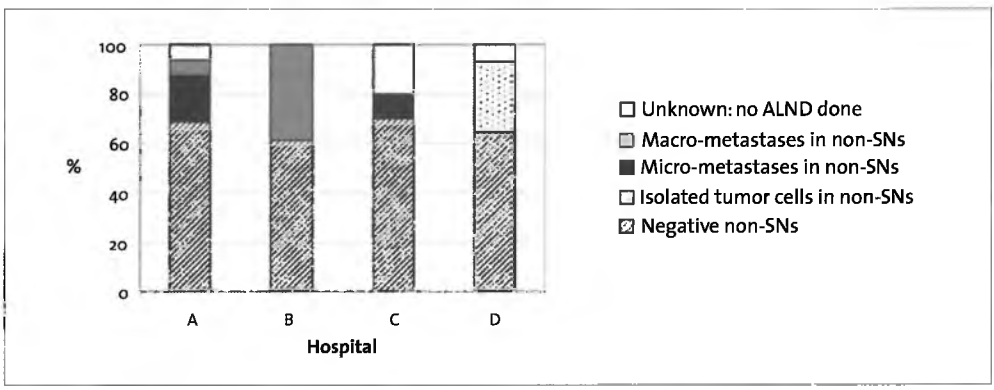


*Figure 3. Status of non-sentinel lymph nodes (non-SNs), removed during completion axillary lymph node dissection (ALND), in cases with micro-metastasis in the sentinel lymph node (SN). In hospital A 15 of 16, in B 13 of 13, in C 8 of 10, and in D 13 of 14 cases with micro-metastasis underwent a completion ALND.*

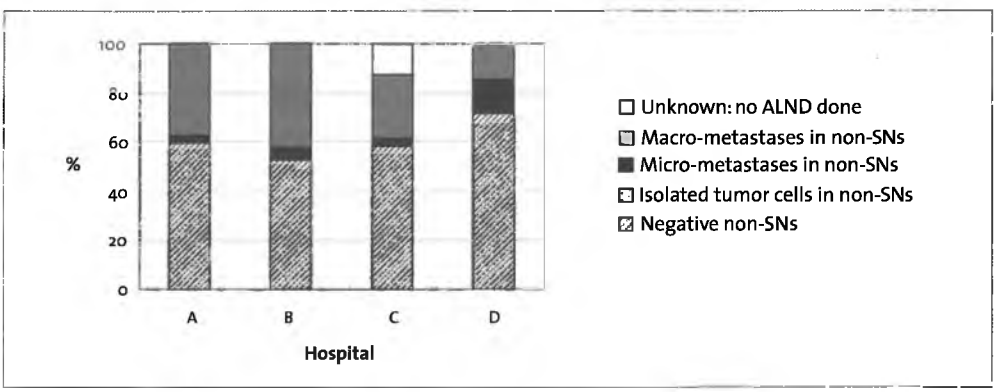


*Figure 4. Status of non-sentinel lymph nodes (non-SNs), removed during completion axillary lymph node dissection (ALND), in cases with macro-metastasis in the sentinel lymph node (SN). In hospital A 32 of 32, in B 19 of 19, in C 27 of 31, and in D 14 of 14 cases with macro-metastasis underwent a completion ALND.*

As in agreement with the guidelines, a completion ALND was recommended in case of a tumor-positive SN. An ALND was performed in 66.3% of patients in hospital D compared with 31.8% of patients in hospital A, 21.6% of patients in hospital B, and 34.6% of patients in hospital C ($P < 0.0001$).

The European working group for breast screening pathology (EWGBSP) evaluated aspects of the practice of SN pathology in breast cancer via a questionnaire based survey. The questionnaire revealed that the pathological examination of SNs throughout Europe varies considerably and is not standardized. Some countries have set up national guidelines, but many institutions have developed their own guidelines for SN processing, which are more intensive than the national guidelines recommended as a minimum, and which are frequently determined by the institution's research strategy[4,5]. The EWGBSP recommended techniques that identify metastases > 2 mm as a minimum standard (levels taken 1 mm apart should be sufficient for this), because macro-metastases have proven prognostic relevance and all should be identified. Uniform reporting of additional findings may also be important, because micro-metastases and isolated tumor cells may in the future be shown to have clinical relevance (step sections taken 200 or 250 µm apart are ideal for this purpose)[11]. The value of more detailed examination using IHC is controversial. Klevesath et al. concluded that all metastatic deposits identified by IHC were either micro-metastasis or isolated tumor cells, and until the prognostic significance of these deposits has been determined, IHC may be of limited value in the histopathological examination of the SN[12].

When looking at large trials we see the same variety. For example the important randomized trial from Veronesi et al., about 15 pairs of sections were cut at 50 µm intervals in each half of the SN, amounting to about 60 sections per SN to be examined[13], whereas in a recent study by Colleoni et al. no details concerning the pathology protocol were mentioned[9]. This shows that, apparently, the influence of pathology protocols on surgical strategies is underestimated. Looking at our study results, we found that differences in pathology protocols do, how-ever, have a large impact on surgical treatment strategies.

The occurrence of SN metastases is associated with the primary tumor size and with lymphovascular invasion. These are the most powerful variables that are independently predictive of positive SN biopsy results[14]. Tan et al. showed in their series the same results for the occurrence of SN macro-metastases[15]. Lack of progesterone receptors is inversely associated with the prevalence of SN metastases[10]. All patients in our study were prospectively registered and considered eligible to undergo a SN procedure on the basis of similar criteria. Indeed, we did not observe gross differences among the 4 hospitals in patient and primary tumor characteristics that could have contributed otherwise to the outcome parameters. Lymph and/or blood vessel invasion was seen more frequently in hospital D, but the higher incidence of a positive SN in hospital D compared with hospitals A and B

remained significant when corrected for lymphovascular invasion ($P < 0.001$). The higher incidence of a positive SN in hospital D compared with hospital C could be partly explained by the presence of lymph and/or blood vessel invasion, but still resulting in borderline significance for the difference between these hospitals ($P = 0.06$). Therefor although there were some differences in primary tumor characteristics, as shown in table 1, this does not explain the differences in SN findings between the hospitals. The differences in pathology protocols between hospitals A, B, and C versus hospital D do explain the differences in SN findings.

The big central issue is whether patients in hospital D are over-treated, or whether patients in hospitals A, B, and C are under-treated. In agreement with the guidelines a completion ALND was recommended in case of a tumor-positive SN. In hospital D an ALND was performed in 66.3% of patients who underwent an SN biopsy, with positive non-SNs in 13.9% of originally included patients. In contrast, in hospitals A, B, and C taken together, an ALND was performed in 29.0% of patients who underwent an SN biopsy, with positive non-SNs in 9.7% of originally included patients. That is, in 52.4% of patients in hospital D, a negative completion ALND was performed compared with in 19.3% of patients in hospitals A, B, and C combined. The question is whether the additional 4.2% of increased detection of non-SN disease outweighs the 37.3% of additional performance of a completion ALND. That is, the number needed to treat is 9 patients to detect 1 patient with non-SN disease.

In breast cancer it may require considerable time before small metastases left behind become clinically manifest as regional recurrences or the source of distant metastases. Also, the use of adjuvant systemic therapy has been demonstrated to decrease the risk of loco-regional recurrence. Currently, most node-negative patients undergo either adjuvant chemotherapy or hormone therapy because of their patient and primary tumor characteristics[16,17]. This may protect against the outgrowth of regional tumor cells that may be left behind.

Smidt et al. found an incidence of 0.46% axillary recurrence after a negative SN biopsy, after a median follow-up of 26 months (1 patient after 4 and 1 patient after 27 months)[18]. Pathologically each half of the SN was step-sectioned at 500 µm intervals at 3 levels. Zavagno et al. found in their series of 479 patients no clinical axillary recurrence after a median follow-up of 35.8 months[19]. For definitive SN examination, 2 sections were cut from a paraffin block at 3 levels, each 40 µm apart. Also, at Memorial Sloan-Kettering Cancer Center a low relapse rate was found. With a median follow-up of 31 months, axillary recurrence occurred in 10 out of 4008 patients (0.25%)[20]. Final pathologic examination of a frozen section-negative SN included 2 sections from each of 2 levels 50 µm apart.

Longer follow-up is required to answer the question properly[21]. The patients in the cohorts of the 4 hospitals will be observed with longer follow-up to get a definitive answer on axillary recurrence rates.

Large (randomized) prospective trials like NSABP B32 and ACOSOG Z10 may provide clinical evidence for the formulation of policies on axillary sparing after a positive SN biopsy. The NSABP B32 compares SN resection to conventional ALND in clinically node-negative breast cancer patients. An objective, among others, of ACOSOG Z10 is to estimate the prevalence and the prognostic significance of SN micro-metastases detected by IHC.

To this end, we conclude that there are differences in SN pathology protocols between hospitals, that do lead to differences in SN findings. These differences have a large effect on subsequent surgical treatment strategies. The question is whether the additional 4.2% of increased detection of non-SN disease outweighs the 37.3% of additional performance of a completion ALND. Longer follow-up will have to decide whether ultra-staging and, thus, additional surgery can offer better survival.

## REFERENCES


1 *Miltenburg DM, Miller C, Karamlou TB, Brunicardi FC. Meta-analysis of sentinel lymph node biopsy in breast cancer. J Surg Res 1999; 84:138-142.*

2 *Van Dijck JA, Coebergh JW, Siesling S, et al. Breast cancer in women. In: Trends of cancer in the Netherlands 1989-1998 (ed). Utrecht, the Netherlands: Association of comprehensive cancer centers/Netherlands Cancer Registry, 2002: 31-32.*

3 *Cserni G, Gregori D, Merletti F, et al. Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer. Br J Surg 2004; 91:1245-1252.*

4 *European Working Group of Breast Screening Pathology: Cserni G, Amendoeira I, Apostolikas N, et al. Pathological work-up of sentinel lymph nodes in breast cancer. Review of current data to be considered for the formulation of guidelines. Eur J Cancer 2003; 39:1654-1667.*

5 *Cserni G, Amendoeira I, Apostolikas N, et al. Discrepancies in current practice of pathological evaluation of sentinel lymph nodes in breast cancer. Results of a questionnaire based survey by the European Working Group of Breast Screening Pathology. J Clin Pathol 2004; 57:695-701.*

6 *Sobin LH, Wittekind C. International union against cancer. TNM classification of malignant tumors, Sixth Edition. New York: Wiley-Liss, 2002.*

7 *National Breast Cancer Organization Netherlands (2004). Guideline treatment of patients with breast cancer. Available: http://www.oncoline.nl.*

8 *Jassem J, Rutgers E, Coleman R. EORTC manual for clinical research and treatment in breast cancer. ISBN 2-930064-31-5.*

9 *Colleoni M, Rotmensz N, Peruzzotti G et al. Size of breast cancer metastases in axillary lymph nodes: clinical relevance of minimal lymph node involvement. J Clin Oncol 2005; 23:1379-1389.*

10 *Viale G, Zurrida S, Maiorano E, et al. Predicting the status of axillary sentinel lymph nodes in 4351 patients with invasive breast carcinoma treated in a single institution. Cancer 2005; 103:492-500.*

11 *Cserni G. A model for determining the optimum histology of sentinel lymph nodes in breast cancer. J Clin Pathol 2004; 57:467-471.*

12 *Klevesath MB, Bobrow LG, Pinder SE, Purushotham AD. The value of immunohistochemistry in sentinel lymph node histopathology in breast cancer. Br J Cancer 2005; 92: 2201-2205.*

13 *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; 349:546-553.*

14 *Chen M, Palleschi S, Khoynezhad A, Gecelter G, Marini CP, Simms HH. Role of primary breast cancer characteristics in predicting positive sentinel lymph node biopsy results: a multivariate analysis. Arch Surg 2002; 137:606-610.*

15 *Tan YY, Wu CT, Fan YG, et al. Primary tumor characteristics predict sentinel lymph node macrometastasis in breast cancer. Breast J 2005; 11:338-343.*

16 *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.*

17 *Goldhirsch A, Glick JH, Gelber RD, Coates AS, Thurlimann B, Senn HJ; Panel members. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 2005; 16:1569-1583.*

18 *Smidt ML, Janssen CM, Kuster DM, Bruggink EDM, Strobbe LJA. Axillary recurrence after a negative sentinel node biopsy for breast cancer: incidence and clinical significance. Ann Surg Oncol 2005; 12:29-33.*

19 *Zavagno G, Carcoforo P, Franchini Z et al. Axillary recurrence after negative sentinel lymph node biopsy without axillary dissection: a study on 479 breast cancer patients. Eur J Surg Oncol 2005; 31:715-720.*

20 *Naik AM, Fey J, Gemignani M, et al. The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection. Ann Surg 2004; 240:462-471.*

21 *Tjan-Heijnen VCG, Bult P, de Widt-Levert LM, Ruers TJM, Beex LVAM. Micrometastases in the sentinel lymph node; a classification and treatment dilemma in breast cancer. Breast Cancer Res Treat 2001; 70:81-88.*

# CHAPTER 5

Chapter 5

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

*M.J. Bolster, M.J. Pepels, C.A.P. Wauters, R.F.M. Schapers, J.W.R. Meijer, L.J.A. Strobbe, C.L.H. van Berlo, J.H.G. Klinkenbijl, T. Wobbes, A.C. Voogd, P. Bult, V.C.G. Tjan-Heijnen*

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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.

## INTRODUCTION

The axillary lymph node status is one of the most important prognostic factors in breast cancer[1]. 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[2].

Therefore, the sentinel lymph node (SN) procedure was introduced during the late 1990s[3]. 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[4].

It is shown that in patients with a negative SN the risk of a positive non-SN varies from only 2% to 9%. For instance, in the NSABP B-32 study the SN biopsy false-negative rate was 9.8%[5]. 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[3]. 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[6]. Minimal involvement was defined as metastases of ≤ 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 haematoxylin-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)[7].

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/T2-N0Mx 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[8], 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[9]. 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.

| Baseline characteristics | Hospital A Number of patients N = 131 (%) | Hospital B Number of patients N = 113 (%) | Hospital C Number of patients N = 59 (%) | Hospital D Number of patients N = 28 (%) | p-value Hospital D versus A, B and C |
|---|---|---|---|---|---|
| **Age (years)** | | | | | 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)[a]** | | | | | 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[b]** | | | | | 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[c]** | | | | | 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) | |

***Table 1. Patient and primary tumor characteristics of SN negative patients per hospital***
a: In 3 patients pathological tumor size was missing, b: In 5 patients histological grade was missing, c: In 2 patients hormone receptor status was missing; ER: estrogen receptor; PgR: progesterone receptor.

Follow-up of patients was done in line with the national guidelines[9]. 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.

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 (figure 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 to 78 months, median time to recurrence was 27 months with a range of 4 to 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[7]. Whether such a policy would reduce the number of recurrences, was the subject of this present study. In hospital D, using ultra-

| | Hospital A Number of patients N (%) | Hospital B Number of patients N (%) | Hospital C Number of patients N (%) | Hospital D Number of patients N (%) | Total Number of patients N (%) |
|---|---|---|---|---|---|
| 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) |

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

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%.

| Patient | Age-group | Tumor size (cm) | Histo-logical grade | Hormone-receptor status | Systemic therapy | Radio-therapy | 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 |

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

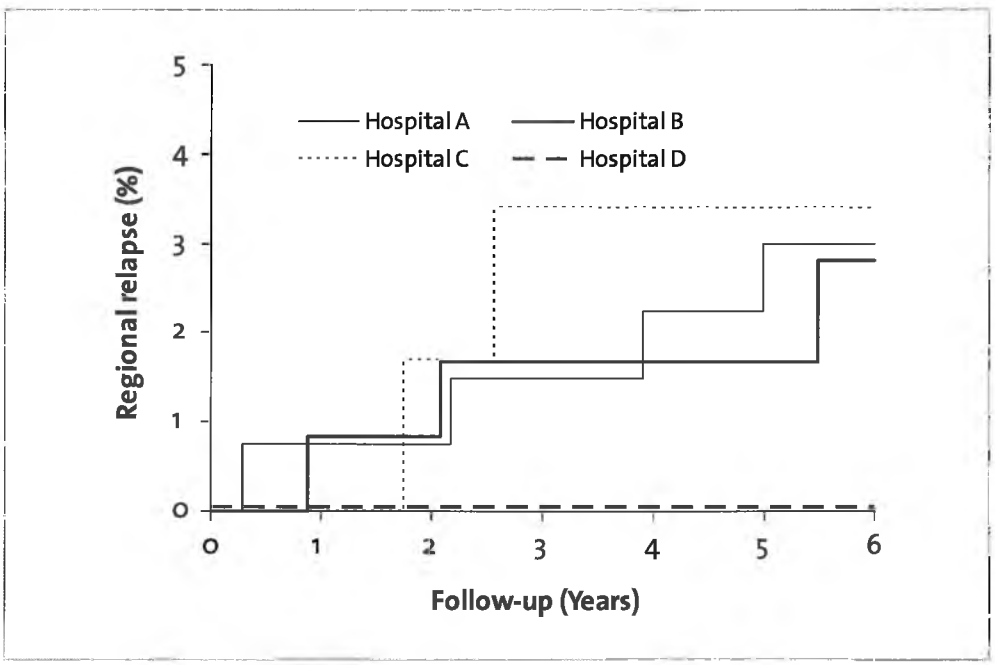


*Figure 1. Cumulative risk for regional lymph node recurrence per hospital*

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[10]. 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[9], 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[11].

In literature, many single center series and 4 randomized trials have been reported on axillary recurrence rates in patients with a negative SN[5,12-14]. The reported recurrence rates in these studies regarding SN negative patients seem 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[15]. In that particular study, approximately 15 pairs of sections were cut at 50 micrometer 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[16].

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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## 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 *Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst 2006;98:599-609*

3 *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*

4 *Van Dijck JA, Coebergh JW, Siesling S, et al. Breast cancer in women. In: Trends of cancer in the Netherlands 1989-1998 (ed). Utrecht, the Netherlands: Association of comprehensive cancer centers/Netherlands Cancer Registry, 2002: 31-32*

5 *Krag DN, Anderson SJ, Julian TB et al. Sentinel lymph node resection compared with conventional axillary lymph node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomized phase 3 trial. Lancet Oncol 2010;11:927-33*

6 *Galimberti V, Cole BF, Zurrida S, et al. Update of International Breast Cancer Study Group Trial 23-01 to compare axillary dissection versus no axillary dissection in patients with clinically node negative breast cancer and micrometastases in the sentinel node. Cancer Res 2011;71(24 Suppl):#S3-1*

7 *Bolster MJ, Bult P, Schapers RF, et al. Differences in sentinel lymph node pathology protocols lead to differences in surgical strategy in breast cancer patients. Ann Surg Oncol 2006;13:1466-73*

8 *Sobin LH, Wittekind C. International union against cancer. TNM classification of malignant tumors, Sixth Edition. New York: Wiley-Liss, 2002*

9 *National Breast Cancer Organization Netherlands (2004). Guideline treatment of patients with breast cancer. Available: http://www.oncoline.nl*

10 *de Boer M, van Deurzen CH, van Dijck JA, et al. Micrometastases or isolated tumor cells and the outcome of breast cancer. N Engl J Med 2009;361:653-63*

11 *Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005;23:7703-20*

12 *Canavese G, Catturich A, Vecchio C, et al. Sentinel node biopsy compared with complete axillary dissection for staging early breast cancer with clinically negative lymph nodes: results of randomized trial. Ann Oncol 2009;20:1001-7*

13 *Zavagno G, De Salvo GL, Scalco G, et al. A randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the Sentinella/GIVOM trial. Ann Surg 2008; 247:207-13*

14 *Veronesi U, Paganelli G, Viale G, et al. Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of a randomized controlled study. Lancet Oncol 2006;7:983-90*

15 *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*

16 *Bolster MJ, Peer PG, Bult P, et al. Risk factors for non-sentinel lymph node metastases in patients with breast cancer. The outcome of a multi-institutional study. Ann Surg Oncol 2007;14:181-89*

# CHAPTER 6

Chapter 6

# Cost-effectiveness of different strategies in axillary staging in patients with primary early stage breast cancer

*Marieke J. Bolster, Theo Wobbes, Peter Bult,*
*Gert Jan van der Wilt, Vivianne C.G. Tjan-Heijnen*

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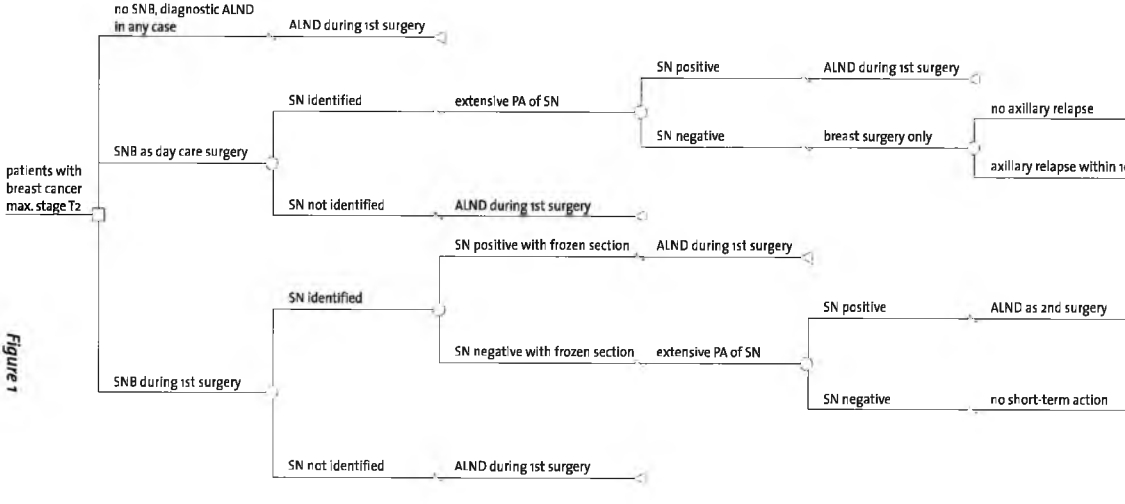
patients with breast cancer max. stage T2
no SNB, diagnostic ALND in any case
ALND during 1st surgery
SNB as day care surgery
SN identified
extensive PA of SN
SN positive
ALND during 1st surgery
SN negative
breast surgery only
no axillary relapse
axillary relapse within 1
SN not identified
ALND during 1st surgery
SNB during 1st surgery
SN identified
SN positive with frozen section
ALND during 1st surgery
SN negative with frozen section
extensive PA of SN
SN positive
ALND as 2nd surgery
SN negative
no short-term action
SN not identified
ALND during 1st surgery

*Figure 1*

ABSTRACT

**Background**

Sentinel lymph node (SN) procedure is now the gold standard for early stage clinically node-negative breast cancer patients. The primary aim of our study was to evaluate cost-effectiveness from a hospital perspective of 3 axillary surgery scenarios: conventional axillary lymph node dissection (ALND), SN procedure as day care surgery prior to breast surgery, and SN procedure during breast surgery.

**Methods**

We prospectively included 541 breast cancer patients who consecutively underwent a SN biopsy in 4 hospitals in the Netherlands. From all these, patient and tumor characteristics were registered. We also collected data on costs and volumes of surgery and pathology procedures. From a hospital perspective, costs were modeled using decision analysis methodology.

**Results**

Completion ALND was performed in 34% of patients, including 10% of patients who had SN isolated tumor cells. In this cohort, we observed that with the introduction of the SN procedure, an extra outlay of € 430 (SN during day care surgery) or € 266 (SN during breast surgery) per patient was needed. This translates into an incremental cost-effectiveness ratio of € 701 and € 440, respectively, per case of ALND avoided.

**Conclusion**

From a hospital perspective the SN procedure is associated with incremental costs, especially if done in a day care surgery procedure prior to breast surgery, and if a completion ALND is performed in patients with SN isolated tumor cells. However, with updated guidelines limiting the need of completion ALND, the SN procedure is expected to have become cost saving.

## INTRODUCTION

Breast cancer is the most common malignancy in women worldwide; this is also the case in the Netherlands[1].

Breast cancer is a substantial health care problem, not only in terms of burden of disease, but also in terms of health care costs. In 1988, the total health care costs of breast cancer in the Netherlands were estimated at 115 million Euro, which was about 13% of the total health care costs of cancer in the Netherlands[2]. Since then, health care costs are exponentially increasing.

In treating breast cancer, knowledge on the axillary lymph node status is crucial, as it gives important prognostic insight. To provide information about the lymph node status, axillary lymph node dissection (ALND) has long been considered as the gold standard. However, because of the substantial morbidity associated with an ALND and the reduced incidence of nodal involvement over time due to earlier diagnosis, the role of an ALND as part of a proper diagnostic work-up has been questioned. During the nineties of the previous century the sentinel lymph node (SN) procedure was shown to be a reliable strategy to replace the ALND in selected patients with primary breast cancer[3]. The SN is the first lymph node(s) upon which the primary tumor drains. In case the SN shows tumor involvement, a completion ALND will still be performed. However, in patients with a negative SN, completion ALND can be avoided, as in that situation the incidence of non-SN metastases is very low[3], and, more relevant, the incidence of regional recurrence without completion ALND is confirmed to be low[4].

In the Netherlands, the SN procedure was at larger scale introduced in 1998. Recently, the variation of SN implementation within the Netherlands during the years 2003-2006 was evaluated[5]. In that period, 51354 patients were newly diagnosed with invasive breast cancer, with an increase in annual incidence rates of 7% over 4 years. The analysis showed that the SN procedure was applied in 59% of clinically T1/T2 No breast cancer patients in the year 2003, increasing to 78% in the year 2006. Consequently, primary ALND decreased over time.

In a detailed prospective study in 4 Dutch hospitals on 541 consecutive patients undergoing a SN procedure, we observed a negative SN in 62% of patients and a tumor-positive SN in 38% of patients[6]. In 10% of the patients the SN contained only isolated tumor cells, in 10% micrometastasis, and in 18% of the patients the SN contained macrometastasis. Out of 203 SN-positive patients, 186 patients underwent a completion ALND, of whom 56 had positive non-SNs. That means that 66% of patients who had a SN procedure, did not have a completion ALND.

In this prospective cohort study, 3 hospitals used a standard pathology protocol with examination of the SN at 3 levels, whereas one hospital used an intensified protocol with examination of at least 7 additional levels[7]. The intensified pathology protocol resulted in a higher detection frequency of tumor-positive SNs, and consequently in the

performance of additional ALNDs (66% versus 29% of patients).

Of interest, in 1 of 4 hospitals most patients underwent the SN procedure in day care before breast surgery[8]. In that hospital a SN procedure in day care surgery was considered a preferable strategy, from a patient's point of view, because the histological diagnosis of the SN(s) is known at time of the primary surgical procedure of the breast. So, in case the SN has a proven metastasis, a completion ALND can be performed in the same surgical session as the breast operation.

The primary aim of the present cost-effectiveness study was to assess whether the extra costs of the SN procedure, with indication of ALND as used in our cohort study was offset by the reduction in number of ALND procedures. The secondary aim was to assess which SN procedure would be the most attractive from a cost viewpoint: SN in day care before the breast operation or SN combined with the breast operation.

## PATIENTS AND METHODS

### *Study design*

We conducted a cost-effectiveness analysis, estimating the incremental costs that are incurred by SN biopsy in order to avoid one extra ALND (figure 1). The analysis was conducted from a hospital perspective, taking into account direct medical costs only. A decision model was built using decision analyses DATA 4.0® software, distinguishing three different axillary strategies in breast cancer patients: (1) routine ALND (reference scenario), (2) SN biopsy in day care surgery, and (3) SN biopsy during breast surgery. To estimate potential monetary savings or monetary investments, actual resource use was assessed in a subgroup of patients from our prospective clinical study[6,7]. Not all necessary input for the model could be derived from the study results, so consequently data from other published sources were used[9-11].

### *Patients*

The analysis is to a large extent based on

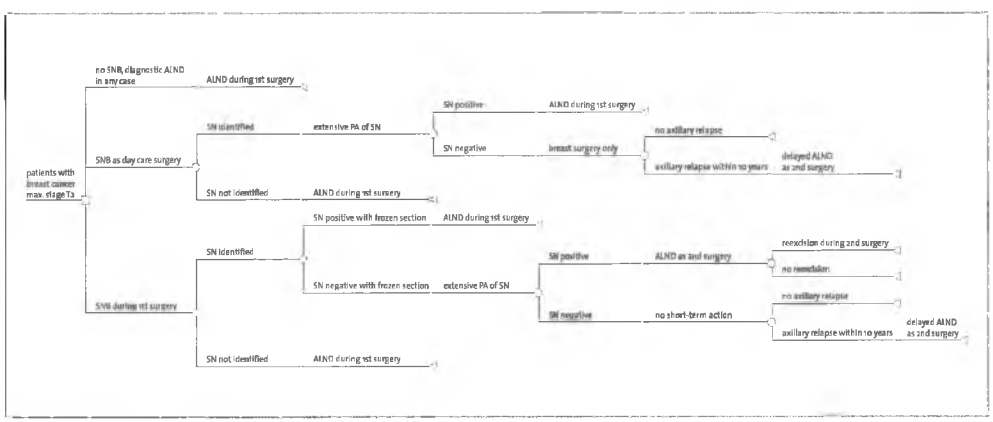


***Figure 1. Structure of the decision model, comparing routine ALND with SN biopsy in day care surgery or SN biopsy performed during surgery of the breast***

input from the clinical outcome from our aforementioned cohort study on risk factors for non-SN metastases in patients with primary breast cancer[6]. In this study, we included patients prospectively when they underwent a SN procedure because of a cytological or histological proven invasive breast cancer with a clinical tumor size of 5 cm or less during 18 months in the years 2002 and 2003 from 4 hospitals (Canisius-

| Model parameter | Base-line value | Range of values, explored in sensitivity analyses |
|---|---|---|
| Probability of identifying SN | 0 98 | 0.80-1 00 |
| Probability of a positive SN | 0 37 | 0.25-0.75 |
| Probability of no axillary relapse | 0.99 | 0.80-1.00 |
| Probability of a positive SN after intra-operative diagnosis (frozen section/imprint cytology) | 0.10 | 0.00-0 25 |
| Probability of breast re-excision | 0.40 | 0.20-0 60 |

*Table 1. Sensitivity analyses: key variables, base-line value, and range*

| Type of surgical operation | Surgical operation time (minutes) (median) | Hospital days (median) | Outpatient visits (median) |
|---|---|---|---|
| SN biopsy | 70 | 1 | 4 |
| ALND | 105 | 6 | 6 |
| Breast surgery | 82 | 3 | 2 |
| SN + breast surgery | 101 | 3 | 5 |
| ALND + breast surgery | 128 | 5 | 6 |
| SN + ALND + breast surgery | 131 | 6 | 6 |

*Table 2. Volumes of resource utilization, used to estimate costs of various procedures. Source: Hospital administration, Radboud University Nijmegen Medical Center*

Wilhelmia Hospital Nijmegen, VieCuri Medical Center Venlo, Rijnstate Hospital Arnhem, Radboud University Nijmegen Medical Center). Patients were excluded for a SN procedure when there was clinical proof of axillary lymph node metastases, evidence of multifocality of the primary breast tumor, radiotherapy of the breast or axilla in the past, when patients had received neo-adjuvant systemic therapy, or when the SN was not detectable.

***Volumes estimate***

Since an incremental cost analysis was conducted, only differential volume items were taken into account, meaning that costs of preoperative work-up, and of pathological examination of the breast and ALND were excluded. Items that were taken into account included surgical operating time, type of surgery (day care surgery or otherwise), number of days of hospitalization, SN diagnostic procedures, and outpatient visits. Volumes of operating time, days of hospitalization, and outpatient visits were derived from the administration of Radboud University Nijmegen Medical Center.

All model parameters are presented in table 1 (probability estimates) and table 2 (volumes of resource utilization). Probability estimates were derived from our patient cohort study and from the literature.

Cost items for the reference scenario included costs of breast surgery in combination with ALND and the costs of a possible breast re-excision, in case the tumor was not radically removed.

In case of a SN procedure in day care surgery, the model included the probability of SN identification and the probability of positivity of the SN. In case of positive findings, an ALND was included in the model, in combination with breast surgery.

Cost items for a SN procedure in day care surgery included costs of SN biopsy, costs of pathological examination of the SN, costs of breast surgery in combination with ALND, and costs of a breast re-excision. In case of a negative SN, the model included performance of breast surgery. Cost items included costs of SN biopsy, costs of pathological examination of the SN, costs of breast surgery, and costs of a breast re-excision. In case of an axillary relapse a delayed ALND was performed. Total costs consisted of costs of SN biopsy, costs of pathological examination of the SN, costs of breast surgery, costs of an ultrasound of the axilla, costs of an axillary biopsy, costs of a delayed ALND, and costs of a breast re-excision.

The model also included the possibility that a SN could not be identified. In that case performance of ALND in combination with breast surgery was assumed. Total costs included costs of SN biopsy, costs of breast surgery in combination with ALND, and costs of a breast re-excision.

With respect to SN biopsy performed during surgery of the breast, 2 options were distinguished in the model: identification of the SN versus failure of identification of the SN. In case of an identified SN, the model included the possibility of a positive SN after intra-operative diagnosis (frozen section/

| Cost-parameter | Unit | Costs/unit | Source |
|---|---|---|---|
| Operation time | Number of minutes of their respective working time | 0.79/minute* | Staff and Organization Radboud University Nijmegen Medical Center (Radboud UMC) |
| Hospitalization | Day | General: 257.75<br>Academic. 362.34<br>Average: 287.87 | Guideline price indexed on 2003 is derived from Oostenbrink et al 2000 |
| Consultant | Outpatient visit | 49 47** | Guideline price indexed on 2003 is derived from Oostenbrink et al 2000 |
| Biopsy (cytology/histology) lymph node | 1 | 28.05 | Department of Pathology Radboud UMC |
| Scintigraphy SN | 1 | 198 27 | Price indexed on 2003 is derived from Diagnostic Compass 2000 |
| Ultrasound breast/axilla | 1 | 66.57 | Price indexed on 2003 is derived from Diagnostic Compass 2000 |
| Pathology SN | 1 | 175.05 | Department of Pathology Radboud UMC |
| Pathology intra-operative diagnosis | 1 | 50.23 | Department of Pathology Radboud UMC |
| Pathology (cytology/histology) lymph node biopsy | 1 | 50.23 | Department of Pathology Radboud UMC |

***Table 3. Costs per unit and sources***
All costs in Euro, * These costs are based on the average monthly fee for specialists of € 8700 gross: € 8700x12x1.085(holiday allowance)/52/46=€ 47.36 each hour, € 0.79 each minute, ** Based on the proportion academic vs. general hospital: 0.14 vs. 0.86.

imprint cytology) followed by an ALND during the same surgical session. Cost items included costs of SN biopsy during breast surgery in combination with ALND, costs of intra-operative diagnosis, and costs of a breast re-excision.

The model also included the possibility of a negative SN after intra-operative diagnosis, in case of an identified SN. In that case extensive pathological examination of the SN was followed. In case of a positive SN, the model included performance of an ALND as a second surgical procedure. The model also included the possibility of a breast re-excision, resulting in 2 secondary surgery options: an ALND with a breast re-excision, or an ALND (without a re-excision). Cost items of an ALND with a breast re-excision included costs of SN biopsy in combination with breast surgery, costs of intra-operative diagnosis, costs of pathological examination of the SN, and costs of an ALND in combination with a breast re-excision. Cost items of an ALND (without re-excision) included costs of SN biopsy in combination with breast surgery, costs of intra-operative diagnosis, costs of pathological examination of the SN, and costs of an ALND.

In case of an identified, negative SN, the model included the possibility of axillary relapse followed by a delayed ALND. Cost items concerning a negative SN without axillary relapse included costs of SN biopsy in combination with breast surgery, costs of intra-operative diagnosis, costs of pathological examination of the SN, and costs of a breast re-excision. Cost items concerning a negative SN with axillary relapse included costs of SN biopsy in combination with breast surgery, costs of intra-operative diagnosis, costs of pathological examination of the SN, costs of an ultrasound of the axilla, costs of a axillary biopsy, costs of a delayed ALND, and costs of a breast re-excision.

### *Unit cost prices*

Prices were retrieved from various sources (table 3). Available guideline prices were used, as defined in 2004 by the Dutch Health Care Insurance Board[12]. If not available, they were obtained from the Financial Department of Radboud University Nijmegen Medical Center. Prices were given in Euro (€).

## RESULTS

### *Cost-effectiveness analysis*

In our model, the 2 SN procedure strategies (strategy 2 and 3) showed to be equally effective in preventing an ALND. The probability of avoiding an ALND was 0.614 in case of a SN procedure in day care surgery, and 0.606 in case of a SN procedure performed during surgery of the breast (table 4).

In case of a SN procedure in day care surgery, an extra outlay of € 430 was required. In case of a SN procedure performed during the surgical procedure of the breast, an extra outlay of € 266 was required.

The above mentioned was translated into an incremental cost-effectiveness ratio, meaning the additional costs associated with avoiding 1 additional case of ALND.

The incremental cost-effectiveness ratio in case of a SN procedure in day care surgery

was € 701 per case of an ALND avoided. The incremental cost-effectiveness ratio in case of a SN procedure performed during surgery of the breast was € 440 per case of an ALND avoided; leaving strategy 2, a SN procedure in day care surgery, as the most expensive strategy to avoid an ALND in patients with primary breast cancer.

### *Sensitivity analyses*

In sensitivity analyses, the robustness of these findings was explored. The key variables, baseline values, and range of values are shown in table 1. The model appeared to be robust, in the sense that the 2 SN procedure strategies remained approximately equally effective in terms of reducing the need for ALND, and incurred extra costs as compared to the ALND reference strategy (data not shown).

## DISCUSSION

We conducted a cost-effectiveness analysis to estimate the incremental costs that are incurred by the SN procedure in order to avoid one extra ALND. With the introduction of the SN procedure, obviating the need for ALND in 66% of patients, an extra outlay of € 430 (SN biopsy during day care surgery) or € 266 (SN biopsy during breast surgery) was needed. This translated into an incremental cost-effectiveness ratio of € 701 and € 440, respectively, per case of ALND avoided. Note that for sake of completeness, cost data of each strategy are presented; these figures do not reflect the true costs, since only differential costs were taken into account.

We postulated at the initiation of our project that the SN procedure might lead to an increased detection of isolated tumor cells and micrometastases due to the intensified work-up of the SN by the pathologist. And if so, this could partially offset the expected reduction in the rate of ALND. Indeed, in our clinical study we observed that with a very intensive pathology protocol, examining 7 additional levels, the number of ALNDs was significantly higher[7]. In the center with the

| Strategy[a] | Costs/ patient (€) | Incremental costs[b] (€) | Effectiveness[c] | Incremental effectiveness[d] | Incremental cost-effectiveness[e] |
|---|---|---|---|---|---|
| 1 | 2133 | | 0 | | |
| 2 | 2563 | 430 | 0.614 | 0.614 | 701 |
| 3 | 2399 | 266 | 0.606 | 0.606 | 440 |

***Table 4. (Incremental) cost-effectiveness of two strategies of a SN procedure in avoiding an ALND***
a: strategy 1: ALND (reference scenario), strategy 2: SN procedure in day care surgery before primary breast surgery, strategy 3: SN procedure performed during primary breast surgery. b: strategy 2 and strategy 3 versus strategy 1. c: probability of avoiding an ALND. d: probability of avoiding an additional case of ALND, strategy 2 and 3 versus strategy 1. e: additional costs associated with avoiding one additional case of ALND.

intensified pathology protocol only 34% of patients did not have a completion ALND, as compared to 71% of patients in the other 3 hospitals. Hence, it is obvious that intensification of the pathology protocol also has a large impact on cost-effectiveness. From another nationwide patient registry we learned that omission of ALND in patients with SN isolated tumor cells can be considered safe, with a 5-year regional recurrence rate of 2.0%[13]. As updated Dutch and international guidelines do, therefore, no longer recommend the performance of a completion ALND in the presence of SN isolated tumor cells, the cost-effectiveness of the SN procedure is nowadays improved.

Although we found an incremental cost-effectiveness ratio for patients undergoing a SN procedure, these costs probably outweigh the burden that is imposed by ALND to the patient and associated costs. For example in the UK ALMANAC trial, it was shown, that the proportion of patients reporting a swollen or tender arm, numbness in the arm, painful and poor range of movement, and stiffness of the arm on the operated side, was significantly higher in the patients who underwent an ALND as compared to patients who underwent a SN procedure[14]. Eighteen months post surgery approximately twice as many patients in the standard group compared with the SN group reported substantial arm swelling (14% versus 7%) (p=0.002) or numbness (19% versus 8.7%) (p<0.001). From the ALMANAC trial it can be estimated that costs for supportive care in relation to an ALND will be on average much higher than the additional costs of € 430 or € 266, respectively, as calculated from our patient cohort. These costs outweigh the burden that is imposed by ALND to the patient and associated costs. We realize, however, that long term costs of physical therapy or lymph edema therapy were not incorporated in this study, as we only included hospital costs.

Only 3 prior studies have compared the costs of a SN procedure with costs of a conventional ALND. One study concluded that costs of patients who had a SN procedure was lower than those who had primary ALND, and attributed this to a longer hospital stay in ALND patients[15]. The 2 other studies showed - similar to our findings - increased costs in patients undergoing a SN procedure, with the highest costs for SN in day care if performed before the breast surgery, but yet at the cost of an acceptable extra amount of money[9]. Two other studies analyzed the impact of different intra-operative pathology techniques such as use of frozen sections, imprint cytology, or molecular techniques in order to reduce the waiting time for the surgeon when SN was combined with the breast surgery, and showed that molecular techniques were costly, while use of frozen section and imprint cytology could be considered cost-effective[16,17].

A limitation of our study is that we collected volumes from only 1 out of 4 participating hospitals. As a consequence, we had no direct information whether the SN procedure in day care surgery lasts longer or shorter compared to SN procedure under general anesthesia, and whether other differences might be present between university and general hospital breast cancer care.

The model appeared to be robust, meaning that the 2 SN strategies remained approximately equally effective in terms of reducing the need for an ALND. Obviously, with similar efficacy, the additional incurred costs as compared to the reference scenario, a routine ALND, remain lower for strategy 3 than for strategy 2. The only way to improve efficacy with current techniques is to accept less patients for a completion ALND, though without compromising safety.

In conclusion, from a hospital perspective, the introduction of the SN procedure is associated with incremental costs, especially if a SN biopsy is performed in day care surgery prior to breast surgery.

From a patient point of view, quality of life of early stage breast cancer patients has increased, due to less mutilating surgery. This might validate the higher costs of a SN biopsy compared to an ALND.

Also from a hospital perspective, a completion ALND performed in patients with SN isolated tumor cells is associated with higher costs. However, with updated guidelines limiting the need of a completion ALND, the SN procedure is expected to become cost saving.

## REFERENCES


1 *van Dijck JA, Coebergh JW, Siesling S, et al. Breast cancer in women. In: Trends of cancer in the Netherlands 1989-1998 (ed). Utrecht, the Netherlands: Association of comprehensive cancer centers/Netherlands cancer registry, 2002:31-32.*

2 *Koopmanschap MA, van Roijen L, Bonneux L, et al. Current and future costs of cancer. Eur J Cancer 1994;30:60-65.*

3 *Miltenburg DM, Miller C, Karamlou TB, et al. Meta-analysis of sentinel lymph node biopsy in breast cancer. J Surg Res 1999;84:138-142.*

4 *Pepels MJ, Vestjens JH, de Boer M, et al. Safety of avoiding routine use of axillary dissection in early breast cancer: a systematic review. Breast Cancer Res Treat 2011;125:301-313.*

5 *van Steenbergen LN, van de Poll-Franse LV, Wouters MW, et al. Variation in management of early breast cancer in the Netherlands, 2003-2006. Eur J Surg Oncol 2010 Sep;36 Suppl 1:S36-43.*

6 *Bolster MJ, Peer PGM, Bult P et al. Risk factors for non-sentinel lymph node metastases in patients with breast cancer. The outcome of a multi-institutional study. Ann Surg Oncol 2007;14:181-189*

7 *Bolster MJ, Bult P, Schapers RF, et al. Differences in sentinel lymph node pathology protocols lead to differences in surgical strategy in breast cancer patients. Ann Surg Oncol 2006;13:1466-1473.*

8 *van Berlo CL, Hess DA, Nijhuis PA, et al. Ambulatory sentinel node biopsy under local anaesthesia for patients with early breast cancer. Eur J Surg Oncol 2003;29:383-385.*

9 *Rönkä R, v. Smitten K, Sintonen H et al. The impact of sentinel node biopsy and axillary staging strategy on hospital costs. Ann Oncol 2004;15:88-94.*

10 *den Bakker MA, van Weeszenberg A, de Kanter AY et al. Non-sentinel lymph node involvement in patients with breast cancer and sentinel node micrometastasis; too early to abandon axillary clearance. J Clin Path 2002;55:932-935.*

11 *Mullenix PS, Cuadrado DG, Steele SR et al. Secondary operations are frequently required to complete the surgical phase of therapy in the era of breast conservation and sentinel lymph node biopsy. Am J Surg 2004;187: 643-646.*

12 *Oostenbrink JB, Bouwmans CAM, Koopmanschap MA, Rutten FFH. Manual for cost analysis, methods, and guideline prices in health care economic evaluations. Dutch Health Care Insurance Board. 2004.*

13 *Pepels MJ, de Boer M, Bult P, et al. Regional recurrence in breast cancer patients with sentinel node micrometastases and isolated tumor cells. Ann Surg 2012;255:116-121.*

14 *Fleissig A, Fallowfield LJ, Langridge CI et al. Post-operative arm morbidity and quality of life. Results of the ALMANAC randomized trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. Breast Cancer Res Treat 2006;95:279-293.*

15 *Perrier L, Nessah K, Morelle M, et al. Cost comparison of two surgical strategies in the treatment of breast cancer: sentinel lymph node biopsy versus axillary lymph node dissection. Int J Technol Assess Health Care 2004;20:449-454.*

16 *Kaminski JP, Case D, Howard-McNatt M, et al. Sentinel lymph node intraoperative imprint cytology in patients with breast cancer-costly or cost effective? Ann Surg Oncol 2010;17:2920-2925.*

17 *Cutress RI, McDowell A, Gabriel FG, et al. Observational and cost analysis of the implementation of breast cancer sentinel node intraoperative molecular diagnosis. J Clin Pathol 2010;63:522-529.*

# CHAPTER 7

Chapter 7

# Cost-effectiveness of new guidelines for adjuvant systemic therapy for patients with primary breast cancer

*W. Kievit*, M.J. Bolster*, G.J. van der Wilt, P. Bult,*
*F.B.J.M. Thunnissen, J. Meijer, L.J.A. Strobbe, J.H.G. Klinkenbijl,*
*Th. Wobbes, E.M.M. Adang, L.V.A.M. Beex, V.C.G. Tjan-Heijnen*
**First two authors contributed equally to this study*

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## ABSTRACT

### Background

In this study, the potential impact of a new national guideline for adjuvant systemic therapy in breast cancer (introduced in The Netherlands in 1998) was assessed, as well as the modifications of this guideline, issued in 2001. Both the change in total number of patients eligible for adjuvant therapy, as well as the cost-effectiveness of the changed clinical management of these patients were analysed.

### Patients and Methods

Percentages of patients who would be eligible for adjuvant therapy in 1994, 1998 and 2001 were estimated, based on clinical data from 127 patients, who were operated in 1994. 10-Years overall survival rates were used as a measure of effectiveness, based on the two most recent EBCTCG meta-analyses. Actual resource costs were calculated. With a decision analytic model, the incremental cost-effectiveness ratios (1998 vs. 1994, and 2001 vs. 1998) were calculated.

### Results

The introduction of the 1998 guideline resulted in a relative increase of 80% in the total number of patients eligible for adjuvant therapy, compared with 1994 (from 40% to 72% of all patients with primary breast cancer). With an estimated absolute increase of 10-years overall survival with 2%, the 1998 guideline was found to have an expected incremental cost-effectiveness ratio of about € 4837 per life-year gained.

### Conclusion

Introduction of the new guideline considerably affected the number of patients eligible for adjuvant systemic therapy for breast cancer. The associated incremental cost-effectiveness ratio is well within the range of values that are generally considered acceptable.

## INTRODUCTION

Breast cancer is a substantial health care problem, both in terms of burden of disease and in terms of health care costs. The total health care costs of breast cancer in The Netherlands were estimated at € 115 million in 1988, which is about 13% of the total health care costs of cancer, and are estimated at € 141 million in 2005[1].

Most patients with primary breast cancer will receive loco regional treatment, i.e. surgery, with adjuvant radiotherapy on indication[2]. The most important prognostic factor in primary breast cancer is the axillary lymph node status[3]. To provide information about the axillary lymph node status, a sentinel lymph node (SLN) biopsy and/or an axillary lymph node dissection (ALND) is performed. Subsequent adjuvant systemic therapy can be given to high-risk patients to eliminate microscopic disseminated tumour cells. Adjuvant systemic therapy for breast cancer may consist of chemotherapy, endocrine therapy or a combination of both. Adjuvant chemotherapy as well as adjuvant endocrine therapy results in a relative reduction in recurrence and mortality of 25 and 16 percent, respectively[4-7]. The relative risk reduction appears to be about the same for node-positive (N+) as high-risk node-negative (No) breast cancer.

In 1998, the Dutch National Breast Cancer Platform and the Dutch Society for Medical Oncology published a new guideline for adjuvant systemic therapy for patients with resectable breast cancer[8], based on the St Gallen guidelines[9,10]. These guidelines are the result of a trade-off of the improved survival that can be achieved on the one hand and, on the other hand, possible side effects and over-treatment. In The Netherlands, it was agreed that adjuvant systemic therapy was indicated in case of an expected absolute increase in 10-year survival of five percent or more[9]. Therefore, the 1998 Dutch guidelines were adjusted with respect to the policy in patients with No disease. These patients were categorized into low- and high-risk, of whom the latter were then advised to receive adjuvant systemic therapy. High-risk was defined by primary tumour characteristics, i.e., tumour size and grade of differentiation or mitotic activity index (MAI).

In 2001, this guideline was slightly modified. Firstly, patients of 35 years of age or younger were now recommended always to be treated with adjuvant systemic therapy, regardless of the lymph node status or primary tumour characteristics. Secondly, postmenopausal patients 50 - 59 years of age, with a hormone-receptor positive tumour, were recommended for adjuvant chemotherapy, in addition to the use of adjuvant endocrine therapy.

To our knowledge, there is only one report on the impact of new guidelines of adjuvant therapies in breast cancer on numbers of patients to be treated[11]. The purpose of the present study is to assess the change in the number of patients eligible for adjuvant systemic therapy for breast cancer after the introduction of the guidelines of 1998 and 2001, and the impact on costs and effectiveness of treatment of patients with primary breast cancer in case of full compliance with these guidelines.

## METHODS

### *Design*

One university hospital and two regional teaching hospitals participated in this study. The design of the study was a retrospective cohort study. Clinical data, involving patients with primary invasive breast cancer operated in 1994, were used to estimate the effect of the various guidelines on the number of patients who would have been candidates for adjuvant systemic treatment. The consequences of this were expressed in terms of survival gain and costs of treatment. The effect on the annual number of patients eligible for adjuvant systemic therapy and on the cost-effectiveness was studied using decision analytic modelling.

### *Patients*

Subjects with histological proven primary invasive breast cancer, in whom a modified radical mastectomy or breast conservative surgery with an ALND was performed, were included in this study. Patients who had an ipsilateral breast carcinoma in the past (prior ALND) or who were classified as having M1- or T4-disease (TNM classification[12]) were excluded.

In the participating hospitals, SLN biopsies have been performed since 1997. Therefore, a retrospective cohort of consecutive patients operated in year 1994 was selected, to prevent biases from changes in pathology procedures. It was estimated that 50% (expert opinion) of all node-negative patients would be eligible for adjuvant therapy based on primary tumour characteristics and 2.5% based on age younger than 35 years[11]. All node-positive patients (40% of all newly diagnosed breast cancer patients) are eligible for adjuvant therapy according to the conventional policy. This results in the estimation that 71.5% of patients would be eligible (40% + (52.5%*60%)) for adjuvant therapy according to the 2001 guidelines. To estimate this percentage with 8% accuracy and a confidence interval of 95%, 110 patients had to be included in this study.

### Decision analytic model: structure, assumptions, input and outcome parameters

#### *Structure*

A decision analytic model was constructed using decision analysis DATA 4.0® (Decision Analysis by TreeAge) software. The structure of the model is shown in figure 1.

#### *Model assumptions*

For the baseline model it was assumed that endocrine therapy consisted of tamoxifen for a period of five years (20 mg a day), and that polychemotherapy consisted of the classical CMF-regimen (Cyclophosphamide, Methotrexate, 5-Fluorouracil) for 6 cycles. Combination therapy consisted of CMF-regimen followed by a five-year period of tamoxifen.

Hormone receptor status was considered positive if either the level of ER or PgR was 10 or more fmol receptor protein per mg of cytosol protein, or if the immunohistochemical assay showed that the quick score was 3 or more. The quick score is the sum of the intensity of the staining (intensity score) and the proportion of tumour cells being

positive (proportion score), and was determined using a modification of the quick score method described by Bames et al.[13].

Patients were considered to be postmenopausal if either (1) the last menstruation was at least 12 months ago and in case of use of contraceptives the last intake was at least 12 months ago and there was no use of hormonal substitution; (2) there was an ovarian ablation performed; (3) patients had biochemical confirmation of lack of ovarian function (FSH and 17β oestradiol levels in postmenopausal range according to local laboratory values).

*Probabilities*

The probability of being eligible for adjuvant systemic therapy and the probabilities for receiving either of the two adjuvant systemic therapies was determined by the characteristics (i.e. nodal status, hormone receptor status, menopausal status, tumour size, Bloom-Richardson differentiation grade or MAI, and age) of the individual patient. These probabilities and their 95%-CI were determined on the basis of data from the clinical records and pathological reports of the patients operated in 1994, using SPSS® software version 11.0.

*Costs*

The study was conducted from a health care perspective, implying that only direct medical costs were included. Full cost prices were calculated for every treatment included in the model, using a time horizon of ten years. Drug costs, costs of personnel, blood tests, use of equipment, annual mammography and anti-emetics were included. In accordance with national guidelines for cost calculations in health care, 35% overhead costs were added to the total direct costs, and future costs were discounted to present values by a discount rate of 4%[14].

*Effectiveness*

Results from the EBCTCG meta-analysis were

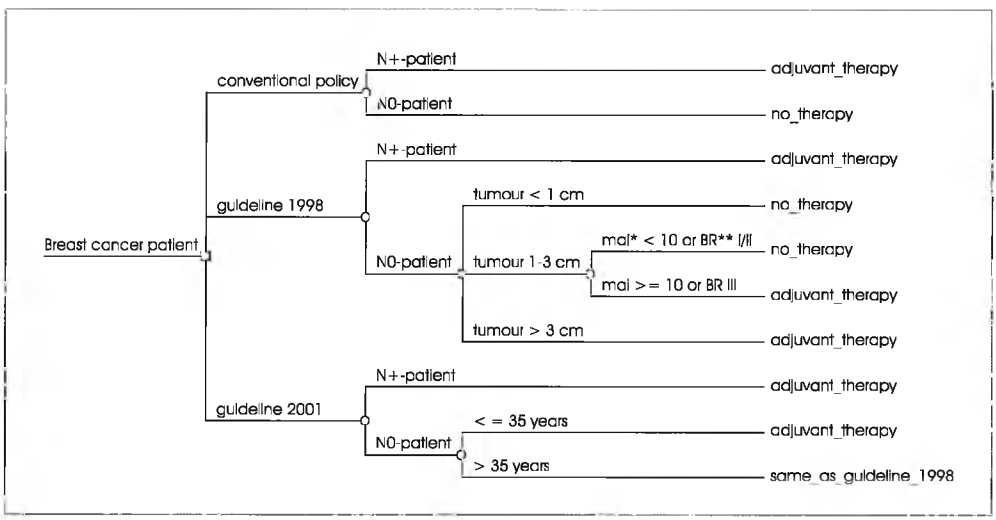


***Figure 1. Decision analytic model.*** MAI = mitotic activity index, BR = Bloom-Richardson differentiation grade.

| | N | (%) |
|---|---|---|
| **Total No of patients** | 127 | (100.) |
| **Age (years)** | | |
| ≤ 35 | 2 | (1.6) |
| 36-49 | 38 | (29 9) |
| 50-59 | 29 | (22.8) |
| 60-69 | 31 | (24.4) |
| ≥ 70 | 27 | (21.3) |
| **Nodal status** | | |
| No | 76 | (59 8) |
| N+ | 51 | (40.2) |
| **Receptor status** | | |
| ER+ and/or PgR+ | 91 | (71.7) |
| ER-, PgR- | 31 | (24.4) |
| Unknown | 5 | (3.9) |
| **Tumor size (cm)** | | |
| < 1 | 5 | (4 0) |
| 1-3 | 100 | (78.7) |
| > 3 | 22 | (17.3) |
| **MAI[a]** | | |
| < 10 | 61 | (48.0) |
| ≥ 10 | 64 | (50.4) |
| Unknown | 2 | (1.6) |
| **BR grade[b]** | | |
| I/II | 79 | (62 2) |
| III | 47 | (37.0) |
| Unknown | 1 | (0.8) |

***Table 1. Patients' demographics.***
a: MAI = mitotic activity index,
b: BR = Bloom-Richardson differentiation grade.

used to estimate effectiveness of the various adjuvant therapies[4-7] for the different subgroups of patients in terms of 10-years overall survival rates. Two experts (V.T.-H. and L.B.) estimated 10-years overall survival rates for subgroups for which no data could be obtained from the literature. The estimated 10-years overall survival rates were discounted to present values by a discount rate of 4%. Life years saved were calculated based on the 10-years survival rate, by determining the area under the curve.

*Cost-effectiveness*

The incremental cost-effectiveness ratio was expressed as costs per life year gained. It was expected that the largest differences in costs and effectiveness would be for No-patients. Therefore, separate incremental cost effectiveness ratios were calculated for this subgroup of patients.

***Sensitivity analysis***

To assess the robustness of the study results, one-way sensitivity analyses were performed for a number of variables. The discount rate was varied from 0% to 6% for cost- and effectiveness data[14]. The probability of having a primary tumour with a diameter of three centimetres or more was varied between 3.4% and 25.9%. The probability of having a primary tumour with a diameter of 1 - 3 centimetres and a MAI ≥ 10 or a differentiation grade III was varied between 22.2% and 62.5%. Both ranges of probabilities were based on the minimum and maximum probability for the three hospitals. Furthermore, a probabilistic sensitivity analysis was performed, where a beta distribution was estimated for every 10-years survival rate. In

| | Conventional policy (N = 127) | 1998 Guidelines (N = 127) | 2001 Guidelines (N = 127) |
|---|---|---|---|
| Do not need adjuvant therapy | 76 (59.8%) | 36 (28.3%) | 36 (28.3%) |
| Candidates for adjuvant therapy | 51 (40.2%) | 91 (71.7%) | 91 (71.7%) |

*Table 2. Total number of patients eligible for adjuvant systemic therapy according to the conventional policy and guidelines 1998 and 2001*

| Treatment option | Costs (€) |
|---|---|
| No therapy | 1278 |
| Chemotherapy (CMF 6 cycles) | 2023 |
| Endocrine therapy (tamoxifen for 5 years) | 2418 |
| Combination therapy (CMF and tamoxifen) | 3164 |

*Table 3. The discounted (4%) costs of all treatment options including 10 years follow-up for a teaching hospital*

| Treatment according to: | Costs (€) | Incremental costs (€) | 10-years OS (%) | Life years | Incremental life years | Incremental costs/life year saves (€) |
|---|---|---|---|---|---|---|
| **All patients** | | | | | | |
| conventional therapy | 1773.40 | | 47.3 | 7.37 | | |
| guidelines 1998 | 2133.82 | 360.43 | 48.7 | 7.44 | 0.07 | 4837 |
| guidelines 2001 | 2153.03 | 19.21 | 48.4 | 7.42 | -0.02 | Dominated |
| **No-patients** | | | | | | |
| conventional therapy | 1277 59 | | 53.5 | 7.68 | | |
| guidelines 1998 | 1876.31 | 598.72 | 55.9 | 7.80 | 0.12 | 4837 |
| guidelines 2001 | 1876.68 | 0.37 | 55.9 | 7.79 | -0.01 | Dominated |

*Table 4. Discount rate (4%) corrected increments in costs and estimated overall survival and incremented costs/life year saved as a result of treatment according to the three different guidelines.* OS: overall survival; No: lymph node negative.

a Monte Carlo simulation 100 drawings were sampled from these distributions resulting in a mean survival rate with 95% confidence intervals for the overall, estimated, survival rates.

## RESULTS

### *Number of patients eligible for adjuvant therapy*

The total number of patients included in this study and used for analysis was 127. The mean age of all patients was 58 years, with a range from 35 to 83 years. The majority of patients was node-negative (60%) and had a hormonal receptor positive tumour (72%). Only 3.9% of patients had a tumour with a size smaller than one centimetre (table 1). Of all patients, 72% were eligible for adjuvant systemic therapy according to the guidelines of 1998 and 2001, in contrast to 40% according to the conventional policy. This resulted in a significant ($P < 0{,}0001$) relative increase of 80% in the total number of eligible patients (table 2).

### *Cost-effectiveness*

Detailed information on the values of the probabilities, costs and survival rates are shown in appendix A. The treatment with a combination of polychemotherapy and endocrine therapy was the most expensive option, and 'no treatment' the least expensive option (table 3). Treatment according to the guidelines 1998 or 2001 was more expensive (10-years incremental discounted costs per patient € 360) than treatment according to the conventional policy. Effectiveness of treatment in accordance with 1998 and 2001 guidelines resulted in an estimated discounted 49% 10-years overall survival for the whole group (treatment and no treatment) (table 4). Treatment with a time horizon of 10 years of follow-up resulted for the 1998 guideline in an additional 1.5% 10-years survival, which equals a 0,07 life-years gain compared with the conventional guideline. The incremental cost-effectiveness ratio was € 4837 per life year saved, in favour of the guidelines 1998 (table 4). Treatment according to 2001 guidelines was slightly more expensive, but not more effective, than treatment according to guidelines 1998.

### *No-patients*

When considering the node-negative patients as a subgroup (N = 77), the discounted 10-years overall survival was 53.5% and 55.9% for all No-patients according to the conventional policy and the guidelines 1998 and 2001, respectively. This resulted in an in cremental cost-effectiveness ratio of € 4837 per life-year saved (table 4) in favour of the 1998 guideline. Treatment according to guidelines 2001 was slightly more expensive, but no more effective, than treatment according to guidelines 1998.

### *Sensitivity analyses*

Results of the sensitivity analyses are shown in table 5. If survival rates were not discounted to present values, the incremental cost-effectiveness ratio decreased to € 3268. The impact of the discount rate on survival rates was thus relatively large. in table 5, it is shown that even substantial variations in incidences of primary tumour characteristics - relevant for treatment decisions in the node-negative group - had little impact on the incremental cost-effectiveness ratios.

The probabilistic sensitivity analysis on survival showed that the mean survival rates (95% CI) were 48.7% (43.7% - 53.0%) and 50.4% (45.3% - 55.0%) according to the conventional policy and the 1998 guideline, respectively. The mean incremental cost-effectiveness ratio (95% CI) was € 4240 per life year saved (€ 4505 - € 3604 per life year saved) in favour of the 1998 guideline.

## DISCUSSION

This modelling study compared the change in number of patients with primary breast cancer receiving adjuvant systemic therapy since the introduction of the Dutch breast cancer guidelines of 1998 and 2001 compared with the conventional policy before. In addition, the potential consequences of introducing these guidelines on cost-effectiveness of the changed clinical management of patients with breast cancer were investigated.

According to the conventional policy (year 1994), 40% of patients with primary breast cancer were eligible for adjuvant therapy. When the new guidelines were applied to this patient population, this figure rose to 72%, a relative increase of 80%, mainly due to the use of adjuvant treatment for patients with high risk No breast cancer.

Treatment according to the 1998 or 2001 guidelines was more expensive than treatment according to the conventional policy and resulted in an additional 1.5% 10-years overall survival per patient (treatment and no treatment) for the whole population, an additional 2.5% 10 year survival for the No population, that is, an additional 5% 10 year survival for the high-risk No population who actually became candidates for adjuvant therapy. The incremental cost-effectiveness ratio was € 4837 per life-year saved, in favour of the 1998 guideline. This figure is well within the range of incremental cost-effectiveness ratios, which are generally considered acceptable[15].

Although no clear statement can be found

| Variable | Base case | Range | Range | incr C/E (€) |
|---|---|---|---|---|
| Discount rate costs | 4% | 0%-6% | 5092 | 4724 |
| Discount rate survival rates | 4% | 0%-6% | 3268 | 5852 |
| Probability for No-patients to have a tumour > 3 cm | 0.16 | 0.034-0.26 | 4747 | 4755 |
| Probability for No-patients to have a tumour of 1 - 3 cm and MAI ≥ 10 or BR III | 0.45 | 0.22-0.63 | 4718 | 5067 |

*Table 5. Results of the sensitivity analyses on the incremental cost-effectiveness (incr C/E)*

on a cost-effectiveness threshold above which health technologies are automatically rejected and below which technologies are accepted, Dutch health authorities have accepted technologies with cost-effectiveness ratios below 50.000 euro[16]. The Australian reimbursement authorities have been unlikely to recommend a drug if the cost-effectiveness ratio exceeded AU $76 000 per life year saved and unlikely to reject it if less than $42 000 per life-year saved[17]. An upper threshold of about £30 000 per quality-adjusted life-year seems to have emerged at NICE[18]. Nevertheless, uncertainty of cost-effectiveness results and the burden of disease explain reimbursement decisions better than cost effectiveness alone[19].

Treatment according to the 2001 guidelines was more expensive, but no more effective, than treatment according to 1998 guidelines for the overall group of patients. For No breast cancer, treatment according to the conventional policy versus the 1998 and 2001 guidelines resulted in an incremental cost-effectiveness ratio of € 4837 per life-year saved in favour of 1998 guidelines.

To our knowledge, there are no cost-effectiveness analyses of the guidelines for adjuvant therapy for breast cancer in literature. However, costs of adjuvant therapy can be found. In this study, the discounted costs of the six-months' polychemotherapy and five-years' tamoxifen, for a follow up period of five years, were estimated to be € 2023 and € 2418, respectively. Messori et al. estimated direct medical costs (including drugs costs, costs of administration, nursing time and device) of six cycles of CMF to be US$ 797,58 (€ 906,45)[20]. Those costs did not include costs generated during follow-up. Furthermore, in literature the costs of polychemotherapy were found to be US$ 3838 (€ 4361,89)[21] and of US$ 6000 (€ 6764,40)[22]. Drummond et al., estimated the costs for tamoxifen treatment to be US$ 1000 (€ 1127,40)[22]. However, Kattlove et al. and Drummond et al. used charges to calculate costs[21,22] as our results were based on real cost prices. Also it should be mentioned that cost prices, charges and procedures are not necessarily equal in different (international) settings.

As all modelling studies, this study had to make certain assumptions. Calculations were made assuming full compliance with the guidelines. in reality, it is not likely that a compliance of 100% will ever be attained. There will always be other factors influencing the choice for treatment. In the literature, a compliance of 90% with guidelines from the National Institute of Health was found for women who received any drug therapy (chemotherapy or endocrine therapy)[23]. Yet, this assumption applies to all three guidelines and a change in compliance will not affect the relevant differences in costs, effectiveness and cost-effectiveness. Furthermore, it was assumed that polychemotherapy treatment consisted solely of a CMF-regimen. An anthracycline- or taxane based regimen is another treatment of choice for polychemotherapy. The use of these treatments will probably affect the outcomes of the cost-effectiveness analyses. When taking only drug costs into account, in the Netherlands the costs of

6 cycles CMF is 492 euro, of 5 cycles $FEC_{90}$ (5-fluorouracil, epirubicine, cyclophosphamide) 2,250 euro and of 6 cycles TAC (docetaxel, adriamycine, cyclophosphamide) 9,000 euro. However, incremental cost-effectiveness ratios cannot simply be translated from one chemotherapy regimen to another by using only drug costs. The extra drug costs of the $FEC_{90}$ regimen may be partially compensated by the lower drug administration costs (5 visits for FEC versus 12 visits for CMF), while the administration of the taxane regimen will bear even more costs. $FEC_{90}$ may result in a 2% 10 years survival benefit compared to classical CMF for the subgroup of patients treated with chemotherapy[5], making the regimen possibly yet more cost-effective compared to CMF despite the additional drug costs of FEC. The TAC regimen was reported to result in a 6% 5 year survival benefit over FAC in node-positive patients[24]. This increased efficacy may outweigh some of the costs, but probably not all. Similarly, it was assumed that endocrine therapy consisted of tamoxifen for a period of five years. But, both the latest St Gallen (2005) guideline and the ASCO now recommended the use of an aromatase inhibitor as initial therapy or after treatment with tamoxifen for postmenopausal women with hormone receptor positive breast cancer[25]. The cost price of tamoxifen is 750 euro per patient, of sequential tamoxifen/aromatase inhibitor 4,000 euro and of upfront aromatase inhibitor 7,500 euro, for 5 years of treatment. Of note, for nearly all studies on adjuvant aromatase inhibitors only disease free survival was significantly improved, not overall survival, at least not within 5 years of follow up. So, with no proof of life years gained, but only quality adjusted life years gained (QALY), the incremental cost-effectiveness ratio of adjuvant endocrine therapy will increase substantiallyn with the routine use of aromatase inhibitors.

Owing to the perspective from which our study was conducted, only direct medical costs were included. It is conceivable, however, that adjuvant systemic therapy also incurs substantial non-medical and personal costs for patients, e.g. travel costs to the hospital, costs due to side effects, home nursing costs, etc. Medical costs involving only short-term side effects of polychemotherapy were included in the calculation of the true resource costs. This means that only the costs of anti-emetics, used during a polychemotherapy treatment, were included. Endometrial cancer, thrombosis, pulmonary emboli and stroke are side effects that can occur in the treatment with tamoxifen. Although these side-effects could induce substantial costs, their incidence is low[26]. For this reason, it was decided to exclude the costs of these side effects.

Effectiveness of adjuvant treatment in terms of increased overall survival was estimated on the basis of the findings of the EBCTCG meta-analyses[5,6]. Although it is preferable to use primary data[27], it was not feasible in our study design. We performed a probabilistic sensitivity analysis on these estimated survival rates in the subclasses of patients as described in Appendix A. This analysis showed that the 95% CI's for the overall survival rates (conventional policy 43.7% - 53.0% and 1998 guideline 45.3% -

55.0%) were acceptable, as well as the 95% CI for the incremental cost-effectiveness ratio (€ 4505 - € 3604 per life year gained).

Another limitation of our study was that we did not include data on the possible consequences of the guidelines on the quality of life of patients with breast cancer. To our knowledge, such data are not available from the literature for the various subgroups, which were included in our model.

In conclusion, it was demonstrated that introduction of new guidelines resulted in a substantial increase in the number of patients eligible for adjuvant systemic therapy, and thus this implies more costs. Of note, the incremental cost-effectiveness ratio is well within the range of values that are generally considered acceptable. When implementing new guidelines, one should consider the effect on efficiency of the new guideline.

## REFERENCES


1 *Koopmanschap MA, van Roijen L, Bonneux L, Barendregt JJ. Current and future costs of cancer. Eur J Cancer 1994; 30: 60-5.*

2 *Bundred NJ. Prognostic and predictive factors in breast cancer. Cancer Treat Rev 2001; 27: 137-42.*

3 *Fisher ER, Swamidoss S, Lee CH et al. Detection and significance of occult axillary node metastases in patients with invasive breast cancer. Cancer 1978; 42: 2025-31.*

4 *Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 Randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet 1992; 339: 1-15.*

5 *EBCTCG. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 1998; 352: 930-42.*

6 *EBCTCG. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998; 351: 1451-67.*

7 *EBCTCG. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 Randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet 1992; 339: 71-85.*

8 *Bontenbal M, Nortier JW, Beex LV et al. Adjuvant systemic therapy for patients with resectable breast cancer: guideline from the Dutch National Breast Cancer Platform and the Dutch Society for Medical Oncology. Ned Tijdschr Geneeskd 2000; 144: 984-9.*

9 *Goldhirsch A, Glick JH, Gelber RD, Senn HJ. Meeting highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. J Natl Cancer Inst 1998; 90: 1601-8.*

10 *Goldhirsch A, Glick JH, Gelber RD et al. Meeting highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. Seventh International Conference on Adjuvant Therapy of Primary Breast Cancer. J Clin Oncol 2001; 19: 3817-27.*

11 *Voogd AC, Louwman WJ, Coebergh JW, Vreugdenhil G. Impact of the new guidelines for adjuvant systemic treatment of breast cancer at hospital level. Ned Tijdschr Geneeskd 2000; 144: 1572-4.*

12 *Sobin LH, Wittekind C. TNM classification of malignant tumours. New York: Wiley-Liss 1997.*

13 *Bames DM, Harris WH, Smith P. Immunohistochemical determination of oestrogen receptor: comparison of different methods of assessment of staining and correlation with clinical outcome of breast cancer patients. Br J Cancer 1996; 74: 1445-51.*

14 *Oostenbrink JB, Koopmanschap MA, Rutten FF. Handleiding voor kostenonderzoek: methoden en richtlijnen voor economische evaluaties in de gezondheidszorg. Amstelveen: College voor zorgverzekeraars 2000.*

15 *Chapman RH, Stone PW, Sandberg EA et al. A comprehensive league table of cost-utility ratios and a sub-table of "panel-worthy" studies. Med Decis Making 2000; 20(4): 451-67.*

16 *Rutten-van Mölken MP, van Busschbach JJ, Rutten FF. Van kosten tot effecten. Een handleiding voor evaluatiestudies in de gezondheidszorg. Maarssen: Elsevier Gezondheidszorg 2000.*

17 *George B, Harris A, Mitchell A. Cost-effectiveness analysis and the consistency of decision making: evidence from pharmaceutical reimbursement in Australia (1991 to 1996). PharmacoEconomics 2001; 19 (11): 1103-9.*

18 *Taylor D. Funding medicines for people with multiple sclerosis. BMJ 2001; 323: 1379-80.*

19 *Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. Health Econ 2004; 13 (5): 437-52.*

20 *Messori A, Becagli P, Trippoli S, Tendi E. Cost-effectiveness of adjuvant chemotherapy with cyclophosphamide+methotrexate+ fluorouracil in patients with node-positive breast cancer. Eur J Clin Pharmacol 1996; 51: 111-6.*

21 *Kattlove H, Liberati A, Keeler E, Brook RH. Benefits and costs of screening and treatment for early breast cancer. Development of a basic benefit package. JAMA 1995; 273: 142-8.*

22 *Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. New York: Oxford University Press inc. 1999.*

23 *Guadagnoli E, Shapiro CL, Weeks JC et al. The quality of care for treatment of early stage breast carcinoma: is it consistent with national guidelines? Cancer 1998; 83: 302-9.*

24 *Martin M, Pienkowski T, Mackey J et al. TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up. Breast Cancer Res Treat 2003; abstract 43.*

25 *Winer EP, Hudis C, Burnstein HJ et al. American society of clinical oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol 2005; 23 (3): 619-29.*

26 *Shapiro CL, Recht A. Side effects of adjuvant treatment of breast cancer. N Engl J Med 2001; 344: 1997-2008.*

27 *van Enckevort PJ, TenVergert EM, Schrantee S et al. Economic evaluations of systemic adjuvant breast cancer treatments: methodological issues and a critical review. Crit Rev Oncol Hematol 1999; 32: 113-24.*

Model variable

**Probabilities: the probability that a breast cancer patient**

Lymph node positive ($N^+$) is
N+ and hormone receptor positive ($ER^-$ or $PgR^+$) is
N+ and $ER^+$ or $PgR^+$ and postmenopausal is
N+ and $ER^+$ or $PgR^+$ and postmenopausal and ≥ 70 years is
N+ and $ER^-$ and $PgR^-$ and postmenopausal is
N+ and $ER^+$ or $PgR^+$ and postmenopausal and 50-59 years is
N+ and $ER^+$ or $PgR^+$ and postmenopausal and 60-69 years is
N+ and $ER^-$ and $PgR^-$ and postmenopausal and ≥ 70 years is
Lymph node negative (No) is and a tumour < 1 cm has
No is and a tumour of 1-3 cm has
No is and a tumour of 1-3 cm and MAI[a] < 10 or BR[b] I/II has
No is and a tumour of 1-3 cm and MAI ≥ 10 or BR III has and $ER^+$ or $PgR^+$ is
No is and a tumour of 1-3 cm and MAI ≥ 10 or BR III has and $ER^+$ or $PgR^+$ and postmenopausal is
No is and a tumour of 1-3 cm and MAI ≥ 10 or BR III has and $ER^+$ or $PgR^+$ and postmenopausal and ≥ 70 years is
No is and a tumour of 1-3 cm and MAI ≥ 10 or BR III has and $ER^-$ and $PgR^-$ and postmenopausal is
No is and a tumour of 1-3 cm and MAI ≥ 10 or BR III has and ER and PgR and postmenopausal and ≥ 70 years is
No is and a tumour > 3 cm has and $ER^+$ or $PgR^+$ is
No is and a tumour > 3 cm has and $ER^+$ or PgR and postmenopausal is
No is and a tumour > 3 cm has and $ER^+$ or $PgR^+$ and postmenopausal and ≥ 70 years is
No is and a tumour > 3 cm has and $ER^-$ and PgR and postmenopausal is
No is and a tumour > 3 cm has and ER and PgR and postmenopausal and ≥ 70 years is
No and ≤ 35 years is
No and ≤ 35 years and $ER^+$ and/or $PgR^+$ is

**Costs**

Nurses wage (per minute)
Specialists wage (per minute)
Blood test (per test)
Mammography (per mammography)
Tamoxifen (per tablet)
CMF chemotherapy (per cycle)

| Base case value | Data source |
|---|---|
| **Probability** | |
| 0.398 | Data from retrospective cohort |
| 0.659 | Data from retrospective cohort |
| 0.586 | Data from retrospective cohort |
| 0.412 | Data from retrospective cohort |
| 0.667 | Data from retrospective cohort |
| 0.188 | Data from retrospective cohort |
| 0 375 | Data from retrospective cohort |
| 0.3 | Data from retrospective cohort |
| 0 052 | Data from retrospective cohort |
| 0 792 | Data from retrospective cohort |
| 0.579 | Data from retrospective cohort |
| 0.583 | Data from retrospective cohort |
| 0.538 | Data from retrospective cohort |
| 0.429 | Data from retrospective cohort |
| 0.7 | Data from retrospective cohort |
| 0.286 | Data from retrospective cohort |
| 0.818 | Data from retrospective cohort |
| 0.75 | Data from retrospective cohort |
| 0.667 | Data from retrospective cohort |
| 0 | Data from retrospective cohort |
| 0 | Data from retrospective cohort |
| 0.013 | Data from retrospective cohort |
| 0 | Data from retrospective cohort |
| **Costs (€)** | |
| 0.37 | Radboud UMC collective agreement |
| 0.90 | Radboud UMC collective agreement |
| 1.32 | COTG |
| 49.01 | COTG |
| 0 50 | Pharmacist |
| 16.49 | Hospital pharmacist |

**Costs**

Anti-emetics (per cycle CMF)
Intravenous system and pump (per cycle CMF)

**Effectiveness**

N+, $ER^+$ or $PgR^+$, postmenopausal, ≥ 70 years, tamoxifen
N+, $ER^+$ or $PgR^+$, postmenopausal, < 70 years, tamoxifen
N+, $ER^+$ or $PgR^+$, postmenopausal, 50-59 years, combination therapy
N+, $ER^+$ or $PgR^+$, postmenopausal, 60-69 years, tamoxifen
N+, $ER^+$ or $PgR^+$, premenopausal, combination therapy
N+, $ER^-$ and $PgR^-$, postmenopausal, ≥ 70 years, no therapy
N+, $ER^-$ and $PgR^-$, postmenopausal, < 70 years, polychemotherapy
N+, $ER^-$ and $PgR^-$, premenopausal, polychemotherapy
No, no therapy
No, low risk[c], no therapy
No, high risk[d], $ER^+$ or $PgR^+$, postmenopausal, ≥ 70 years, tamoxifen
No, high risk, $ER^+$ or $PgR^+$, postmenopausal, < 70 years, tamoxifen
No, high risk, $ER^+$ or $PgR^+$, premenopausal, combination therapy
No, high risk, $ER^-$ and $PgR^-$, postmenopausal, ≥ 70 years, no therapy
No, high risk, $ER^-$ and $PgR^-$, postmenopausal, < 70 years, polychemotherapy
No, high risk, $ER^-$ and $PgR^-$, premenopausal, polychemotherapy
No, ≤ 35 years, $ER^+$ or $PgR^+$, combination therapy
No, ≤ 35 years, $ER^-$ and $PgR^-$, polychemotherapy

***Appendix A. Detailed information on the model input)***

| Costs (€) | |
|---|---|
| 13.82 | Hospital pharmacist |
| 4.05 | Purchase department Radboud UMC |
| **10-years overall survival** | |
| 30 | EBCTCG overview |
| 62 | EBCTCG overview |
| 64 | Expert opinion |
| 62 | EBCTCG overview |
| 70 | Expert opinion |
| 15 | EBCTCG overview |
| 49 | EBCTCG overview |
| 53 | EBCTCG overview |
| 80 | Expert opinion |
| 90 | EBCTCG overview |
| 65 | EBCTCG overview |
| 81 | EBCTCG overview |
| 86 | Expert opinion |
| 53 | EBCTCG overview |
| 69 | EBCTCG overview |
| 78 | EBCTCG overview |
| 86 | Expert opinion |
| 78 | Expert opinion |

a: MAI = mitotic activity index. b: BR = Bloom-Richardson differentiation grade. c: Low risk is defined as a tumour < 1 cm or a tumour of 1-3 cm and MAI < 10 or BR I/II. d: High risk is defined as a tumour 1-3 cm and MAI ≥ 10 or BR III or a tumour > 3 cm.

Chapter 8

# General Discussion, Future Perspectives, and Summary

The most important prognostic factor in primary breast cancer is the axillary lymph node status. During the late 1990s, the sentinel lymph node (SN) procedure was introduced, and was shown to be a reliable strategy to replace routine axillary lymph node dissection (ALND) in selected patients with primary breast cancer. In this thesis we questioned whether part of the advantages associated with the introduction of the SN procedure, might be lost due to the intensified pathological examination of the SN. In addition, we questioned whether a completion ALND is necessary in case of isolated tumor cells or micrometastases in the SN.

The first results of our multi-institutional prospective study, including 541 eligible patients with primary breast cancer, are described in **Chapter 2**. We evaluated whether we could identify risk factors predictive for non-sentinel lymph node (non-SN) metastases in patients with a positive SN. We also tried to identify a specific group of patients with a positive SN in whom the risk for non-SN metastases was less than 5%. Three predictive factors for non-SN metastases were identified: size of the SN metastasis, primary tumor size, and presence of lymphovascular invasion. We were not able to identify a specific low-risk group, in whom the risk for non-SN metastases was less than 5%, in whom a completion ALND might not be justified.

Intensified pathological examination of the SN may result in increased detection of tumor affected nodes. In **Chapter 3**, we studied whether the introduction of the SN procedure has led to stage migration due to the intensified work-up of the SN by the pathologist. Three hundred and sixty patients with operable breast cancer were prospectively included and compared with 88 historical controls from the year 1994, which were diagnosed with primary breast cancer before the introduction of the SN procedure. We concluded that the introduction of the SN procedure has led to the detection of more tumor affected lymph nodes due to the intensified pathological examination. However, stage migration did not occur when tumor deposits of ≤ 0.2mm were categorized as node-negative disease, according to the 2002 TNM classification.

Internationally, there is no consensus on the pathology protocol to be used to examine the SN. At present, therefore, various hospitals use different SN pathology protocols. In **Chapter 4**, we analyzed whether differences between hospitals in SN pathology protocols have an impact on subsequent surgical treatment strategies. We prospectively collected clinical and pathological data on 541 breast cancer patients who underwent a SN biopsy in four different hospitals. In the four involved hospitals, different SN pathology protocols existed. In hospitals A, B, and C, three levels of the paraffin block of the SN were pathologically examined (minimal recommendations according to the Dutch breast cancer guideline), whereas in hospital D, at least seven additional levels were examined (at least ten levels in total). We reported more patients diagnosed with a positive SN in hospital D as compared to hospitals A, B, and C ($p<0.001$), mainly due to increased detection of isolated tumor cells. This led to performing more completion ALNDs in hospital D ($p<0.0001$). In 52%

of patients in hospital D a negative completion ALND was performed compared to in 19% of patients in hospitals A, B, and C combined. We concluded that differences in SN pathology protocols between hospitals do have a substantial impact on SN findings and subsequent surgical treatment strategies. Our obvious question was, whether ultrastaging, and thus more patients needing to undergo an additional ALND, is effective in reducing the risk of regional relapse.

We reported the follow-up data of 341 patients who had a negative SN, and therefore did not undergo an additional ALND, in **Chapter 5**. At five years follow-up, nine (2.6%) patients had developed a regional lymph node relapse. In hospital D none of the patients had a regional recurrence, as compared to nine (2.9%) cases of recurrence in hospitals A, B, and C combined. We concluded that 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 pathology protocol of hospital D.

Breast cancer is not only a substantial health care problem in terms of burden of disease, but also in terms of health care costs. In chapters 6 and 7 we presented cost-effectiveness studies. The primary aim of our study in **Chapter 6** was to evaluate cost-effectiveness from a hospital perspective of three axillary staging scenarios: a conventional ALND versus a SN procedure in day care surgery prior to breast surgery versus a SN procedure performed during surgery of the breast. We observed that with the introduction of the SN procedure, an extra outlay of € 430 (SN procedure in day care surgery) or € 266 (SN procedure during breast surgery) per patient was needed. This translated into an incremental cost-effectiveness ratio of € 701 and € 440, respectively, per case of an ALND avoided.

In **Chapter 7** we evaluated the potential impact of new national guidelines for adjuvant systemic therapy in breast cancer patients, introduced in the Netherlands in 1998 and 2001. The change in number of patients eligible for adjuvant systemic therapy after the introduction of these new guidelines, as well as the cost-effectiveness of treatment of patients with breast cancer was analyzed. We reported an 80% relative increase in patients eligible for adjuvant systemic therapy, since the introduction of the new national guideline in 1998, compared to the 1994 guideline. With an estimated 2% absolute increase of 10-years overall survival, the 1998 guideline was found to have an expected incremental cost-effectiveness ratio of € 4837 per life-year gained.

We reported the first study that analyzed the impact of different SN pathology protocols on decision making for a completion ALND in breast cancer patients. In one hospital (D) the SN was routinely examined at, at least, ten levels, whereas the other three hospitals routinely examined the SN at three levels of the paraffin block. With similar eligibility criteria for a SN biopsy, the detection frequency of isolated tumor cells was almost 35% in hospital D, compared to respectively, 8%, 3%, and 4% in the other hospitals. The detection frequency of micro-

metastases was 16% in hospital D, compared to respectively, 8%, 9%, and 10% in hospitals A, B, and C. These differences had a large impact on subsequent surgical treatment strategies. In hospital D 66% of patients underwent a completion ALND, compared to 29% of patients in the other three hospitals combined. Positive non-SNs were detected in 14% of patients in hospital D, compared to 10% in hospitals A, B, and C combined (p=0.70).

At five years follow-up we concluded no significant differences in regional recurrence rate between hospital D and the other three hospitals combined. We reported 3% regional recurrence rate in hospitals A, B, and C combined, compared to 0.0% in hospital D (p=0.37). Assuming that there is an absolute difference in regional recurrence risk of 3% between the hospitals with a 'standard intensified' pathology protocol and those which perform ultra-staging of the SN, the question raises whether performing 37% more completion ALNDs is worthwhile in order to prevent three regional recurrences. We concluded that a more than 'standard intensified' pathology protocol, in terms of morbidity of the surgical procedure and in terms of costs, is not of value. A SN pathology protocol as is used in most centers nowadays, with on average three levels per paraffin block, seems to be adequate, at five years follow-up.

At the time of execution of the study presented in this thesis, a completion ALND was common practice in case the SN showed tumor involvement, including isolated tumor cells and micrometastases. During later years this policy changed, in agreement with the American Society of Clinical Oncology (ASCO) guidelines. ASCO guidelines do not recommend a routine ALND if only isolated tumor cells are detected in the SN[1]. The Dutch MIRROR study showed 12% non-SN metastases in case isolated tumor cells were present in the SN. In agreement with other studies, the MIRROR study presented a very low regional recurrence rate when a completion ALND was omitted in this situation[2]. Based on these data, among others, in the Netherlands a completion ALND is not recommended in case of isolated tumor cells in the SN[3].

The Dutch guidelines of diagnosis and treatment of breast cancer were, at the time of execution of this study, quite conservative with respect to the recommendations for adjuvant systemic therapy. As reported in Chapter 5, nine out of 341 SN negative patients showed, at five years follow-up, a regional lymph node relapse (2.6%). Only four out of these nine patients had received adjuvant systemic therapy. If more patients would have had adjuvant systemic therapy, we would expect a lower risk of regional relapse. In the Netherlands, the indications for adjuvant systemic therapy based on primary tumor characteristics have broadened over the years.

The results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, in which patients with early stage breast cancer and one to two SNs containing metastases were randomized to undergo completion ALND or no further axillary treatment, showed that completion ALND can be

omitted for patients with a clinically node-negative axilla, who underwent lumpectomy and tangential whole breast irradiation, and were treated with systemic therapy, without adversely affecting the prognosis. After a median follow-up of 6.3 years, the regional recurrence rate was extremely low, and comparable in both groups. No difference in disease-free survival and overall survival was found[4]. Of note, the convincing results of this trial are thought to be related to patient selection, the use of systemic therapy in nearly all patients, and the use of tangential whole-breast irradiation as part of, for inclusion requested, breast conserving surgery.

In our study, five out of nine patients showing regional lymph node relapse, were treated with mastectomy without radiotherapy. It is unknown whether omission of completion axillary treatment is safe in patients with SN metastases who undergo mastectomy without radiotherapy. The recent St Gallen International Breast Cancer Conference Expert Panel agreed that patients undergoing mastectomy, patients who will not receive whole-breast tangential irradiation, patients with involvement of more than two positive SNs, and patients receiving neoadjuvant systemic therapy, should have completion axillary treatment[5].

It is unclear whether axillary radiation therapy can replace axillary dissection, in case of a positive SN. The recently closed 'After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) trial will answer this question. Patients with clinically negative lymph nodes were randomly assigned between ALND and axillary radiation therapy in case of a tumor-positive SN[6].

As we described risk factors predictive for non-SN metastases in patients with a positive SN in Chapter 2, currently, traditional prognostic factors are used to assess the benefit of adjuvant systemic therapy and the risk of recurrence. To improve the selection of patients who will benefit from adjuvant systemic therapy, molecular prognostic tools such as the Oncotype DX®[7] and the MammaPrint® test[8] were developed. However, the most important prognostic factor remained the axillary lymph node status. Future studies have to define the role of axillary staging when using molecular prognostic tools (gene expression profiling techniques). Is there, in clinically node negative patients, still a role for the SN procedure? Or can a SN biopsy be omitted in patients with a good prognosis signature, or in patients with a poor prognosis signature, because these patients will receive adjuvant systemic therapy anyhow? All these questions need to be addressed in future clinical trials.

## REFERENCES


1 *Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005;23:7703-7720.*

2 *Pepels MJ, de Boer M, Bult P, et al. Regional recurrence in breast cancer patients with sentinel node micrometastases and isolated tumor cells. Ann Surg 2012;255:116-121.*

3 *Updated Dutch guidelines of diagnosis and treatment of breast cancer. National Breast*

*Cancer Organization of the Netherlands; www.oncoline.nl (2012) (In Dutch).*

4 *Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis. JAMA 2011;305:569-575.*

5 *Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes-dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 2011;22:1736-1747.*

6 *Straver ME, Meijnen P, van Tienhoven G, et al. Role of axillary clearance after a tumor-positive sentinel node in the administration of adjuvant therapy in early breast cancer. J Clin Oncol 2010;28:731-737.*

7 *Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24: 3726-3734.*

8 *Knauer M, Mook S, Rutgers EJ, et al. The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer. Breast Cancer Res Treat 2010;120: 655-661.*

# CHAPTER 9

Chapter 9

# Nederlandse samenvatting

In Nederland wordt jaarlijks bij 14.000 vrouwen de diagnose borstkanker gesteld. De belangrijkste prognostische factor bij borstkanker wordt bepaald door de af- of aanwezigheid van uitzaaiingen in de lymfeklieren in de oksel. Eind jaren negentig van de vorige eeuw werd binnen een geselecteerde groep patiënten de primaire okselklierdissectie, inhoudende het verwijderen van alle oksellymfeklieren, vervangen door de schildwachtklierprocedure. Het principe hiervan gaat uit van een bepaald lymfedrainagepatroon vanaf de tumor, waarbij de eerste lymfeklier waarnaar de tumor draineert ook als eerste mogelijke uitzaaiingen bevat de schildwachtklier genoemd. Afhankelijk van het wel of niet bevatten van uitzaaiingen in deze één to drie klier(en) kan verder beleid gemaakt worden ten aanzien van verdere lokale en systemische behandeling. Vanuit het patiëntenperspectief is het grootste voordeel het achterwege laten van een aanvullende okselklierdissectie indien er geen sprake is van uitzaaiingen in de schildwachtklier. Dit kan bij deze patiënten complicaties zoals armoedeem voorkomen. De verwijderde schildwachtklieren worden, in vergelijking met de oksellymfeklieren die tijdens een okselklierdissectie worden verwijderd, door de patholoog veel intensiever onderzocht. Door minutieus pathologisch onderzoek van de schilwachtklier worden frequent zeer kleine uitzaaiingen zoals geïsoleerde tumorcellen (≤ 0,2 mm) en micrometastasen (> 0,2 mm - ≤ 2,0 mm) gedetecteerd. In een multicentrische prospectieve studie met 541 patiënten met borstkanker, waarvan de resultaten in dit proefschrift zijn beschreven hebben we ons afgevraagd of naast voordelen van de introductie van de schildwachtklierprocedure ook eventuele nadelen bestaan met name door het intensieve pathologische onderzoek van de schildwachtklier. We beschrijven de klinische betekenis van geïsoleerde tumorcellen en micrometastasen in de schildwachtklier bij patiënten met borstkanker.

In **Hoofdstuk 1** hebben we een inleiding op het proefschrift gegeven en hebben we beschreven welke onderwerpen in de verschillende hoofdstukken aan de orde worden gesteld.

In **Hoofdstuk 2** hebben we de resultaten beschreven van het onderzoek naar risicofactoren die van voorspellende waarde zijn op het hebben van uitzaaiingen in de resterende oksellymfeklieren na een schildwachtklierprocedure, de zogenaamde niet-schildwachtklieren, die werden verkregen na een aanvullende okselklierdissectie bij patiënten met uitzaaiingen in de schildwachtklier. We hebben drie risicofactoren met voorspellende waarde voor uitzaaiingen in deze niet-schildwachtklieren kunnen identificeren: de grootte van de uitzaaiing in de schildwachtklier, de grootte van de primaire borsttumor en de aanwezigheid van lymfe- en/of bloedvatinvasie. Ook hebben we geprobeerd een specifieke groep van patiënten te identificeren met uitzaaiingen in de schildwachtklier bij wie de kans op uitzaaiingen in de niet-schildwachtklieren kleiner is dan 5%. Bij patiënten uit deze laag-risico-groep zou het achterwege laten van een aanvullende okselklierdissectie immers gerechtvaardigd kunnen zijn. Deze specifieke laag-risico-groep hebben we met onze data echter niet kunnen aantonen.

Geïntensiveerd pathologisch onderzoek van de schildwachtklier zou kunnen resulteren in een toename van het aantal positieve lymfeklieren (lymfeklieren met uitzaaiingen). In **Hoofdstuk 3** hebben we onderzocht of de introductie van de schildwachtklierprocedure heeft geleid tot stadiummigratie als gevolg van geïntensiveerd pathologisch onderzoek van de schildwachtklier(en). Driehonderdzestig patiënten met operabele borstkanker werden prospectief in een studie geïncludeerd en vergeleken met een controlegroep bestaande uit 88 patiënten die werden geopereerd in het jaar 1994, ruim voor de introductie van de schildwachtklierprocedure. We concludeerden dat de introductie van de schildwachtklierprocedure heeft geleid tot het detecteren van meer (kleine) uitzaaiingen in de lymfeklieren door geïntensiveerd pathologisch onderzoek. Dit heeft echter niet geleid tot stadiummigratie omdat de TNM-classificatie 2002 geïsoleerde tumorcellen (uitzaaiingen ≤ 0,2 mm) niet classificeert als lymfeklieruitzaaiing (pNo).

Internationaal bestaat er geen consensus over het te gebruiken pathologieprotocol voor het onderzoeken van de schildwachtklier. Vandaag de dag worden door verschillende ziekenhuizen hiervoor verschillende pathologieprotocollen gebruikt. In **Hoofdstuk 4** hebben we onderzocht of de verschillende ziekenhuisprotocollen consequenties hebben voor de eventuele aanvullende chirurgische behandeling. We hebben prospectief klinische en pathologische data verzameld van 541 borstkankerpatiënten die een schildwachtklierprocedure ondergingen in vier verschillende ziekenhuizen (A-D). In deze vier ziekenhuizen werden verschillende pathologieprotocollen gebruikt voor het analyseren van de schildwachtklier. In ziekenhuizen A, B en C werd protocollair het paraffineblok van de schildwachtklier op drie niveaus aangesneden en onderzocht (het minimale advies voor de bewerking van de schildwachtklier volgens de Richtlijn Mammacarcinoom). In ziekenhuis D daarentegen werden protocollair ten minste zeven extra niveaus onderzocht (totaal ten minste tien niveaus). We constateerden meer positieve schildwachtklieren in ziekenhuis D in vergelijking met ziekenhuizen A, B en C ($p<0,001$), vooral als gevolg van het frequenter detecteren van geïsoleerde tumorcellen. Dit leidde tot een toename in het uitvoeren van aanvullende okselklierdissecties in ziekenhuis D ($p<0,0001$). Bij 52% van de patiënten in ziekenhuis D werd een aanvullende okselklierdissectie verricht zonder positieve niet-schildwachtklieren in vergelijking tot 19% van de patiënten in ziekenhuizen A, B en C samen. We hebben geconcludeerd dat verschillende pathologieprotocollen voor de beoordeling van de schildwachtklier impact heeft op de pathologische stadiëring en daarmee ook gevolgen heeft voor de eventuele aanvullende chirurgische behandeling. De hieruit volgende logische vraag was of geïntensiveerd pathologisch onderzoek van de schildwachtklier, resulterend in toename van het aantal patiënten bij wie een aanvullende okselklierdissectie moet worden verricht, een afname in regionaal recidief tot gevolg heeft.

In **Hoofdstuk 5** hebben we de follow-up data van 341 patiënten met een negatieve schildwachtklier, en dus zonder aanvullende oksel-

klierdissectie beschreven. Na vijf jaar follow-up hadden negen (2,6%) patiënten regionaal recidief ontwikkeld. In ziekenhuis D trad geen regionaal recidief op, in de ziekenhuizen A, B en C samen bij negen (2,9%) patiënten. We hebben geconcludeerd dat een minder intensief onderzoek van de schildwachtklier lijkt samen te hangen met een toename van regionaal recidief. Het absolute risico was echter minder dan 3%, en lijkt het geïntensiveerde pathologie protocol van ziekenhuis D niet te rechtvaardigen.

In hoofdstuk 6 en 7 hebben we onze kosteneffectiviteitstudies beschreven. Het primaire doel van onze studie zoals beschreven in **Hoofdstuk 6** was het evalueren van de kosteneffectiviteit van drie verschillende scenario's om de oksel te stadiëren: de primaire okselklierdissectie versus een poliklinisch uitgevoerde schildwachtklierprocedure vóór de borstoperatie tegenover de schildwachtklierprocedure tijdens de borstoperatie. We constateerden dat met de introductie van de schildwachtklierprocedure extra kosten gemaakt werden: € 430 per patiënt bij de poliklinisch uitgevoerde schildwachtklierprocedure of € 266 per patiënt bij de schildwachtklierprocedure tijdens de borstoperatie waarvoor de patient werd opgenomen. Dit verschil werd vertaald naar een kosteneffectiviteit ratio van respectievelijk € 701 en € 440 om één okselklierdissectie te voorkomen.

In **Hoofdstuk 7** hebben we de mogelijke gevolgen van nieuwe richtlijnen voor adjuvante systeemtherapie bij borstkankerpatiënten die werd geïntroduceerd in Nederland in 1998 en 2001, geëvalueerd. We hebben het verschil in aantal patiënten dat in aanmerking komt voor adjuvante systeemtherapie na de introductie van nieuwe richtlijnen geanalyseerd, en ook de kosteneffectiviteit van de adjuvante systeemtherapie. We constateerden een stijging van 80% van het aantal patiënten dat in aanmerking komt voor adjuvante systeemtherapie sinds de introductie van de nieuwe nationale richtlijn in 1998, vergeleken met de richtlijn uit 1994. De introductie van de nieuwe richtlijn in 1998 resulteerde in een toegenomen 10-jaars overleving van 2%, waarbij de kosten per gewonnen levensjaar € 4837 bedragen.

Tot slot beschouwen we in **Hoofdstuk 8** onze resultaten vanuit de huidige ontwikkelingen in de behandeling van patiënten met borstkanker.

# List of Publications

V.C.G. Tjan-Heijnen, P. Bult, **M.J. Bolster**, P.G. Peer, T. Wobbes.

Detailed pathological examination of the sentinel lymph nodes in order to detect micrometastases: no clinical relevance in patients with breast cancer.

*Nederlands Tijdschrift voor Geneeskunde (2005) 149(9): 494.*

W. Kievit, **M.J. Bolster**, G.J. van der Wilt, P. Bult, F.B.J.M. Thunnissen, J. Meijer, L.J.A. Strobbe, J.H.G. Klinkenbijl, T. Wobbes, E.M.M. Adang, L.V.A.M. Beex, V.C.G. Tjan-Heijnen.
*(First two authors contributed equally to this study)*

Cost-effectiveness of new guidelines for adjuvant systemic therapy for patients with primary breast cancer.

*Annals of Oncology (2005) 16(12): 1874-1881.*

**M.J. Bolster**, P. Bult, R.F.M. Schapers, J.W.R. Meijer, L.J.A. Strobbe, C.L.H. van Berlo, J.H.G. Klinkenbijl, P.G.M. Peer, T. Wobbes, V.C.G. Tjan-Heijnen.

Differences in sentinel lymph node pathology protocols lead to differences in surgical strategy in breast cancer patients.

*Annals of Surgical Oncology (2006) 13(11): 1466-1473.*

**M.J. Bolster**, P.G.M. Peer, P. Bult, F.B.J.M. Thunnissen, R.F.M. Schapers, J.W.R. Meijer, L.J.A. Strobbe, C.L.H. van Berlo, J.H.G. Klinkenbijl, L.V.A.M. Beex, T. Wobbes, V.C.G. Tjan-Heijnen.

Risk factors for non-sentinel lymph node metastases in patients with breast cancer. The outcome of a multi-institutional study.

*Annals of Surgical Oncology (2007) 14(1): 181-189.*

**M.J. Bolster**, P. Bult, C.A.P. Wauters, L.J.A. Strobbe, P.G.M. Peer, T. Wobbes, V.C.G. Tjan-Heijnen.

More tumor-affected lymph nodes because of the sentinel lymph node procedure but no stage migration, because the 2002 TNM classifies small tumor deposits as pathologic No breast cancer.

*Cancer (2009) 115(23): 5589-5595.*

**M.J. Bolster**, M.J. Pepels, C.A.P. Wauters, R.F.M. Schapers, J.W.R. Meijer, L.J.A. Strobbe, C.L.H. van Berlo, J.H.G. Klinkenbijl, T. Wobbes, A.C. Voogd, P. Bult, V.C.G. Tjan-Heijnen.

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

*European Journal of Surgical Oncology (2013) 39(5): 437-441.*

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Winanda de Ruijter, lieve Winan, jij bent mijn heelkundemaatje vanaf dag 1. Vanaf onze eerste cursus zijn we roommates. Ik heb je vandaag dan ook gewoon nodig aan mijn zij. Helaas hebben we ons perifere opleidingsdeel niet in dezelfde kliniek doorlopen en door onder andere onze drukke gezinnen spreken en zien we elkaar veel te weinig. Hoe leuk zou het zijn in de toekomst weer samen te werken? Heel fijn dat je vandaag mijn paranimf wil zijn.

Mirjam Huis in 't Veld, lieve Mir, onze vriendschap begon op de middelbare school, het Pius X college in Almelo. In Nijmegen werd dat verstevigd door huisgenoten te zijn. Wij spreken en zien elkaar veel te weinig, maar ik weet dat we anytime de draad weer kunnen oppakken. Het staat al heel lang vast dat jij mijn paranimf bent vandaag. Ik hoop dat je trots op me bent zoals ik was op 29 augustus 2011 tijdens jouw promotie.

Familie van Eenennaam, lieve schoonfamilie, dank voor jullie onophoudelijke interesse.

Mijn broer en zus, lieve Koen en Janneke, wat is het ongelooflijk fijn dat wij vrienden zijn. Mede dankzij jullie, en Margreet en Taco's, onophoudelijke support ligt mijn boek er. Hoe bijzonder is het broer, om onze dochters samen te zien opgroeien. En zusje, hoe bijzonder is het dat we (bijna) hetzelfde vak uitoefenen. Ik ben erg trots op alles wat jullie tot nu toe al hebben bereikt.

Mijn ouders, lieve pap en mam, aan jullie is dit boek opgedragen omdat ik door jullie onophoudelijke steun en onvoorwaardelijke liefde bereik wat ik graag wil bereiken. Ik weet dat jullie vandaag trots als een pauw op rij 1 zullen zitten.

Onze prachtige, fantastische ladies, Charlotte en Lobke, jullie zijn de drijfveer geweest achter het afronden van dit boek. Ik ben apetrots op jullie en verheug me erop jullie te zien opgroeien.

Als laatste (!) mijn Hans, lieve vanE, wat bof ik met jou! Niemand kent mij beter dan jij. Het is heerlijk hoe jij alles weet te relativeren. Door jouw positieve stimulans en je onmeetbare hulp is dit boek nu af. Laat dat draaiorgel maar draaien, ik hou van je!

# Curriculum Vitae

Marieke Johanna Bolster is geboren op 6 mei 1975 te Neede als dochter van Ria ter Braak en Ton Bolster. Zij is opgegroeid in Neede en Tubbergen en behaalde in 1993 het vwo-diploma aan het Pius X College te Almelo. Aansluitend ging ze geneeskunde studeren aan de Radboud Universiteit te Nijmegen. Tijdens haar studie was zij lid van de Nijmeegse Studentenroeivereniging Phocas. Ze was van 1997 - 1998 lid van het bestuur van de Medische Faculteit Vereniging Nijmegen.

Marieke sloot in 2001 haar geneeskundestudie af met een wetenschappelijke stage op het gebied van de chirurgie onder supervisie van dr. Luc. J.A. Strobbe in het Canisius-Wilhelmina Ziekenhuis te Nijmegen.

Van 2002 tot en met 2004 werkte zij als assistent-geneeskunde-niet-in-opleiding op de afdeling Heelkunde van het UMC St Radboud te Nijmegen. Tevens startte zij in deze periode het onderzoek dat is beschreven in dit proefschrift.

In 2005 is Marieke verhuisd naar Boston (MA) waar ze diverse stages op radiologische afdelingen heeft gelopen (Dana-Farber Cancer Institute en het Brigham and Women's Hospital te Boston).

Terug in Nijmegen, startte ze in september 2006 met de opleiding Heelkunde in het UMC St Radboud te Nijmegen onder begeleiding van prof. dr. R.P. Bleichrodt en later prof. dr. C.M.J.H. van Laarhoven. Sinds september 2008 vervolgt ze deze opleiding in het Canisius-Wilhelmina Ziekenhuis te Nijmegen onder begeleiding van dr. W.B. Barendregt en later dr. C. Rosman. Ze differentieert zich als oncologisch chirurg. Tijdens haar opleiding is zij actief betrokken geweest bij de organisatie van verschillende CARS-symposia (2006 - 2009). In april 2014 verwacht ze haar opleiding in de Heelkunde af te ronden.

Marieke heeft de onderzoeksresultaten zoals ze zijn beschreven in dit proefschrift, gepresenteerd op verschillende wetenschappelijke congressen zoals San Antonio Breast Cancer Conference, Society of Surgical Oncology (VS), European Breast Cancer Conference en Chirurgendagen.

Marieke is getrouwd met Hans van Eenennaam en moeder van Charlotte en Lobke.

## Stellingen bij het proefschrift
## **The sentinel lymph node in breast cancer, a re-appraisal**

1 'Less is more' lijkt op te gaan voor het pathologische onderzoek van de schildwachtklier(en). *Dit proefschrift*

2 Het blijkt moeilijk een laag-risico-groep aan te wijzen waarbij een aanvullende behandeling van de oksel achterwege gelaten kan worden bij een positieve schildwachtklier. *Dit proefschrift*

3 Zeer intensief pathologisch onderzoek van de schildwachtklier(en) leidt tot overbehandeling. *Dit proefschrift*

4 De introductie van de schildwachtklierbiopsie bij borstkankerpatiënten heeft niet geleid tot stadiummigratie. *Dit proefschrift*

5 Een poliklinisch uitgevoerde schildwachtklierbiopsie is een relatief dure maar patiëntvriendelijke ingreep. *Dit proefschrift*

6 In victory I deserve champagne; in defeat I need it. *Napoleon Bonaparte*

7 In baseball it is not always true, but in oncology it is: METS always win. *Dana-Farber Cancer Institute*

8 Ik leer wat ik lees
Of het nou leuk is of niet
Hoe meer ik kan
Hoe meer ik lees
Hoe meer ik zal weten
Slim word ik ervan
Maar ik zal het ooit weer vergeten
*Wouter Out*

9 Wining is for dinner

10 Many people will walk in and out of your life, but only true friends will leave footprints in your heart. *Eleanor Roosevelt*

*Marieke Bolster, 6 december 2013*