

Survival after negative sentinel lymph node biopsy in breast cancer at least equivalent to after negative extensive axillary dissection

G.P. Kuijt^{a,b,*}, L.V. van de Poll-Franse^c, A.C. Voogd^{c,d},
G.A.P. Nieuwenhuijzen^e, R.M.H. Roumen^b

^a Department of Surgery, University Medical Centre St. Radboud, Nijmegen, The Netherlands

^b Department of Surgery, Máxima Medical Centre, P.O. Box 7777, 5500 MB Veldhoven, The Netherlands

^c Eindhoven Cancer Registry, Comprehensive Cancer Centre South, Eindhoven, The Netherlands

^d Department of Epidemiology, Maastricht University, Maastricht, The Netherlands

^e Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands

Accepted 13 November 2006

Available online 29 December 2006

Abstract

Aim: Sentinel lymph node biopsy (SLNB) without completion axillary lymph node dissection (ALND) is replacing ALND as the axillary staging procedure of choice in breast cancer patients with a clinically negative axilla even though it is unclear whether this influences patient survival. Our aim was to compare the survival of breast cancer patients with a negative SLNB without completion ALND to that of extensive ALND-negative patients.

Methods: Eindhoven Cancer Registry data on breast cancer patients diagnosed between 1989 and 2002 with follow-up to 1 January 2005 was used. Survival was compared between 880 SLNB-negative women (median follow-up 3.6 years) without completion ALND and 1681 ALND-negative women (median follow-up 7.7 years) with at least 10 axillary nodes removed. Conclusions were made after correcting for age, tumour size, tumour location, tumour histology, tumour grade, mitotic activity index (MAI), hormone receptor status, and local and systemic treatment in uni- and multivariate analyses.

Results: Crude 5-year survival rates were 85% for ALND-negative and 89% for SLNB-negative breast cancer patients ($p = 0.026$). After correction for potential confounders in a multivariate Cox regression analyses, the hazard ratio for overall mortality of ALND-negative compared to SLNB-negative patients without completion ALND was 1.23 (95% confidence interval: 0.93–1.64).

Conclusion: Survival after a SLNB without completion ALND is at least equivalent to after an extensive ALND in node-negative breast cancer patients. This means that the SLNB only can safely replace ALND as the procedure of choice for axillary staging in breast cancer patients with a clinically negative axilla.

© 2006 Elsevier Ltd. All rights reserved.

Keywords: Breast cancer; Sentinel lymph node biopsy; Lymph node dissection; Prognosis; Survival

Introduction

The axillary lymph node status has independent prognostic value in staging breast cancer patients.¹ During the past decade, a paradigm shift has occurred in axillary staging, from a standard complete axillary lymph node dissection (ALND) for every patient with breast cancer to a sentinel lymph node biopsy (SLNB) in the group of patients with

a clinically negative axilla. This change has been motivated by the high morbidity of the ALND procedure.^{2–4}

The sentinel node is defined as “the first lymph node to receive lymphatic drainage from a primary tumour”.⁵ If this sentinel lymph node, sometimes physically consisting of more than one lymph node, contains no metastatic tumour, then it is unlikely other lymph nodes will contain metastasis.⁵ In breast cancer this means that when a SLNB contains no metastasis, it is unnecessary to perform a completion ALND.

When the SLNB does contain metastasis, a completion ALND is recommended in order to further stage the axilla and to maintain local control. A false-negative SLNB procedure will result in omitting an ALND and possibly in

* Corresponding author. Department of General Surgery, University Hospital St. Radboud, Geert Grooteplein-Zuid 10, 6525GA Nijmegen, The Netherlands. Tel.: +31 32 14479768; fax: +31 40 888 8565.

E-mail address: gert.kuijt@skynet.be (G.P. Kuijt).

under staging the disease, then resulting in the withholding of adjuvant systemic therapy and inferior prognosis.

To avoid false-negative procedures, the introduction of the SLNB has been accompanied by multiple validation studies. Initial studies focused on feasibility issues including performing a completion ALND after SLNB in a single session as proof of performance.⁶ More recently SLNB-negative patient series reporting axillary recurrence have been published.^{7–10} These studies show that the SLNB is reliable in detecting axillary metastasis and that it has a low axillary recurrence rate. Before SLNB is completely accepted as the procedure of choice in the staging of clinically node-negative breast cancer patients, survival after both procedures must be compared, especially since a meta-analysis has shown that ALND in itself increases survival in clinically node-negative breast cancer patients.¹¹

The aim of this study was to confirm the validity of the SLNB by comparing the survival rate of breast cancer patients with negative lymph node following SLNB without completion ALND to the survival rate of breast cancer patients with negative lymph nodes following an extensive ALND. The hypothesis is that survival following a SLNB is at least equivalent to survival following an adequate ALND. This would constitute definitive evidence that the SLNB can safely replace ALND as the gold standard for axillary staging in breast cancer patients with a clinically negative axilla.

Patients and methods

Patient selection

Patient data were retrieved from the Eastern area of the population-based Eindhoven Cancer Registry¹² serving a population of one million inhabitants in the south-eastern Netherlands. Trained registry clerks collected data from hospital records in 10 hospitals, consisting of large non-university teaching hospitals as well as community hospitals, and from two radiotherapy departments. Collected data is continually internally monitored for completeness and accuracy.¹²

Patients were selected from those registered with breast cancer in the period 1989–2002. A SLNB group was defined as those patients having undergone a negative SLNB without further ALND. The ALND group was defined as those patients having undergone a negative ALND where 10 or more lymph nodes were found at pathological investigation. The choice of defining an extensive ALND as containing 10 or more lymph nodes was made to minimize the risk of erroneous classification of the axilla.^{13,14}

Treatment guidelines

The regional Breast Cancer Study Group has been responsible for the development of multidisciplinary guidelines for the management of breast cancer since 1978.

Surgical treatment during the study period consisted of primary tumour resection via lumpectomy or mammary ablation as well as axillary staging. Complete axillary dissection was recommended for all patients with resectable breast cancer. The borders of the dissection were the latissimus dorsi muscle (dorsal), the thoracic wall (medial), the pectoral muscles (ventral), and the lower border of the axillary vein (cranial). The SLNB was introduced in the registry region in 1995, starting with validation studies including subsequent axillary dissection.⁶ In 1997, surgeons in three of the 10 hospitals started performing SLNB procedures in clinically node-negative patients as a routine staging procedure without completion ALND in cases with a negative sentinel node, and since 2002 is has been routinely performed in all hospitals. Lymphatic mapping included the use of both radioactive lymphoscintigraphy and blue dye.¹⁵

The axillary lymph nodes in the ALND group were evaluated histologically with haematoxylin and eosin (H&E) stains of one or two sections. Analysis of the sentinel lymph nodes additionally included serial sectioning and immuno-histochemical staining if no metastasis was found on the H&E stain. All patients were staged according to the Tumour-Node-Metastasis (TNM) classification system of the International Union Against Cancer.

Until 2000, adjuvant hormone or chemotherapy treatment was only recommended for axillary node-positive patients. Since 2000, guidelines have evolved to also recommend systemic treatment to selective node-negative patients depending on additional factors other than the lymph node status, such as the size and the histological grade of the tumour and the steroid receptor status.¹⁶ In the present study population of lymph node-negative breast cancer patients, radiotherapy was mostly applied to the breast in the context of breast conserving treatment although sporadically other indications existed.

Data available for analysis

The following data for each patient were available for analysis: period of diagnosis, age at diagnosis, tumour size defined at pathological evaluation, tumour location, tumour histology, tumour grade, mitotic activity index (MAI), oestrogen and progesterone receptor status, treatment of the primary tumour, and whether or not systemic therapy was administered. The MAI is a standardized method of assessing the mitotic count of a tumour and is defined as the sum of mitoses in 10 high-power microscope fields, equivalent to a surface area of 1.59 mm², at the periphery of the tumour.¹⁷ The mitotic count is considered the most predictive component of the histological grade.

Follow-up was completed through January 1, 2005, and was obtained from municipal registries and the Central Bureau for Genealogy. The latter is an institution that collects data on all deceased Dutch citizens via all municipal registries. This way, information on patients who had moved

outside the registry area was also obtained. Patients who died outside the Netherlands were wrongly considered as “being alive”. The estimated proportion of these patients was approximately 0.3%.

Statistical analysis

Statistical analyses were performed using SAS (version 9.1 for Windows, SAS institute Inc., Cary, NC). Differences in patient characteristics between those with SLNB without completion ALND and those with ALND were tested by means of chi-square statistics. Survival analysis was carried out using the Kaplan–Meier method to evaluate the prognosis after the diagnosis of breast cancer. Survival time was defined as the period between the date of diagnosis and the date of death or last follow-up. Patients with incomplete follow-up were censored at the date of last follow-up. The overall survival of patients with node-negative breast cancer following a sentinel node procedure was compared with the survival rates of patients with 10 or more tumour-negative lymph nodes following axillary lymph node dissection. The survival curves were compared by means of the two-tailed log-rank test.

Univariate analysis were performed to assess the relationship of overall survival to the following variables: axillary staging procedure, period of diagnosis, age at diagnosis, tumour size, tumour location, tumour histology, tumour grade, MAI, oestrogen and progesterone receptor status, tumour treatment, and whether or not systemic therapy was given.

Multivariate Cox proportional hazards regression analyses were carried out to adjust for potential confounding effects. Co-variables found to be significant in the univariate analysis were analyzed with respect to the relationship between mortality risk and the axillary staging procedure performed. Period of diagnosis was excluded in the multivariate analysis because it was estimated that including period of diagnosis would overcorrect for the variable “axillary staging procedure”. Hazard ratios (HR) with 95% confidence intervals (95% CI) and *p* values were estimated with respect to the reference category for each covariate.

Results

There were 7974 patients documented as having had breast cancer between 1989 and 2002. This study compared the 880 of these patients having undergone a SNLB procedure without completion ALND to the 1681 patients having undergone an ALND where 10 or more lymph nodes were found at pathological examination. The remaining patients were excluded: 2869 were node positive; 754 lacked information on the number of lymph nodes; and 1790 patients were reported as having less than 10 lymph nodes found at pathological examination.

Demographic and clinical characteristics are presented in Table 1. Age at diagnosis and tumour histology were comparable in both groups while all other parameters were significantly different. The patients who underwent SLNB without completion ALND were more likely to

Table 1

General characteristics of patients with lymph node-negative breast cancer according to number of lymph nodes (*n* = 2561)

	Axillary staging procedure		χ^2 -test <i>p</i> value
	SLNB <i>n</i> = 880	ALND, ≥ 10 nodes examined <i>n</i> = 1681	
Period of diagnosis			
1989–1993	0	487	
1994–1998	64	889	
1999–2002	816	305	<0.0001
Age (years)			
<50	219	439	
50–69	470	859	
70+	191	383	0.54
Tumour size (pT)			
T1	671	1077	
T2	178	480	
T3	4	21	
T4	13	51	
Unknown	14	52	<0.0001
Tumour location			
Lateral	451	774	
Medial/central	219	442	
Overlapping	186	431	
Missing	24	34	0.02
Tumour histology			
Ductal	654	1252	
Lobular mixed	158	296	
Mucinous	49	110	
Other	19	23	0.37
Tumour grade			
1	166	137	
2	224	360	
3	142	251	
Missing	348	933	<0.0001
MAI			
<10	608	354	
≥ 10	149	147	
Missing	123	1180	<0.0001
ER			
Positive	610	849	
Negative	122	297	
Missing	148	535	<0.0001
PR			
Positive	471	625	
Negative	156	331	
Missing	253	725	<0.0001
Tumour treatment			
BCS + RT	697	938	
BCS – RT	41	33	
Mastectomy – RT	131	583	
Other	11	127	<0.0001
Systemic therapy			
No	661	1531	
Yes	219	150	<0.0001

MAI, mitotic activity index; ER, oestrogen receptor; PR, progesterone receptor; BCS, breast conserving surgery; RT, radiotherapy.

have small tumours, laterally located tumours, well differentiated tumours and hormone receptor positive tumours, and were more likely to have had breast conserving treatment and systemic therapy than the patients in the ALND group.

Crude 5-year survival rates were 85% for ALND-negative and 89% for SLNB-negative breast cancer patients ($p = 0.026$) (Fig. 1).

Univariate analysis showed a significant survival disadvantage for the ALND group compared to the SLNB without completion ALND group, hazard ratio 1.37 (95% CI: 1.04–1.80) (Table 2). Other variables in univariate analysis significantly associated with an increased hazard ratio were the earlier periods of diagnosis, older age (70+) at diagnosis, increasing tumour size, higher tumour grade, mucinous tumour histology, and not having had radiotherapy.

After adjustment for age, tumour size, tumour histology, tumour grade, and local tumour treatment in multivariate Cox-regression analyses, the hazard ratio for ALND-negative versus SLNB-negative patients without completion ALND was: 1.23 (95% CI: 0.93–1.64) (Table 2). Other variables independently associated with an increased hazard ratio were age at diagnosis (70+ vs. <50: HR 3.18; CI 2.45–4.11), tumour size (>2–5 cm vs. ≤2 cm: HR 1.47; CI 1.20–1.80), tumour grade (poorly vs. well differentiated: HR 1.74; CI 1.14–2.67), and breast conserving treatment without versus with radiotherapy (HR 1.74; CI 1.03–2.95) (Table 2).

Discussion

Main message

In this population-based study, the overall survival of breast cancer patients undergoing SLNB without completion ALND was better than that of patients undergoing an extensive ALND where at least 10 lymph nodes were removed. However, this survival advantage disappeared after

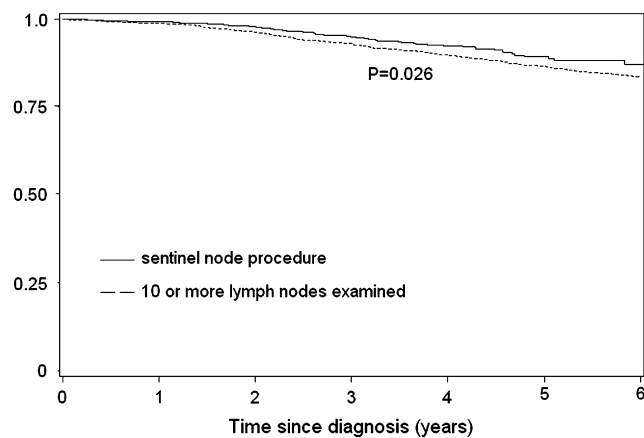


Figure 1. Overall survival of lymph node-negative breast cancer patients according to either SN procedure or 10 or more lymph nodes examined.

accounting for known prognostic factors in multivariate analysis. The conclusion is that survival was similar between the two groups.

The introduction of a new procedure in medicine is rightly only accepted after proof that it works and that it is safe to use it. That the SLNB procedure, including lymphatic mapping, surgery, and pathological analysis, works in detecting axillary lymph node metastasis has been well evaluated.¹⁸ That it does not influence survival without a completion ALND has not yet been proven. Ideally, proof of safety of the SLNB in staging the axilla in breast cancer patients should be determined in a controlled randomized trial comparing the SLNB without completion ALND to the ALND with survival as endpoint. Such studies are running but are not yet completed.⁴ In the meantime, this study made use of the large body of outcome data in the Eindhoven Cancer Registry to answer this question, compensating for potential bias in a multivariate analysis.

Possible bias and confounding

Patient selection in this population-based study is a possible source of bias. Out of the 7974 patients registered as having breast cancer between 1989–2002, 754 had no information on their axillary status, 434 reported zero lymph nodes found, and 1356 reported less than 10 lymph nodes found. Analysis of these sub-groups showed that these were primarily older patients in the earlier periods of this study. In very elderly patients it was customary to do only a limited ALND or even no ALND because it was thought they would not live long enough to profit from an extensive ALND. A multivariate analysis using only the patients from the most recent period 1999–2002, with many less missing values, did not significantly change the results. The hazard ratio of ALND versus SLNB without completion ALND for the period 1999–2002 was 1.02 (CI 0.69–1.51). This means that these missing values do not essentially change the results found in this study.

Tumour grade is well recognized as having strong prognostic value, and this study has many missing values for this parameter. Because of problems with uniformity and reproducibility of tumour differentiation grade, it was accepted practice during the period included in this study in the Netherlands for pathologists to report either the Bloom Richardson grade or the Mitotic Activity Index (MAI), or both. In order to reduce the number of missing values for this parameter, a separate analysis was done combining the Bloom Richardson grade with the MAI as a measure for tumour differentiation grade. When known, the Bloom Richardson grade was used and if unknown, then MAI was used with MAI greater or equal to 10 treated as tumour grade three and MAI less than 10 treated as tumour grade one.^{17,19} This reduced the missing values to 7% in the SLNB group and 44% in the ALND group. This only marginally changed the hazard ratio for tumour grade, from 1.74 (CI: 1.14–2.67) when analysing tumour grade and

Table 2
Multivariate analyses of overall survival in lymph node-negative breast cancer patients ($n = 2561$)

	Univariate		Multivariate ^a	
	HR	(95% CI)	HR	(95% CI)
Axillary staging procedure				
SLNB	1		1	
≥10 nodes examined	1.37	(1.04–1.80)*	1.23	(0.93–1.64)
Period				
1989–1993	1			
1994–1998	0.79	(0.63–0.98)*		
1999–2002	0.75	(0.57–0.99)*		
Age (years)				
<50	1		1	
50–69	0.95	(0.74–1.22)	0.98	(0.76–1.27)
70+	3.28	(2.56–4.21)**	3.18	(2.45–4.11)**
Tumour size (pT)				
T1	1		1	
T2	1.79	(1.48–2.18)**	1.47	(1.20–1.80)*
T3	1.78	(0.84–3.76)	2.04	(0.94–4.47)
T4	2.04	(1.31–3.19)*	1.57	(0.95–2.58)
Tumour location				
Lateral	1			
Medial/central	1.23	(0.99–1.53)		
Overlapping	1.14	(0.91–1.43)		
Tumour grade				
1	1		1	
2	1.28	(0.86–1.93)	1.28	(0.85–1.93)
3	1.57	(1.04–2.38)*	1.74	(1.14–2.67)*
MAI				
<10	1			
≥10	1.37	(0.94–2.00)		
Tumour histology				
Ductal	1		1	
Lobular mixed	0.92	(0.72–1.17)	0.81	(0.63–1.05)
Mucinous	0.56	(0.35–0.90)*	0.64	(0.40–1.04)
ER				
Negative	1			
Positive	1.02	(0.79–1.30)		
PR				
Negative	1			
Positive	0.81	(0.64–1.03)		
Tumour treatment				
BCS + RT	1		1	
BCS – RT	1.87	(1.11–3.14)*	1.74	(1.03–2.95)*
Mastectomy – RT	1.70	(1.40–2.07)**	1.19	(0.96–1.47)
Other	1.59	(1.13–2.24)*	0.99	(0.67–1.47)
Systemic therapy				
No	1			
Yes	1.16	(0.85–1.58)		

HR, hazard ratio; MAI, mitotic activity index; ER, oestrogen receptor; PR, progesterone receptor; BCS, breast conserving surgery; RT, radiotherapy.

* $p < 0.05$; ** $p < 0.0001$.

^a In the multivariate model, all variables were included that showed a significant univariate association. Period was not included in the model as this was thought to result in an overcorrection of the variable of interest.

MAI separately to 1.57 (CI: 1.13–2.18) when combining MAI with the tumour grade. This study presents the results separately so that readers can form their own opinion. It was outside the scope of this study to form conclusions about the nature and the strength of the relationship between MAI and tumour grade.

There was a significant difference in the distribution of tumour size and grade between the SNLB and ALND groups, as well as differences in local tumour treatment

and the administration of systemic therapy. The SLNB group included more patients with small tumours and well differentiated tumours, as well as more patients undergoing breast conserving treatment and receiving systemic treatment. A sub-analysis of these phenomena showed that this is primarily explained by the period in which the patient was diagnosed with breast cancer. Initial treatment guidelines advised against the use of SLNB in patients with tumours larger than 2 cm in diameter, with more

than one primary tumour, and with a clinically positive axilla.²⁰ Also, guidelines evolved over time to recommend hormone therapy and chemotherapy to selected node-negative patients.¹⁶ This is why this study did not include period of diagnosis as a separate parameter in the multivariate analysis. It would have overcompensated for recognized differences in tumour size, tumour grade, tumour treatment, and the administration of systemic treatment between the two groups as described above.

Conclusion

The introduction of the SLNB for staging the axilla rightly raised concerns about its feasibility, safety and accuracy. The results of this population-based study show that, after correction for known prognostic variables, breast cancer patients with a negative SLNB without completion ALND had survival similar to ALND-negative patients who had 10 or more axillary nodes examined. ALND therefore has no independent survival benefit in node-negative breast cancer patients, meaning that the SLNB without completion ALND can safely replace ALND as the procedure of choice for axillary staging in breast cancer patients with a clinically negative axilla.

References

1. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer* 1989;**63**(1): 181–7.
2. Purushotham AD, Upponi S, Klevesath MB, et al. Morbidity after sentinel lymph node biopsy in primary breast cancer: results from a randomized controlled trial. *J Clin Oncol* 2005;**23**(19):4312–21.
3. Schulze T, Mucke J, Markwardt J, Schlag PM, Bembenek A. Long-term morbidity of patients with early breast cancer after sentinel lymph node biopsy compared to axillary lymph node dissection. *J Surg Oncol* 2006;**93**(2):109–19.
4. 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**(9):599–609.
5. International Union Against Cancer (UICC). *TNM classification of malignant tumours*. 6th ed. New York: Wiley-Liss; 2002.
6. Roumen RM, Valkenburg JG, Geuskens LM. Lymphoscintigraphy and feasibility of sentinel node biopsy in 83 patients with primary breast cancer. *Eur J Surg Oncol* 1997;**23**(6):495–502.
7. Roumen RM, Kuijt GP, Liem IH, van Beek MW. Treatment of 100 patients with sentinel node-negative breast cancer without further axillary dissection. *Br J Surg* 2001;**88**(12):1639–43.
8. Smidt ML, Janssen CM, Kuster DM, Bruggink ED, Strobbe LJ. Axillary recurrence after a negative sentinel node biopsy for breast cancer: incidence and clinical significance. *Ann Surg Oncol* 2005;**12**(1):29–33.
9. de Kanter AY, Menke-Pluymers MM, Wouters MW, Burgmans I, van Geel AN, Eggermont AM. 5-Year follow-up of sentinel node negative breast cancer patients. *Eur J Surg Oncol* 2006;**32**(3):282–6.
10. 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: a follow-up study of 4008 procedures. *Ann Surg* 2004;**240**(3):462–8.
11. Orr RK. The impact of prophylactic axillary node dissection on breast cancer survival—a Bayesian meta-analysis. *Ann Surg Oncol* 1999;**6**(1): 109–16.
12. Eindhoven Cancer Registry, Comprehensive Cancer Centre South. <http://www.ikcnet.nl/ikz>. 27-4-2006.
13. Mathiesen O, Carl J, Bonderup O, Panduro J. Axillary sampling and the risk of erroneous staging of breast cancer. An analysis of 960 consecutive patients. *Acta Oncol* 1990;**29**(6):721–5.
14. Kiricuta CI, Tausch J. A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in patients with breast carcinoma. *Cancer* 1992;**69**(10):2496–501.
15. Roumen RM, Geuskens LM, Valkenburg JG. In search of the true sentinel node by different injection techniques in breast cancer patients. *Eur J Surg Oncol* 1999;**25**(4):347–51.
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 Geneesk* 2000;**144**(21):984–9 [in Dutch].
17. van Diest PJ, van der WE, Baak JP. Prognostic value of proliferation in invasive breast cancer: a review. *J Clin Pathol* 2004;**57**(7):675–81.
18. Liberman L. Pathologic analysis of sentinel lymph nodes in breast carcinoma. *Cancer* 2000;**88**(5):971–7.
19. Baak JP, van Diest PJ, Voorhorst FJ, et al. Prospective multicenter validation of the independent prognostic value of the mitotic activity index in lymph node-negative breast cancer patients younger than 55 years. *J Clin Oncol* 2005;**23**(25):5993–6001.
20. Roumen RM, Pijpers HJ, Thunnissen FB, Ruers TJ. Summary of the guideline ‘Sentinel node biopsy in breast cancer.’ Dutch Work Group ‘Sentinel Node Biopsy for Breast Cancer’. *Ned Tijdschr Geneesk* 2000;**144**(39):1864–7 [in Dutch].