Acta Oncologica, 2014; 53: 209–215

informa
healthcare

ORIGINAL ARTICLE

Robust and validated models to predict high risk of non-sentinel node metastases in breast cancer patients with micrometastases or isolated tumor cells in the sentinel node

TOVE F. TVEDSKOV[1], MAJ-BRITT JENSEN[2], EVA BALSLEV[3] & NIELS KROMAN[1]

[1]*Department of Breast Surgery, Copenhagen University Hospital, Copenhagen, Denmark,* [2]*Danish Breast Cancer Cooperative Group, Copenhagen, Denmark and* [3]*Department of Pathology, Herlev Hospital, Herlev, Denmark*

Abstract

Background. Benefit from axillary lymph node dissection in sentinel node positive breast cancer patients is under debate. Based on data from 1820 Danish breast cancer patients operated in 2002–2008, we have developed two models to predict high risk of non-sentinel node metastases when micrometastases or isolated tumor cells are found in sentinel node. The aim of this study was to validate these models in an independent Danish dataset. *Material and methods.* We included 720 breast cancer patients with micrometastases and 180 with isolated tumor cells in sentinel node operated in 2009–2010 from the Danish Breast Cancer Cooperative Group database. Accuracy of the models was tested in this cohort by calculating area under the receiver operating characteristic curve (AUC) as well as sensitivity and specificity. *Results.* AUC for the model for patients with micrometastases was comparable to AUC in the original cohort: 0.63 and 0.64, respectively. The sensitivity and specificity for predicting risk of non-sentinel node metastases over 30% was 0.36 and 0.81, respectively, in the validation cohort. AUC for the model for patients with isolated tumor cells decreased from 0.73 in the original cohort to 0.60 in the validation cohort. When dividing patients with isolated tumor cells into high and low risk of non-sentinel node metastases according to number of risk factors present, 37% in the high-risk group had non-sentinel node metastases. Specificity and sensitivity was 0.48 and 0.88, respectively, in the validation cohort when using this cut-point. *Conclusion.* In this independent dataset, the model for patients with micrometastases was robust with accuracy similar to the original cohort, while the model for patients with isolated tumor cells was less accurate. The models may be used to identify patients where axillary lymph node dissection should still be considered.

Today, sentinel lymph node dissection (SLND) has replaced axillary lymph node dissection (ALND) as standard procedure for staging of the axilla in clinically node negative breast cancer. SLND can accurately stage the axilla by removing on average only two lymph nodes. In case of metastatic spread to sentinel nodes an ALND is still recommended. Removing fewer nodes has made more extensive histopathological examinations of the lymph nodes possible and as a consequence more metastases are found, especially more micrometastases and isolated tumor cells (ITC) [1]. The overall benefit from ALND in patients with minor spread to axillary lymph nodes is now under debate [2]. Cohort studies have not been able to show an increased risk of axillary recurrence if ALND is omitted in patients with micrometastases or ITC in the sentinel node [3,4]. Furthermore, the newly published randomized IBCSG 23-01 trial could not show a difference in disease-free survival after five years of follow-up, between patients with sentinel node micrometastases, with and without ALND [5]. This has, together with the results from the randomized trial from American College of Surgeons Oncology Group (ACOSOC) (Z0011), where no difference was found in axillary recurrence rate or survival between sentinel node positive patients with or without ALND [6,7], started a trend towards omitting ALND in breast cancer patients with minimal metastatic disease in the sentinel node. However, a minor risk of axillary recurrence still exists if ALND is completely omitted in patients with micrometastases or ITC in

Correspondence: T. Filtenborg Tvedskov, Department of Breast Surgery, 4124, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark. Tel: +45 25454576. Fax: +45 35453642. E-mail: tft@dadlnet.dk

(Received 6 March 2013; accepted 15 May 2013)

ISSN 0284-186X print/ISSN 1651-226X online © 2014 Informa Healthcare
DOI: 10.3109/0284186X.2013.806993

the sentinel node [8]. To assure a safe omission of ALND a tool is needed to identify patients where ALND may still be offered in the future due to a high risk of recurrence. The presence of non-sentinel node metastases can be considered as a surrogate endpoint for axillary recurrence. Several models for predicting the risk of non-sentinel node metastases in patients with positive sentinel nodes have been developed [9,10], but only three of these models have been developed in a population of patients with micrometastases or ITC in the sentinel node [11,12]. Moreover, the existing models have been directed towards identifying patients with a low risk of non-sentinel node metastases. To identify patients with a potentially high risk of relapse, a model predicting patients with high risk of non-sentinel node metastases is needed.

We have previously developed two models for predicting patients with high risk of non-sentinel node metastases when only micrometastases or ITC are found in the sentinel node, based on a large population-based data material [13].

The aim of this study was to validate these models in a large independent group of Danish breast cancer patients with micrometastases or ITC in the sentinel node.

Material and methods

In Denmark, all SLND are performed according to national guidelines described by the Danish Breast Cancer Cooperative Group (DBCG). A combination of radioactive tracer and blue dye is recommended, while lymphoscintigraphy is not used as a routine [14]. All removed sentinel nodes are examined with at least two step sections 500 μm apart of the bivalved sentinel node. If no metastases are found by hematoxylin-eosin staining, immunohistochemical cytokeratin staining is performed. Lymph nodes removed by ALND are examined by bisectioning and hematoxylin-eosin staining. Since 2005, metastases have in Denmark been classified according to the 6th American Joint Committee on Cancer (AJCC) staging manual [15] in combination with cell count, where metastases between 0.2 and 2 mm or between 10 and 100 tumor cells are defined as micrometastases, and single cells or cell clusters less than 0.2 mm or less than 10 cells are defined as ITC [14].

Clinical and histopathological data on Danish women with breast cancer are prospectively collected and registered on standardized forms in a national database managed by the DBCG [16]. Based on data from this database we have developed two models to predict non-sentinel node metastases in breast cancer patients with micrometastases or ITC in the sentinel node. The models were based on 299 patients with ITC and 1521 patients with micrometastases in the sentinel node, operated in 2002–2008 with SLND and a completion ALND (original cohort) [13].

In patients with ITC, from this original cohort, the risk of non-sentinel node metastases was significantly associated with younger age at diagnosis, increasing tumor size and increasing proportion of positive sentinel nodes in a multivariate analysis.

In patients with micrometastases, from the original cohort, the risk of non-sentinel node metastases was significantly associated with increasing tumor size, lymphovascular invasion, negative hormone receptor status, location of tumor in the upper lateral quadrant of the breast and increasing proportion of positive sentinel nodes in a multivariate analysis. Based on these five risk factors a logistic regression model for predicting non-sentinel node metastases was developed for patients with micrometastases:

$$\begin{aligned}\text{Logit}(p) = &-2.5822 + 0.1945^{*}\times 1 + 0.5516^{*}1_{\text{LVI}} \\ &+ 0.3857^{*}1_{\text{HRneg}} + 0.5395^{*}1_{\text{UL}} \\ &+ 0.5257^{*}1_{\text{proportion100\%}}\end{aligned}$$

[where $\times 1 = 1,2,3,4,5,6$ (tumor size ≤ 10, 11–20, 21–30,31–40,41–50,51 + mm)]

A significant interaction between tumor size and lymphovascular invasion was found in the original cohort, with lymphovascular invasion being a stronger risk factor in larger tumors. However, this interaction did not change the accuracy of the model substantially and was subsequently not included in the model for validation analysis.

In 2009 and 2010, a total number of 1072 breast cancer patients were registered in the DBCG database, with micrometastases or ITC in the sentinel node. A total of 147 patients did not have an ALND and five patients had less than seven lymph nodes removed by ALND. These 152 patients were excluded. The remaining 920 patients were eligible for the validation study. From the database we retrieved information on age at diagnosis, tumor size, hormone receptor status, number of removed sentinel nodes, number of positive sentinel nodes, lymphovascular invasion, location of tumor in the breast and presence of non-sentinel node metastases. Location of tumor in the breast was divided into location in upper lateral quadrant versus located in other quadrants, centrally or on the edge of the upper lateral quadrant. Data were validated, and missing information collected if possible, using the original pathology files. Nineteen patients with micrometastases and one with ITC in the sentinel node were excluded from validation analysis due to missing information on variables. The remaining 900 patients constituted the validation cohort.

Statistical analyses

The multivariate models of the original cohort were examined to evaluate risk factors for non-sentinel node metastases when ITC or micrometastases were found in the sentinel node. In the validation cohort associations between presence of non-sentinel node metastases and the risk factors listed in Table I were analyzed by χ^2 test and Fischer's exact test, excluding unknowns, for patients with ITC and patients with

Table I. Patient, tumor and sentinel node characteristics according to risk of NSN metastases in 181 Danish breast cancer patients with ITC and 739 patients with micrometastases in the SN operated between 2009 and 2010.

	Isolated tumor cells				Micrometastases			
	NSN metastases				NSN metastases			
Variables	No	Yes	%	p-value	No	Yes	%	p-value
Total	158	23	12.7		614	125	16.9	
Age, years				0.49				0.53
<40	3	0	0		23	1	4.2	
40–49	19	5	20.8		88	19	17.8	
50–59	58	8	12.1		200	44	18.0	
60–69	66	7	9.6		232	48	17.1	
≥70	12	3	20.0		71	13	15.5	
Tumor size, cm				0.32				0.0005
≤1	32	2	5.9		126	9	6.7	
>1–≤2	72	9	11.1		315	64	16.9	
>2–≤3	36	8	18.2		130	38	22.6	
>3	17	4	19.0		43	14	25.0	
Unknown	1	0	0					
WHO type				0.86				0.63
Ductal	93	15	13.9		527	109	17.1	
Lobular	48	6	11.1		52	8	13.3	
Other	16	2	11.1		31	8	20.5	
Unknown	1	0	0		4	0	0	
Grade				0.04				0.01
Grade I	38	6	13.6		207	27	11.5	
Grade II	73	7	8.8		236	64	21.3	
Grade III	21	8	27.6		94	22	19.0	
Unknown/other	26	2	7.1		77	12	13.5	
LVI				0.63				0.0007
Present	9	2	18.2		68	28	29.2	
Absent	148	21	12.4		537	96	15.2	
Unknown	1	0	0		9	1	10.0	
Hormone receptor status				0.47				0.68
Positive	138	22	13.8		556	111	16.6	
Negative	18	1	5.3		57	13	18.6	
Unknown	2	0	0		1	1	50.0	
HER2 status				0.51				0.13
Positive	19	4	17.4		68	19	21.8	
Negative	127	18	12.4		511	93	15.4	
Unknown	12	1	7.7		35	13	27.1	
Location of tumor in breast				0.77				0.03
Upper lateral	83	13	13.5		337	81	19.4	
Not upper lateral	73	10	12.0		273	42	13.3	
Unknown	2	0	0		4	2	33.3	
No. removed SN				0.36				0.20
1	48	11	18.6		212	54	20.3	
2	64	6	8.6		224	32	12.5	
3	22	4	15.4		110	24	17.9	
4	18	1	5.3		48	10	17.2	
5	6	1	14.3		20	5	20.0	
Positive SN/Removed SN				0.22				0.33
100%	58	13	18.3		248	58	19.0	
>33% , <100%	70	6	7.9		220	34	13.4	
>25; ≤33	16	3	15.8		89	20	18.3	
≤25%	14	1	6.7		57	13	18.6	

ITC, isolated tumor cells; LVI, lymphovascular invasion; NSN, non-sentinel nodes; SN, sentinel node.

Table II. Multivariate analyses of patients and tumor characteristics according to non-sentinel node metastases in Danish breast cancer patients with ITCs or micrometastases in the sentinel node.

	Original cohort 2002–2008			Validation cohort 2009–2010		
	Isolated tumor cells					
	n = 299			n = 180		
	OR	95% CI	p-value	OR	95% CI	p-value
Tumor size, > 2 vs. ≤ 2 cm	4.21	1.74–10.2	0.001	2.04	0.84–4.96	0.12
Age at diagnosis, < 40 vs. ≥ 40 years	3.57	1.11–11.4	0.03	–	–	–
Proportion of pos SN, 100% vs. < 100%	2.90	1.27–6.60	0.01	2.12	0.87–5.17	0.10
	Micrometastases					
	n = 1521			n = 720		
Tumor size, cm, Trend	1.22	1.06–1.39	0.005	1.34	1.12–1.60	0.002
Proportion of pos SN, 100% vs. < 100%	1.69	1.29–2.21	0.0001	1.32	0.88–1.97	0.18
Lymphovascular invasion	1.74	1.18–2.55	0.005	2.26	1.37–3.74	0.001
HR status, neg vs. pos	1.47	1.00–2.16	0.049	1.06	0.55–2.03	0.86
Location of tumor in upper lateral quadrant	1.72	1.30–2.26	0.0003	1.47	0.97–2.23	0.07

CI, confidence interval; HR, hormone receptor; neg, negative; OR, odds ratio; pos, positive; SN, sentinel node.

micrometastases, respectively, in the sentinel node. Multivariate logistic regression models were applied to examine the influence of age at diagnosis, tumor size, as well as the proportion of positive sentinel nodes among removed sentinel nodes, and for patients with micrometastasis in the sentinel node also lymphovascular invasion, hormone receptor status and location of tumor in the breast, on the risk of non-sentinel node metastases. Adjusted odds ratio (OR) and 95% confidence intervals (CI) were calculated and the Wald test was used to test the significance of each variable. Discrimination of the models was assessed by area under the receiver operating characteristic curve (AUC) for both the original and the validation cohort. For ITC number of risk factors was used to define a cut-point. A score was assigned to each patient with micrometastases by adding the relevant β-coefficients from the multivariate logistic regression model of the original cohort. A cut-off value separating patients with more than 30% observed risk of non-sentinel node metastases in the original cohort was applied to both cohorts. Sensitivity and specificity were determined for these thresholds. SAS version 9.2 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

The study was approved by the Danish Data Protection Agency (J.nr. 2009-41-3703).

Results

Of the 920 eligible patients in the validation cohort 739 had micrometastases and 181 had ITC in the sentinel node. Patient, tumor and sentinel node characteristics of patients in the validation cohort are shown in Table I. Characteristics of patients in the original cohort have been reported elsewhere [13]. The proportion of patients with non-sentinel node metastases was not significantly different in the validation and original cohorts; 13% (23/181) and 9% (28/304), respectively, for patients with ITC, and 17% (125/739) and 18% (283/1577), respectively, for patients with micrometastases. The identified risk factors for non-sentinel node metastases in the original cohort remained associated with an increased risk of further spread beyond the sentinel node in the validation cohort (Table II) but the association only remained statistical significant for tumor size and lymphovascular invasion. In the validation cohort, no patients with ITC under 40 years at diagnosis had non-sentinel node metastases.

In the original cohort, 17% of patients with ITC had more than one risk factor present. The risk of further spread beyond sentinel node in this group was 23%, compared to 6% in patients with only one or none of the risk factors present. In the validation cohort, a similar proportion (17%) had more than one risk factor present. Thirty-seven percent of these patients had non-sentinel node metastases, compared to only 8% of patients with only one or none of the risk factors present. Dividing patients into high- and low-risk groups for having non-sentinel node metastases with a cut-point of more than one risk factor present the sensitivity and specificity was 0.48 and 0.88, respectively, in the validation cohort compared to 0.43 and 0.85, respectively, in the original cohort. AUC for a model based on the three risk factors was 0.73 (95% CI 0.64–0.82) in the original cohort, but

Table III. Performance of models predicting non-sentinel node metastases in original and validation cohorts of Danish breast cancer patients with ITCs or micrometastases in the sentinel node.

Model	Cohort	Operation year	No. of patients	Sensitivity	Specificity	AUC (95%CI)
ITC	Original cohort	2002–2008	299	0.43*	0.85*	0.73 (0.64–0.82)
	Validation cohort	2009–2010	180	0.48*	0.88*	0.60 (0.46–0.75)
MIC	Original cohort	2002–2008	1521	0.25‡	0.88‡	0.64 (0.60–0.67)
	Validation cohort	2009–2010	720	0.36‡	0.81‡	0.63 (0.57–0.68)

ITC, isolated tumor cells; MIC, micrometastases.
*For cut-point of more than one risk factor present; ‡For cut-point of 30% observed risk of non-sentinel node metastases.

decreased to 0.60 (95% CI 0.46–0.75) in the validation cohort (Table III).

When a score was assigned to each patient with micrometastases in the original cohort by adding the relevant β-coefficients from the multivariate logistic regression model, a cut-off value on −1.128 could separate patients in the original cohort into a group with less than 30% risk of non-sentinel node metastases and a high-risk group with at least 30% risk of further spread. This high-risk group represented 14% of patients in the original cohort. In the validation cohort, 22% of patients had a risk score above −1.128, and 28% of these high-risk patients had non-sentinel node metastases. Using this cut-point the sensitivity and specificity was 0.36 and 0.81, respectively, in the validation cohort compared to 0.25 and 0.88, respectively, in the original cohort (Table III). The AUC for the model for patients with micrometastases changed only slightly from 0.64 (95% CI 0.60–0.67) in the original cohort to 0.63 (95% CI 0.57–0.68) in the validation cohort.

Discussion

We have previously developed two models for predicting breast cancer patients with high risk of non-sentinel node metastases when only minimal metastatic disease is found in the sentinel node. The models are now validated in a large independent Danish data material. Especially the model for patients with micrometastases showed to be robust with only a slight change in accuracy in the new data material.

By using the DBCG database, the models could be based on a data material of a unique size of more than 1800 patients. In addition, the database allowed us to validate the models in an independent data material of 900 patients. This comprehensive and nationwide data material made the models very robust when validated.

All risk factors for non-sentinel node metastases, identified in the original cohort, remained associated with an increased risk of non-sentinel node metastases in the validation cohort, although several of the factors were no longer statistical significant. This can partly be explained by the lower number of patients in the validation cohort on 900 patients compared to 1820 patients in the original cohort.

Despite being a robust model, AUC was only 0.63 for the model for patients with micrometastases, and AUC for the model for patients with ITC decreased to 0.60 when validated. The possibilities of increasing the accuracy of the models are limited. It is possible that the search for new biochemical markers will reveal new clinically significant predictors for non-sentinel node metastases that can improve the models [17,18].

Only two earlier studies have tried to construct a predictive model based on a population of patients with micrometastases or ITC [11,12]. Like us, these studies included large sample sizes of 484 and 909 patients. Nevertheless, AUC was only 0.68 and 0.66, respectively, for the two models. Validation of the first model resulted in an AUC on 0.79, but only 51 patients were included in the validation series [12]. The second model has been validated in a series of 484 patients but the AUC was not reported [19]. These earlier models have focused on predicting a group of patients with low risk of non-sentinel node metastases, where ALND could be omitted without compromising locoregional disease control.

Locoregional disease control is however not only based on surgical treatment but on adjuvant treatment as well. The criteria for offering adjuvant systemic treatment have changed over years [20] and there is a trend towards inclusion of several new high-risk criteria in the decision for adjuvant systemic treatment. This has led to a larger proportion of patients offered systemic treatment. It is possible that systemic treatment together with whole breast irradiation can eliminate low volume axillary metastases. This could explain the increasing evidence indicating that ALND can safely be omitted in sentinel node positive patients despite the risk of leaving non-sentinel node metastases in the axilla [3–6]. In cohort studies based on data from the National Cancer institute's surveillance Epidemiology, and

End Results database [4] and the American National Cancer Data Base [3] there was no difference in outcome between patients with and without ALND when only micrometastases were found in the sentinel node. Results from only two randomized trials exist. In the IBCSG 23-01 trial no significant difference in disease-free survival was found between patients with and without ALND after five years of follow-up, when only micrometastases was found in the sentinel node [5]. Likewise, the ACOSOC Z0011 trial found no significant difference in loco-regional recurrence and overall survival between sentinel node positive patients with and without ALND [6,7]. In the light of these studies, the prediction of a very low risk of non-sentinel node metastases is irrelevant. Still, a small group of sentinel node positive patients will experience an axillary recurrence despite having only minimal metastatic disease in the sentinel node, and these patients might benefit from an ALND. In a recent Dutch cohort study, including more than 2600 patients, the adjusted hazard ratio for regional recurrence was 4.39 if ALND was omitted in patients with micrometastases in the sentinel node. A similar but insignificant trend was seen for patients with ITC [21]. Therefore a predictive model may be needed to identify patients where adjuvant treatment might not be sufficient to eliminate residual axillary metastases resulting in a high risk of relapse. High risk of non-sentinel node metastases can be considered as a surrogate endpoint for axillary recurrence. In contrast to earlier models predicting the risk of non-sentinel node metastases [11,12] we focused our models on patient at the high end of the risk scale. In patients with micrometastases, we choose a cut-point that identified patients with more than 30% risk of non-sentinel node metastases in the original cohort, which is at a level comparable to patients with macrometastases [22]. This group of patients may still benefit from an ALND. For patients with ITC the cut-point was guided by the number of risk factors present. In the original cohort, only 23% of patients with more than one risk factor present had non-sentinel node metastases, which could argue for an even higher cut-point on more than two risk factors present. Still, 37% of patients in the high-risk group of the validation cohort had non-sentinel node metastases when a cut-point of more than one risk factor was used, indicating that this is a reasonable cut-point.

The two validated models seem to be suitable for a Danish population of breast cancer patients. However, when models are tested in a foreign population, they generally tend to work poor and a high variation in model performance between different centers has been shown [12]. For example, the Tenon score was developed in a French population and worked well in the French validation study [10], but did not perform very well in a Swedish population [23]. Likewise, the model from the Memorial Sloan-Kettering Cancer Center [9] worked well in other American populations [24], but was not very precise in a Hungarian population [25]. Finally, only two of 12 tested models worked well in a Chinese population [26]. Accordingly, validation of the models on an external data material outside Denmark is necessary to ensure international validity.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

The study was supported by IMK common foundation, HOC research initiative foundation, Danish Cancer Research Foundation and A.P. Møller Foundation for the Advancement of Medical Science.

References

[1] Tvedskov TF, Jensen MB, Balslev E, Ejlertsen B, Kroman N. Stage migration after introduction of sentinel lymph node dissection in breast cancer treatment in Denmark: A nationwide study. Eur J Cancer 2011;47:872–8.

[2] Croshaw RL, Erb KM, Shapiro-Wright HM, Julian TB. The need for axillary dissection in patients with positive axillary sentinel lymph nodes. Curr Oncol Rep 2011;13:5–10.

[3] Bilimoria KY, Bentrem DJ, Hansen NM, Bethke KP, Rademaker AW, Ko CY, et al. Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer. J Clin Oncol 2009;27:2946–53.

[4] Yi M, Giordano SH, Meric-Bernstam F, Mittendorf EA, Kuerer HM, Hwang RF, et al. Trends in and outcomes from sentinel lymph node biopsy (SLNB) alone vs. SLNB with axillary lymph node dissection for node-positive breast cancer patients: Experience from the SEER database. Ann Surg Oncol 2010;17:343–51.

[5] Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): A phase 3 randomised controlled trial. Lancet Oncol 2013;14:297–305.

[6] Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: A randomized clinical trial. JAMA 2011;305:569–75.

[7] Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: The American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 2010;252:426–32.

[8] Pepels MJ, Vestjens JH, de BM, Smidt M, van Diest PJ, Borm GF, et al. Safety of avoiding routine use of axillary dissection in early stage breast cancer: A systematic review. Breast Cancer Res Treat 2011;125:301–13.

[9] Van Zee KJ, Manasseh DM, Bevilacqua JL, Boolbol SK, Fey JV, Tan LK, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. Ann Surg Oncol 2003;10:1140–51.

[10] Coutant C, Olivier C, Lambaudie E, Fondrinier E, Marchal F, Guillemin F, et al. Comparison of models to predict nonsentinel lymph node status in breast cancer patients with metastatic sentinel lymph nodes: A prospective multicenter study. J Clin Oncol 2009;27:2800–8.

[11] Houvenaeghel G, Nos C, Giard S, Mignotte H, Esterni B, Jacquemier J, et al. A nomogram predictive of non-sentinel lymph node involvement in breast cancer patients with a sentinel lymph node micrometastasis. Eur J Surg Oncol 2009; 35:690–5.

[12] Meretoja TJ, Strien L, Heikkila PS, Leidenius MH. A simple nomogram to evaluate the risk of nonsentinel node metastases in breast cancer patients with minimal sentinel node involvement. Ann Surg Oncol 2012;19:567–76.

[13] Tvedskov TF, Jensen MB, Lisse IM, Ejlertsen B, Balslev E, Kroman N. High risk of non-sentinel node metastases in a group of breast cancer patients with micrometastases in the sentinel node. Int J Cancer 2012;131:2367–75.

[14] Christiansen P, Friis E, Balslev E, Jensen D, Moller S. Sentinel node biopsy in breast cancer: Five years' experience from Denmark. Acta Oncol 2008;47:561–8.

[15] Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 2002;20:3628–36.

[16] Moller S, Jensen MB, Ejlertsen B, Bjerre KD, Larsen M, Hansen HB, et al. The clinical database and the treatment guidelines of the Danish Breast Cancer Cooperative Group (DBCG); its 30-years experience and future promise. Acta Oncol 2008;47:506–24.

[17] Kwon Y, Ro J, Kang HS, Kim SK, Hong EK, Khang SK, et al. Clinicopathological parameters and biological markers predicting non-sentinel node metastasis in sentinel node-positive breast cancer patients. Oncol Rep 2011;25:1063–71.

[18] Tvedskov TF, Bartels A, Jensen MB, Paaschburg B, Kroman N, Balslev E, et al. Evaluating TIMP-1, Ki67, and HER2 as markers for non-sentinel node metastases in breast cancer patients with micrometastases to the sentinel node. APMIS 2011;119:844–52.

[19] Houvenaeghel G, Bannier M, Nos C, Giard S, Mignotte H, Jacquemier J, et al. Non sentinel node involvement prediction for sentinel node micrometastases in breast cancer: Nomogram validation and comparison with other models. Breast 2012;21:204–9.

[20] Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, Senn HJ. 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;22:1736–47.

[21] Pepels MJ, de BM, Bult P, van Dijck JA, van Deurzen CH, Menke-Pluymers MB, et al. Regional recurrence in breast cancer patients with sentinel node micrometastases and isolated tumor cells. Ann Surg 2012;255:116–21.

[22] Noguchi M. Avoidance of axillary lymph node dissection in selected patients with node-positive breast cancer. Eur J Surg Oncol 2008;34:129–34.

[23] Andersson Y, Frisell J, de BJ, Bergkvist L. Prediction of non-sentinel lymph node status in breast cancer patients with sentinel lymph node metastases: Evaluation of the tenon score. Breast Cancer (Auckl.) 2012;6:31–8.

[24] Hessman CJ, Naik AM, Kearney NM, Jensen AJ, Diggs BS, Troxell ML, et al. Comparative validation of online nomograms for predicting nonsentinel lymph node status in sentinel lymph node-positive breast cancer. Arch Surg 2011; 146:1035–40.

[25] Kocsis L, Svebis M, Boross G, Sinko M, Maraz R, Rajtar M, et al. Use and limitations of a nomogram predicting the likelihood of non-sentinel node involvement after a positive sentinel node biopsy in breast cancer patients. Am Surg 2004;70:1019–24.

[26] Chen K, Zhu L, Jia W, Rao N, Fan M, Huang H, et al. Validation and comparison of models to predict non-sentinel lymph node metastasis in breast cancer patients. Cancer Sci 2011;103:274–81.