Nomograms for preoperative prediction of axillary nodal status in breast cancer

L. Dihge[1,3], P.-O. Bendahl[2] and L. Rydén[1,4]

Departments of [1]Surgery and [2]Oncology and Pathology, Clinical Sciences Lund, Lund University, Lund, and Departments of [3]Plastic and Reconstructive Surgery and [4]Surgery, Skåne University Hospital, Malmö, Sweden
Correspondence to: Professor L. Rydén, Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Surgery, Medicon Village, SE-223 81, Lund, Sweden (e-mail: lisa.ryden@med.lu.se)

Background: Axillary staging in patients with breast cancer and clinically node-negative disease is performed by sentinel node biopsy (SLNB). The aim of this study was to integrate feasible preoperative variables into nomograms to guide clinicians in stratifying treatment options into no axillary staging for patients with non-metastatic disease (N0), SLNB for those with one or two metastases, and axillary lymph node dissection (ALND) for patients with three or more metastases.

Methods: Patients presenting to Skåne University Hospital, Lund, with breast cancer were included in a prospectively maintained registry between January 2009 and December 2012. Those with a preoperative diagnosis of nodal metastases were excluded. Patients with data on hormone receptor status, human epidermal growth factor receptor 2 and Ki-67 expression were included to allow grouping into surrogate molecular subtypes. Based on logistic regression analyses, nomograms summarizing the strength of the associations between the predictors and each nodal status endpoint were developed. Predictive performance was assessed using the area under the receiver operating characteristic (ROC) curve. Bootstrap resampling was performed for internal validation.

Results: Of the 692 patients eligible for analysis, 248 were diagnosed with node-positive disease. Molecular subtype, age, mode of detection, tumour size, multifocality and vascular invasion were identified as predictors of any nodal disease. Nomograms that included these predictors demonstrated good predictive abilities, and comparable performances in the internal validation; the area under the ROC curve was 0·74 for N0 *versus* any lymph node metastasis, 0·70 for one or two involved nodes *versus* N0, and 0·81 for at least three nodes *versus* two or fewer metastatic nodes.

Conclusion: The nomograms presented facilitate preoperative decision-making regarding the extent of axillary surgery.

Introduction

In patients with a clinically negative axilla, axillary lymph node dissection (ALND) has been replaced by sentinel lymph node biopsy (SLNB) as an axillary staging procedure[1,2]. Even though there is concordance between metastatic involvement of the axilla and the prognostic outcome, the quantitative relationship remains controversial. There has been a fundamental shift in management of the axilla since the introduction of SLNB. An increasing number of reports have questioned the need for ALND after a positive SLNB result, including those from the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial[3,4] and the International Breast Cancer Study Group (IBCSG) trial 23-01[5], which compared ALND *versus* no further axillary surgery, whereas the AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery?) trial[6] compared ALND *versus* postoperative axillary radiotherapy. The results from the ACOSOG Z0011 trial suggested that ALND might be omitted without a negative impact on prognosis in selected patients with a limited number of sentinel node metastases undergoing breast-conserving surgery and postoperative radiotherapy.

Since the introduction of public screening mammography programmes, the size of detected primary tumours has decreased, as has the incidence of axillary nodal metastases[7]. With more widespread and added use of adjuvant therapy, the advantage of extensive axillary staging in improving prognosis may also diminish. The majority of patients with breast cancer have node-negative disease, and SLNB could be avoided if reliable diagnostic evaluation of the axilla were available before surgery. The recommended preoperative evaluation includes ultrasound examination of the axilla and biopsy of the tumour, both of which allow preoperative diagnosis and biomarker assessment. Axillary ultrasonography has limited sensitivity for minor axillary metastatic burden[8] and so cannot currently replace SLNB as an axillary staging procedure. The nodal axillary status reflects the timeline of tumour development, as illustrated by tumour size and biology of the primary breast tumour; assessment of tumour characteristics could therefore be of importance in guiding the extent of axillary surgery[9]. Previous studies[10−12] have demonstrated that oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) are predictive of nodal involvement. Most studies[13−19] reporting prediction models and/or nomograms for axillary lymph node status have focused on calculating the risk of additional non-sentinel node disease in patients with node-positive disease verified by SLNB. Although validation studies have confirmed the satisfactory precision of these models, their accuracy is often reduced outside the centre where they were initially developed[20−24]. Limited evidence is available on the association of factors that could be available in a preoperative clinical setting, taking into account the pooled impact of breast cancer biology, radiological features and clinicopathological data on the extent of nodal lymphatic spread, in a population-based cohort.

The first aim of this study was to provide tools for use in predicting the patient's nodal status based on variables available before surgery in order to decide the best treatment option: no axillary staging for patients with no axillary lymph node involvement (N0), SLNB for patients with one or two nodal metastases, and ALND for those with three or more metastatic lymph nodes. The second aim was to determine the impact of tumour heterogeneity, number and size of the primary tumour, and mode of detection on axillary nodal status in a population-based prospective cohort.

Methods

Patients with primary breast cancer who underwent breast surgery and axillary staging between January 2009 and December 2012 at Skåne University Hospital, Lund, Sweden, were identified in a prospectively maintained pathology-based registry. Exclusion criteria were: men, previous ipsilateral breast or axillary surgery owing to a history of invasive breast cancer or *in situ* ductal cancer, neoadjuvant chemotherapy, bilateral tumours, cytologically confirmed nodal metastasis and non-standard axillary staging. Only patients with complete data on ER, PR, HER2 and Ki-67 status were included. Data from the national mammography screening programme were retrieved, and the mode of detection was dichotomized as either screening or symptomatic presentation. Patient medical records and the Swedish National Quality Registry for Breast Cancer were reviewed for data regarding age at diagnosis and previous operations on the breast or axilla. SLNB was the standard axillary staging procedure. All patients with micrometastasis or macrometastasis detected by SLNB routinely underwent ALND according to the Swedish National Guidelines[25]. Patients with multifocal breast cancer were screened for inclusion in a prospective trial assessing the rate of false-negative SLNB; all study participants were by study protocol predetermined for SLNB as well as completion ALND. The study was approved by the regional ethical review board of Lund University (reference EPN 2012/340).

Pathological evaluation

Any suspicious lesion detected in routine preoperative evaluation by mammography or ultrasonography was assessed by core needle biopsy (CNB) or fine-needle aspiration cytology. When multiple indeterminate or suspicious foci were revealed by preoperative breast imaging, each lesion was sampled to determine multifocality. A breast pathologist extracted the following histopathological information: tumour size, multifocality, histological type, Nottingham histological grade, ER and PR, HER2 status based on immunohistochemistry and *in situ* hybridization, Ki-67 status (threshold over 20 per cent), and vascular invasion. Multicentricity was not documented as a separate entity; the finding of simultaneous multiple invasive foci separated by benign breast tissue, irrespective of the distance between the lesions, was classified as multifocal disease. Tumour size was defined by the greatest dimension of the largest invasive cancer focus measured. Tumours were classified into five breast cancer subtypes according to the clinicopathological surrogate definitions adopted by the 2013 St Gallen consensus[26]: luminal A-like (LumA), luminal B-like/HER2-negative (LumB/HER2−), luminal B-like/HER2-positive (LumB/HER2+), HER2-positive/ non-luminal (HER2+/non-luminal) and triple-negative.
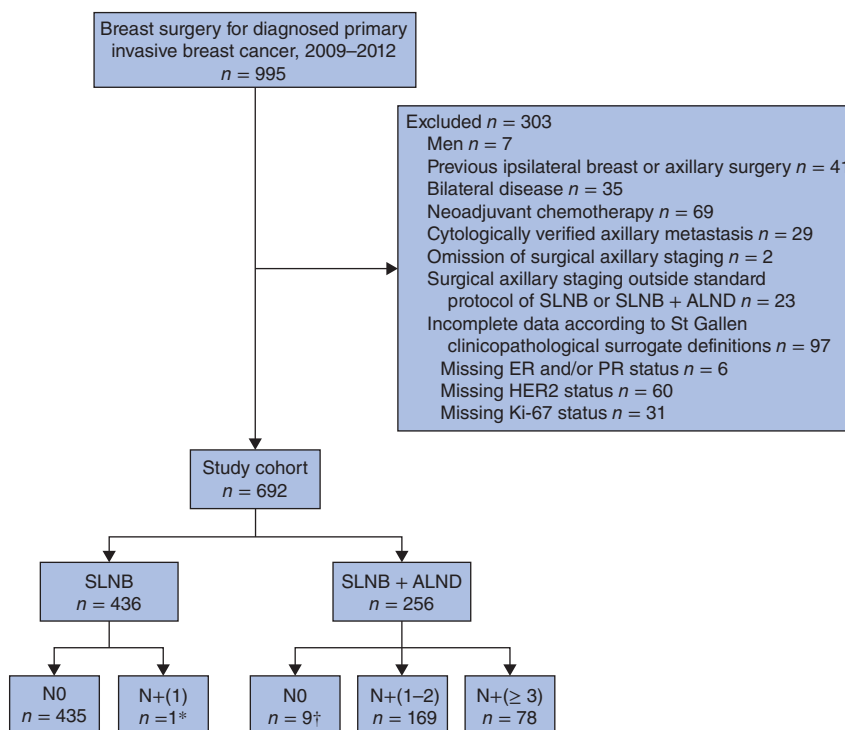
Fig. 1 Study flow chart. *Sentinel node biopsy (SLNB) showed solitary micrometastasis; false-negative frozen section of the involved node. †Presumed multifocality at the time of diagnosis; represents a selected group included in a study protocol with preplanned SLNB + axillary lymph node dissection (ALND). ER, oestrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; N0, lymph node-negative; N+(1), solitary lymph node metastasis; N+(1–2), lymph node metastasis involving one or two nodes; N+(≥ 3), lymph node metastasis involving at least three nodes

The presence of macrometastases or micrometastases on SLNB was defined as axillary node-positive; these patients were offered completion ALND according to the Swedish National Guidelines. Isolated tumour cells were classified as node-negative. Patients were categorized into groups according to the number of metastatic axillary nodes (node-negative (N0), 1 or 2 positive nodes, at least 3 positive nodes), which reflected the essential cut-offs for axillary surgery based on the ACOSOG Z0011 criteria.

Statistical analysis

The distribution of clinicopathological variables and modes of detection across the five cancer subtypes was assessed by using the Pearson χ^2 test and Fisher's exact test for categorical variables, and Kruskal–Wallis test for continuous variables. Logistic regression analysis was used to quantify the strength of the associations between predictors and each outcome variable in patients with T1–T2 tumours: disease-free axilla (N0), low metastatic axillary burden (1–2 positive nodes) and heavy metastatic burden (at least 3 positive nodes). If two or more variables were highly correlated, only one of them was retained in the final model to minimize the risk of multicollinearity. The regression coefficients estimated from the multivariable logistic regression models were illustrated graphically in nomograms, which provide a straightforward method of prediction of the extent of axillary disease. The user-contributed program nomolog for Stata[27] was used to construct the nomograms. The discriminatory ability of the nomograms was represented by receiver operating characteristic (ROC) analysis and area under the curve (AUC) values. Bootstrap resampling with 1000 replicates was used to estimate the accuracy of the prediction models. The bias-corrected AUC was calculated as the average AUC over the predictions from the 1000-replicate bootstrap data set applied to the original data set[28].

SPSS® Statistics for Windows® version 22.0 (IBM, Armonk, New York, USA) and Stata® version 14.1 (StataCorp, College Station, Texas, USA) were used for statistical computations and graphics. All statistical tests were two-sided, and $P < 0.050$ was taken as statistically significant.

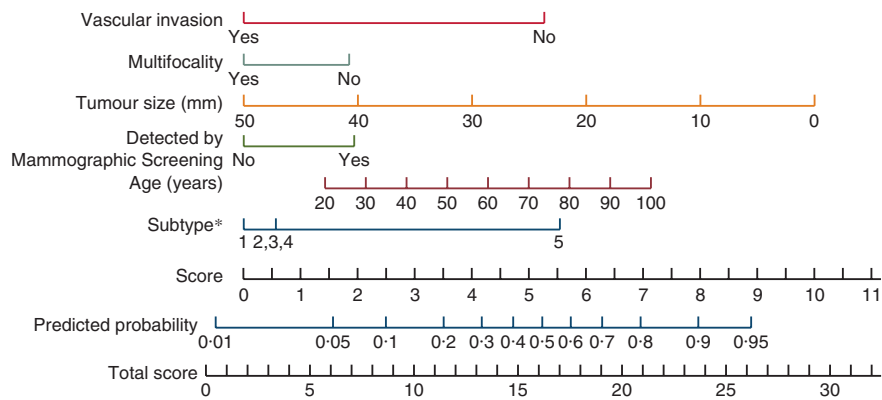**Table 1** Baseline patient and tumour characteristics

	All (n = 692)	LumA (n = 372)	LumB/HER2− (n = 198)	LumB/HER2+ (n = 64)	HER2+/non-luminal (n = 17)	Triple-negative (n = 41)	P‡
Age (years)*	62 (24–92)	63 (24–92)	63 (31–90)	58 (34–91)	55 (25–73)	60 (29–83)	0·006§
Mode of detection							0·001
Mammographic screening	412 (59·5)	246 (66·1)	99 (50·0)	36 (56)	12 (71)	19 (46)	
Symptomatic	280 (40·5)	126 (33·9)	99 (50·0)	28 (44)	5 (29)	22 (54)	
Tumour size (mm)†							< 0·001
≤ 20 (pT1)	495 (71·5)	295 (79·3)	123 (62·1)	40 (63)	10 (59)	27 (66)	
21–49 (pT2)	192 (27·7)	74 (19·9)	73 (36·9)	24 (37)	7 (41)	14 (34)	
> 50 (pT3)	5 (0·7)	3 (0·8)	2 (1·0)	0 (0)	0 (0)	0 (0)	
Histological type							0·001
Ductal	554 (80·0)	284 (76·3)	155 (78·3)	61 (95)	16 (94)	38 (93)	
Lobular	88 (12·7)	58 (15·6)	29 (14·6)	1 (2)	0 (0)	0 (0)	
Other	50 (7·2)	30 (8·1)	14 (7·1)	2 (3)	1 (6)	3 (7)	
Histological grade							< 0·001¶
I	164 (23·9)	140 (37·9)	21 (10·7)	1 (2)	0 (0)	2 (5)	
II	314 (45·8)	214 (58·0)	80 (40·6)	10 (16)	4 (24)	6 (15)	
III	208 (30·3)	15 (4·1)	96 (48·7)	51 (82)	13 (76)	33 (80)	
Missing	6	3	1	2	0	0	
Multifocality							0·924
No	513 (74·9)	275 (74·1)	146 (75·6)	46 (73)	13 (76)	33 (80)	
Yes	172 (25·1)	96 (25·9)	47 (24·4)	17 (27)	4 (24)	8 (20)	
Missing	7	1	5	1	0	0	
Vascular invasion							< 0·001
No	515 (85·1)	293 (91·3)	141 (80·1)	41 (75)	10 (71)	30 (77)	
Yes	90 (14·9)	28 (8·7)	35 (19·9)	14 (25)	4 (29)	9 (23)	
Missing	87	51	22	9	3	2	
Regional lymph node metastases							0·027¶#
N0	444 (64·2)	248 (66·7)	115 (58·1)	36 (56)	12 (71)	33 (80)	
N+	248 (35·8)	124 (33·3)	83 (41·9)	28 (44)	5 (29)	8 (20)	
1–2 positive nodes	170 (24·6)	88 (23·7)	58 (29·3)	16 (25)	3 (18)	5 (12)	
≥ 3 positive nodes	78 (11·3)	36 (9·7)	25 (12·6)	12 (19)	2 (12)	3 (7)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †According to the TNM classification for breast cancer, seventh edition[29]. LumA, luminal A-like; LumB, luminal B-like; HER2, human epidermal growth factor receptor 2; N0, lymph node-negative; N+, any lymph node metastasis. ‡Fisher's exact test, except §Kruskal–Wallis test and ¶Pearson χ^2 test. #Comparison of distribution of N0 and N+ among subtypes.
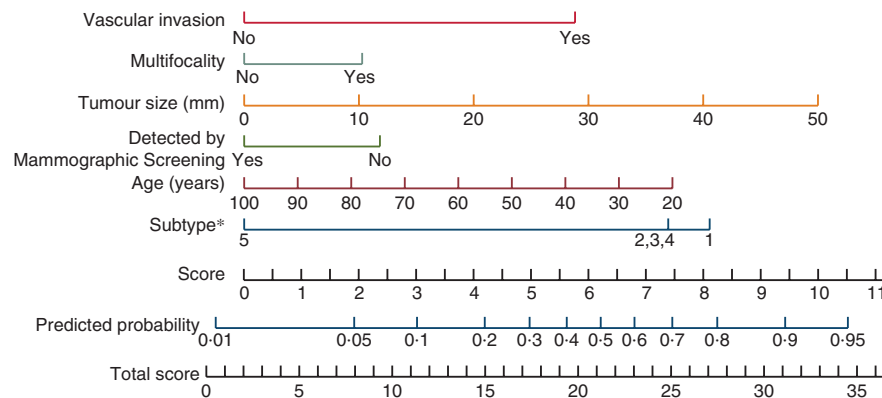
Table 2 Multivariable logistic regression for prediction of axillary nodal status

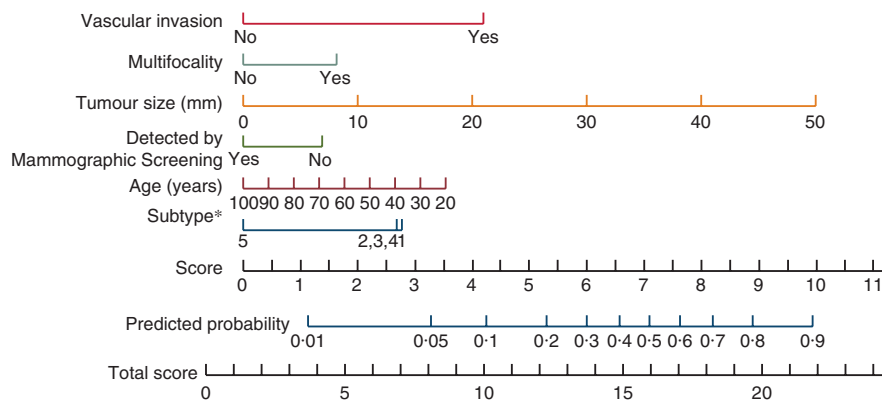|	Axillary nodal status					
	N0 versus N+ (n = 598)		N+(1–2) versus N0 (n = 535)		N+(≥ 3) versus N0 and N+(1–2) (n = 598)	
	Odds ratio	P	Odds ratio	P	Odds ratio	P
Subtype		0·031		0·063		0·470
LumA	1·00		1·00		1·00	
LumB/HER2−	1·18 (0·76, 1·84)		0·87 (0·53, 1·41)		0·84 (0·42, 1·67)	
LumB/HER2+	1·11 (0·56, 2·21)		0·87 (0·40, 1·88)		1·43 (0·59, 3·48)	
HER2+/non-luminal	1·48 (0·40, 5·44)		0·66 (0·16, 2·73)		0·79 (0·13, 5·03)	
Triple-negative	5·06 (1·89, 13·50)		0·17 (0·05, 0·54)		0·36 (0·09, 1·46)	
Age (per year)	1·02 (1·00, 1·04)	0·013	0·98 (0·96, 1·00)	0·023	0·99 (0·96, 1·01)	0·227
Mode of detection		0·006		0·021		0·079
Symptomatic	1·00		1·00		1·00	
Mammographic screening	1·75 (1·18, 2·61)		0·60 (0·39, 0·93)		0·58 (0·32, 1·06)	
Tumour size (per mm)	0·94 (0·92, 0·97)	< 0·001	1·05 (1·02, 1·07)	< 0·001	1·08 (1·04, 1·11)	< 0·001
Multifocality		0·015		0·064		0·053
Yes	1·00		1·00		1·00	
No	1·72 (1·11, 2·65)		0·64 (0·39, 1·03)		0·54 (0·29, 1·00)	
Vascular invasion		< 0·001		< 0·001		< 0·001
Yes	1·00		1·00		1·00	
No	4·67 (2·70, 8·09)		0·28 (0·15, 0·51)		0·21 (0·11, 0·39)	

Values in parentheses are 95 per cent confidence intervals. N0, lymph node-negative; N+, any lymph node metastasis; N+(1–2), lymph node metastasis involving one or two nodes; N+(≥ 3), lymph node metastasis involving at least three nodes; LumA, luminal A-like; LumB, luminal B-like; HER2, human epidermal growth factor receptor 2.

Fig. 2 Nomograms predicting the extent of axillary nodal disease: **a** disease-free axilla (N0) *versus* any nodal metastasis (N+); **b** low-volume axillary disease involving one or two nodes (N+(1–2)) *versus* N0; and **c** high-volume axillary disease involving at least three nodes (N+(≥ 3)) *versus* N0 and N+(1–2). The total score for each patient is assigned by drawing a vertical line from the appropriate point for each predictor down to the score scale, and summing these scores. To obtain the predicted probability of a specific nodal status, a vertical line is drawn from the total score scale up to the predicted probability scale in the lower part of the nomogram. *Subtypes: 1, luminal A-like; 2, luminal B-like (LumB)/human epidermal growth factor receptor 2 (HER2)-negative; 3, LumB/HER2-positive; 4, HER2-positive/non-luminal; 5, triple-negative
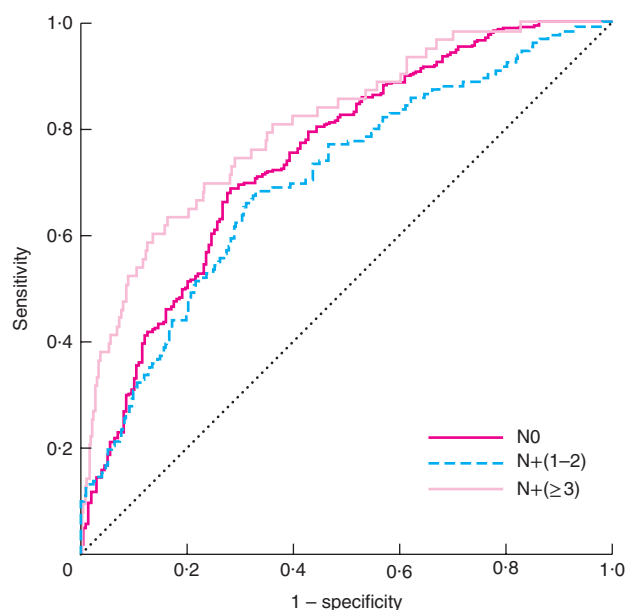
Fig. 3 Receiver operating characteristic (ROC) curves representing the discriminatory ability of the nomograms in predicting axillary nodal status. N0, lymph node-negative; N+(1–2), lymph node metastasis involving one or two nodes; N+(≥ 3), lymph node metastasis involving at least three nodes

Results

Between January 2009 and December 2012, 995 patients were diagnosed with invasive breast cancer and scheduled for primary surgery at Skåne University Hospital, Lund. The overall study cohort consisted of 692 patients who met the inclusion criteria, and had complete records on the expression of ER, PR, HER2 and Ki-67. All patients undergoing neoadjuvant treatment were excluded; 39 of these patients had cytologically verified axillary metastasis, and an additional 29 patients were excluded solely because of biopsy-confirmed axillary metastasis (*Fig. 1*). The clinical and histopathological characteristics of the overall study population and in subgroups categorized by breast cancer molecular subtype are presented in *Table 1*. Axillary nodal metastases were detected in 248 patients (35·8 per cent).

Clinicopathological characteristics across molecular subtypes

According to the 2013 St Gallen surrogate definition of breast cancer subtypes, 372 tumours (53·8 per cent) were identified as LumA, 198 as LumB/HER2– (28·6 per cent), 64 (9·2 per cent) as LumB/HER2+; 17 (2·5 per cent) as HER2+/non-luminal and 41 (5·9 per cent) as triple-negative (*Table 1*). Age, mode of detection, tumour size, histological type, histological grade, presence of

vascular invasion and axillary nodal metastasis (N0 *versus* any nodal metastasis (N+)) varied significantly across the subtypes. There were no significant differences in multifocality across the five subtypes.

Predictors of nodal status identified by multivariable logistic regression analysis

Associations with any of the three outcomes (N0 *versus* N+), low burden of metastatic axillary disease (1–2 positive nodes *versus* N0) or heavy burden of metastatic axillary disease (at least 3 positive nodes *versus* 2 or fewer positive nodes) were studied by multivariable logistic regression analysis (*Table 2*). Predictors identified were molecular subtype, patient age, mode of detection, tumour size, presence of multifocality and vascular invasion. Histological type was not identified as a predictor of lymph node metastasis in univariable logistic regression analysis, and not included in the multivariable logistic regression analyses and nomograms. A strong correlation was found between tumour grade and Ki-67 (the latter of which is incorporated into the St Gallen definition of subtypes), and so tumour grade was excluded from the multivariable analyses. Increasing age, detection of the primary tumour by mammographic screening (in contrast to symptomatic presentation), and the absence of multifocality and vascular invasion were all associated positively with a disease-free axilla (*Table 2*). When the prediction model was adjusted for the other factors, the odds of having N0 disease was more than five times higher for the triple-negative subtype than for the LumA subtype (odds ratio (OR) 5·06, 95 per cent c.i. 1·89 to 13·50).

Tumour size was strongly associated with axillary node negativity as well as a low (1–2 positive nodes) and heavy (at least 3 positive nodes) burden of axillary disease. Increasing tumour size was negatively associated with N0 disease (OR 0·94, 0·92 to 0·97). Conversely, for each millimetre increase in size of the primary tumour, the odds of having one or two metastatic lymph nodes and three or more metastatic lymph nodes were increased by 5 and 8 per cent respectively.

Evidence for the discriminatory effects of the presence of multifocality and the mode of detection was weaker. Vascular invasion was strongly associated with a heavy metastatic axillary burden. Factors associated with axillary metastatic disease involving one or two lymph nodes were: young age, symptomatic presentation of the breast tumour, large tumour size and vascular invasion.

Nomograms predicting axillary nodal status

The results from the multivariable regression analyses were used to construct three nomograms that predicted
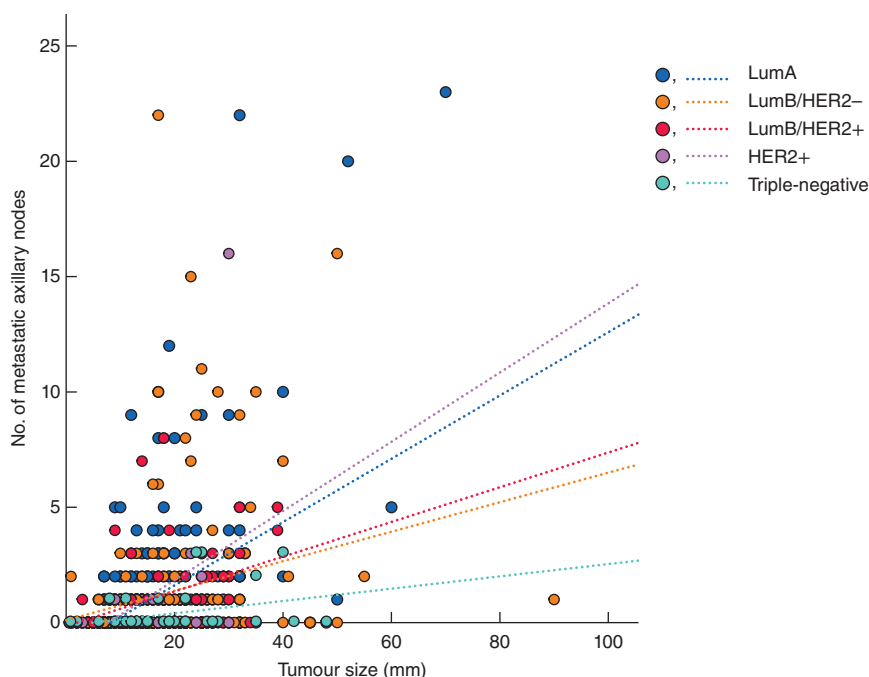
Fig. 4 Scatterplot of number of metastatic axillary nodes *versus* tumour size stratified by breast cancer molecular subtype. Trend lines (dotted) are shown only to facilitate comparison among the five molecular subtypes. LumA, luminal A-like; LumB, luminal B-like; HER2, human epidermal growth factor receptor 2

the extent of axillary nodal disease (*Fig. 2*). A score proportional to the log of the OR (estimated regression coefficient) was assigned to each independent predictor. The scaling of these scores was determined by arbitrarily setting the score to 10 points for an extreme tumour size relative to the observed range (0 and 50 mm respectively for prediction of node negativity and node positivity). Four dummy variables were initially used in the prediction models for the five breast cancer molecular subtypes, but the relative effects were found to be essentially the same for the LumB/HER2−, LumB/HER2+ and HER2+/non-luminal subtypes in all three prediction models. As LumA was the principal subtype in this study cohort, and the triple-negative subtype was shown to diverge most widely from the LumA subtype in predicting the outcome of axillary nodal involvement, the decision was taken to cluster the LumB/HER2−, LumB/HER2+ and HER2+/non-luminal subtypes into a single category and compared this with the LumA and the triple-negative subtypes.

Receiver operating characteristic curve analysis and internal validation

The discriminatory ability of the nomograms for predicting each of the three classes of axillary nodal status

was investigated using ROC curves (*Fig. 3*). The AUC for a disease-free axilla was 0·74 (95 per cent c.i. 0·70 to 0·79). Using 1000 resampled bootstrap data sets, the bias-corrected AUC for N0 was 0·74 with only a slight decrease (−0·009) in discriminative ability. The AUC for one or two positive nodes was 0·70 (0·65 to 0·75) with a bias-corrected AUC of 0·69 (−0·013), and that for at least three metastatic nodes was 0·81 (0·75 to 0·86) with a bias-corrected AUC of 0·79 (−0·013).

Number of metastatic lymph nodes in relation to tumour size

Tumour size was the single most significant factor associated with nodal status, regardless of the chosen endpoint. *Fig. 4* shows a scatterplot of the number of metastatic axillary lymph nodes in relation to the tumour size stratified by the five breast cancer subtypes. In accordance with the multivariable regression results, which showed higher odds of having N0 disease among patients with the triple-negative subtype than for those with LumA tumours, the scatterplot indicates that an increase in tumour size is less often associated with metastatic nodal involvement of the axilla in the triple-negative subtype than in the non-triple-negative subtypes. Crude ORs for N+ *versus*

Table 3 Univariable logistic regression models for axillary lymph node metastasis with tumour size in four categories as the only co-variable among patients with triple-negative disease and all other patients

Tumour size (mm)	No. of patients		Odds ratio	P
	N0	N+		
Non-triple-negative (n = 651)				< 0·001
1–10	139	30	1·00 (reference)	
11–20	192	107	2·58 (1·63, 4·09)	< 0·001
21–30	65	73	5·20 (3·10, 8·73)	< 0·001
> 30	15	30	9·27 (4·45, 19·32)	< 0·001
Triple-negative (n = 41)				0·342
1–10	6	1	1·00 (reference)	
11–20	18	2	0·67 (0·05, 8·73)	0·757
21–30	6	3	3·00 (0·24, 37·67)	0·395
> 30	3	2	4·00 (0·25, 63·95)	0·327

Values in parentheses are 95 per cent confidence intervals. N0, lymph node-negative; N+, any lymph node metastasis.

N0 disease for four categories of tumour size in the triple-negative subtype, and in the remaining four molecular subtypes clustered as non-triple-negative, are shown in *Table 3*.

Discussion

Axillary lymph node status remains an important factor for tailoring the management of patients with primary breast cancer and underscores the importance of accurate nodal staging[30–32]. This study has provided evidence of the independent impact of routine clinicopathological parameters, St Gallen molecular subtypes, tumour size and detection mode on the lymphatic spread of breast cancer in a consecutive population-based cohort. Nomograms were developed based on comprehensive data, with the aim of allowing the clinician to evaluate the risk of axillary metastatic disease and the extent of lymph node involvement more accurately, as a tool for determining the appropriate method of axillary surgery.

ACOSOG Z0011 was a randomized non-inferiority trial, which enrolled women with cT1–2 N0 breast cancer undergoing breast-conserving therapy and adjuvant whole-breast radiotherapy. The initial results, with a median follow-up of 6·3 years, demonstrated no differences in overall or disease-free survival for patients with one to two metastatic sentinel nodes who had ALND *versus* those who had SLNB alone[3]. Despite criticisms of the initial results of this trial, including issues regarding appropriate power and potential selection bias, the study was attempting to answer an important clinical question on the need for ALND in patients with node-positive disease. The updated report of the trial[4], with a median follow-up

of 9·25 years, supported the initial conclusion indicating no clinical benefit of completion axillary dissection for patients with one or two involved lymph nodes. The AMAROS trial also addressed the omission of ALND, comparing completion ALND *versus* radiotherapy to the axilla in patients with cT1–2 N0 disease and a maximum of two metastatic sentinel nodes. The IBCSG trial 23-01 was designed to determine whether omission of ALND was non-inferior to axillary dissection in patients with micrometastatic sentinel nodes and tumour no larger than 5 cm, irrespective of type of breast surgery. The results supported the notion that axillary dissection can be safely avoided in patients with early breast cancer and micrometastatic sentinel node involvement. Although the results of IBCSG 23-01 and a systematic review[33] have improved the evidence for dispensing with ALND in patients with micrometastases, the Swedish National Guidelines for the management of sentinel node micrometastases still recommended ALND during the present study interval; patients with micrometastases in the study cohort were therefore offered completion ALND.

In this study, the endpoints of the analyses were chosen after applying criteria from the ACOSOG Z0011 trial, which showed no benefit of completion axillary dissection for patients with one or two involved lymph nodes. The present cohort was thus divided into patients with no axillary disease, patients with one or two positive nodes and those with at least three metastatic nodes, and the predictors for these categories were developed and displayed graphically in three different nomograms. The proposed predictive models had AUCs of 0·70–0·81 in ROC curve analysis; internal validation demonstrated good discrimination in predicting the three categories of axillary nodal status. These nomograms could be used to provide clinical guidance regarding appropriate axillary treatment as no further staging (N0), sentinel node staging (1–2 positive nodes) and completion axillary dissection or neoadjuvant therapy (at least 3 positive nodes). By categorizing the endpoints into low- and high-risk groups based on the extent of nodal metastatic involvement and not solely counting on sentinel node status as a benchmark, the present nomograms were able to identify patients at risk of metastatic disease who may benefit from neoadjuvant therapy and/or direct ALND, thus bypassing SNLB.

SLNB remains the standard in axillary staging in clinically node-negative breast cancer. Several studies are examining whether SLNB may be omitted in low-risk patients, including trials evaluating preoperative imaging of the axilla, with specific attention to the performance of axillary ultrasonography. Ongoing prospective randomized studies on the use of axillary ultrasound examination,

including the SOUND (Sentinel node *vs* Observation after axillary UltrasouND) trial[34], will also contribute to answering the question of whether SLNB is needed in early breast cancer with a clinically and sonographically disease-free axilla. The results from that trial may further increase the importance of non-invasive predictive models for the pooled risk evaluation of extent of axillary disease. Existing scoring systems for axillary lymph node status either give estimated risks of sentinel lymph node metastasis[35,36] or, more commonly, predict the risk of additional non-sentinel lymph node disease after a verified positive sentinel node biopsy[13–19,37]. Meretoja and colleagues[38] presented a non-invasive predictive model, with an internally validated AUC of 0·73, to evaluate the patient-specific likelihood of axillary lymph node metastases in patients with normal axillary ultrasound findings. The suggested predictive model includes clinicopathological parameters such as tumour size, multifocality and vascular invasion, but lacks a report on the mode of detection. However, palpability of the primary tumour was incorporated as an independent predictor of lymph node metastasis. Evaluation of palpability, and especially axillary ultrasonography, may differ considerably between examiners. Although non-invasive, preoperative axillary ultrasound imaging is operator-dependent, and its overall accuracy remains controversial[8,39,40], especially for assessing low-burden nodal disease. Tumour palpability and axillary ultrasound data were not included in the present study as these were not recorded in all included patients, and the latter was introduced at the end of the study period. On the other hand, all patients with a preoperative diagnosis of nodal metastasis were excluded.

The nomograms presented here are based on data that can be obtained in a preoperative setting. In accordance with the majority of previous publications, the present results confirmed that, apart from vascular invasion, tumour size is one of the significant predictors of axillary lymph node involvement[12,13,16,35–38]. The mode of detection was associated with nodal status independent of tumour size and the St Gallen molecular subtypes, supporting the notion that mode of detection adds important clinical information aside from diagnosis at an earlier time point and smaller size of the detected tumour[7].

Although clinicopathological variables that may be available in the preoperative setting were considered here, the value of the present predictive models and nomograms in preoperative guidance will depend on the information obtained from histopathological evaluation of the tissue. Each suspicious lesion identified by preoperative imaging should be assessed by CNB or fine-needle aspiration cytology to confirm the diagnosis of invasive breast malignancy,

either involving a unifocal site or multiple foci. The prognostic and predictive factors in CNB have been assessed in previous publications. CNB has been reported to be accurate in evaluating ER, PR and HER2 status, and molecular subtype[41–43]. Owing to its microfocal characteristics, a 30 per cent failure rate in detecting vascular invasion in the CNB has been reported[44,45], which is a limitation of the proposed nomograms, and caution is therefore warranted in interpreting vascular invasion on CNB. Waaijer and colleagues[46] concluded that the assessment of tumour grade by CNB is feasible, whereas Focke *et al.*[47] demonstrated that the reliability of this depends on the size of the biopsy. Ki-67 is used as an alternative marker of cell proliferation. In the present cohort, an association was found between histological grade and Ki-67, the latter of which is incorporated in the St Gallen definition of molecular subtypes; therefore, tumour grade was excluded from the multivariable models to reduce the risk of multicollinearity.

The present study included only patients with complete data on ER, PR, HER2 and Ki-67 status, as defined by the surrogate immunohistochemical criteria of the St Gallen consensus[26], and, accordingly, reports on the impact of these subtypes on nodal status. There was a clear association between breast cancer subtypes and the presence of any nodal involvement, whereas the relative effect on axillary metastasis was found to be similar for the LumB/HER2–, LumB/HER2+ and HER2+/non-luminal subtypes. In contrast, Ugras and colleagues[12] reported the HER2+ subtype (luminal and non-luminal) as an independent predictor of high-volume nodal involvement compared with the LumA subtype in a cohort including patients with cN1 disease and a larger fraction of patients with node-positive disease than in the present population-based cohort. Additionally, patients who had biopsy-proven axillary metastasis at the time of diagnosis were excluded from the present study. In a study based on the Surveillance, Epidemiology, and End Results Program registry, Mattes and co-workers[48] showed that breast cancer subtype is an independent risk factor for lymph node positivity, with the hormone receptor-positive and HER2-negative subtypes carrying a greater risk of nodal involvement than the triple-negative subtype. The authors suggested the inability to detect differences between hormone receptor-negative/HER2+ tumours and other subtypes was related to the lack of power to detect differences between small subgroups of patients. Both publications[12,48], however, lack information on Ki-67, which is a criterion for the St Gallen subgroup classification.

In the present study, the majority of patients with triple-negative tumours had node-negative disease, in

agreement with previous publications indicating that the triple-negative subtype is more likely to be node-negative than the LumA subtype[49,50]. In the present multivariable analysis, the triple-negative subtype was also an independent predictor of disease-free axilla after adjustment for increasing tumour size. Patients with triple-negative tumours may thus gain limited benefit from extensive axillary surgery and adjuvant axillary radiotherapy. The results also indicate that the established correlation between tumour size and nodal status is less evident for triple-negative tumours. This is in line with the findings of Foulkes *et al.*[51], who reported a correlation between increasing tumour size and increasing number of involved lymph nodes in non-basal-like breast cancer; a similar correlation was not noted for basal-like breast cancer. It should be stated, however, that basal-like and triple-negative breast cancers are similar, but not identical[26].

This study has a number of limitations in addition to its retrospective nature. Even though the use of a population-based cohort with data from a prospectively maintained registry minimized the likelihood of selection bias, the study population comprised a single-centre cohort, with recruitment of the majority of patients from a public mammography screening programme. However, by excluding patients scheduled for neoadjuvant therapy, those with preoperative verification of nodal metastasis and patients who had previously undergone ipsilateral surgery, the confounding influences of these parameters on the evaluation of nodal status was reduced. Although internal validation was performed by bootstrapping, external validation in independent cohorts is needed before the nomograms can be applied clinically. Detailed pathological evaluation of all tumour and lymph node specimens was carried out by experienced breast pathologists, enabling the classification of breast cancer subtypes using the current St Gallen consensus definitions. The highest AUC observed (0·81) suggests that many factors beyond the clinicopathological risk variables included in the models influence nodal metastasis, but a truly comprehensive model may be too complex and render the nomograms unusable. Vascular invasion is an important variable in predicting nodal metastasis using the nomograms. Although inclusion of vascular invasion in the standard report is recommended[45], this variable cannot always be evaluated in a CNB, so nomogram results should be interpreted with caution. Finally, the value of the nomograms as preoperative guidance tools will depend on the data obtained during histopathological evaluation of tumour biopsies and radiological assessments; therefore, methodological limitations and interlaboratory variations in histopathology, and discrepancies in radiological evaluations between the available diagnostic modalities, must be taken into consideration when validating these risk prediction tools.

References

1 Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V *et al.* A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003; **349**: 546–553.

2 Lyman GH, Giuliano AE, Somerfield MR, Benson AB III, Bodurka DC, Burstein HJ *et al.*; American Society of Clinical Oncology. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol* 2005; **23**: 7703–7720.

3 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**: 569–575.

4 Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P *et al.* Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 randomized trial. *Ann Surg* 2016; **264**: 413–420.

5 Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P *et al.*; International Breast Cancer Study Group Trial 23-01 Investigators. 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 Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE *et al.* Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014; **15**: 1303–1310.

7 Cady B, Stone MD, Schuler JG, Thakur R, Wanner MA, Lavin PT. The new era in breast cancer. Invasion, size, and nodal involvement dramatically decreasing as a result of mammographic screening. *Arch Surg* 1996; **131**: 301–308.

8 Diepstraten SC, Sever AR, Buckens CF, Veldhuis WB, van Dalen T, van den Bosch MA *et al.* Value of preoperative ultrasound-guided axillary lymph node biopsy for preventing completion axillary lymph node dissection in breast cancer: a systematic review and meta-analysis. *Ann Surg Oncol* 2014; **21**: 51–59.

9 Smeets A, Ryckx A, Belmans A, Wildiers H, Neven P, Floris G *et al.* Impact of tumor chronology and tumor biology on lymph node metastasis in breast cancer. *Springerplus* 2013; **2**: 480.

10 Crabb SJ, Cheang MC, Leung S, Immonen T, Nielsen TO, Huntsman DD *et al.* Basal breast cancer molecular subtype predicts for lower incidence of axillary lymph node metastases in primary breast cancer. *Clin Breast Cancer* 2008; **8**: 249–256.

11 Wiechmann L, Sampson M, Stempel M, Jacks LM, Patil SM, King T *et al.* Presenting features of breast cancer differ by molecular subtype. *Ann Surg Oncol* 2009; **16**: 2705–2710.

12 Ugras S, Stempel M, Patil S, Morrow M. Estrogen receptor, progesterone receptor, and HER2 status predict lymphovascular invasion and lymph node involvement. *Ann Surg Oncol* 2014; **21**: 3780–3786.

13 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**: 1140–1151.

14 Barranger E, Coutant C, Flahault A, Delpech Y, Darai E, Uzan S. An axilla scoring system to predict non-sentinel lymph node status in breast cancer patients with sentinel lymph node involvement. *Breast Cancer Res Treat* 2005; **91**: 113–119.

15 Degnim AC, Reynolds C, Pantvaidya G, Zakaria S, Hoskin T, Barnes S *et al.* Nonsentinel node metastasis in breast cancer patients: assessment of an existing and a new predictive nomogram. *Am J Surg* 2005; **190**: 543–550.

16 Kohrt HE, Olshen RA, Bermas HR, Goodson WH, Wood DJ, Henry S *et al.* New models and online calculator for predicting non-sentinel lymph node status in sentinel lymph node positive breast cancer patients. *BMC Cancer* 2008; **8**: 66.

17 Pal A, Provenzano E, Duffy SW, Pinder SE, Purushotham AD. A model for predicting non-sentinel lymph node metastatic disease when the sentinel lymph node is positive. *Br J Surg* 2008; **95**: 302–309.

18 Gur AS, Unal B, Ozbek U, Ozmen V, Aydogan F, Gokgoz S *et al.* Validation of breast cancer nomograms for predicting the non-sentinel lymph node metastases after a positive sentinel lymph node biopsy in a multi-center study. *Eur J Surg Oncol* 2010; **36**: 30–35.

19 Canavese G, Bruzzi P, Catturich A, Vecchio C, Tomei D, Del Mastro L *et al.* A risk score model predictive of the presence of additional disease in the axilla in early-breast cancer patients with one or two metastatic sentinel lymph nodes. *Eur J Surg Oncol* 2014; **40**: 835–842.

20 Moghaddam Y, Falzon M, Fulford L, Williams NR, Keshtgar MR. Comparison of three mathematical models for predicting the risk of additional axillary nodal metastases after positive sentinel lymph node biopsy in early breast cancer. *Br J Surg* 2010; **97**: 1646–1652.

21 Yildiz R, Urkan M, Hancerliogullari O, Kilbas Z, Ozturk E, Mentes MO *et al.* Comparison of five different popular scoring systems to predict nonsentinel lymph node status in patients with metastatic sentinel lymph nodes: a tertiary care center experience. *Springerplus* 2015; **4**: 651.

22 Zhu L, Jin L, Li S, Chen K, Jia W, Shan Q *et al.* Which nomogram is best for predicting non-sentinel lymph node metastasis in breast cancer patients? A meta-analysis. *Breast Cancer Res Treat* 2013; **137**: 783–795.

23 Dingemans SA, de Rooij PD, van der Vuurst de Vries RM, Budel LM, Contant CM, van der Pool AE. Validation of six nomograms for predicting non-sentinel lymph node metastases in a Dutch breast cancer population. *Ann Surg Oncol* 2016; **23**: 477–481.

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**: 1035–1040.

25 Regionala cancercentrum i samverkan. *National Guidelines for the Treatment of Breast Cancer* 2014. http://www.cancercentrum.se/globalassets/cancerdiagnoser/brost/vardprogram/vp-brostcancer.pdf [accessed 7 October 2016].

26 Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B *et al.*; Panel Members. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol* 2013; **24**: 2206–2223.

27 Zlotnik A, Abraira V. A general-purpose nomogram generator for predictive logistic regression models. *Stata J* 2015; **15**: 537–546.

28 Steyerberg EW. *Clinical Prediction Models. A Practical Approach to Development, Validation, and Updating.* Springer: New York, 2009.

29 Sobin LH, Gospodarowicz MK, Wittekind C; International Union Against Cancer. *TNM Classification of Malignant Tumours* (7th edn). Wiley-Blackwell: Chichester, 2009.

30 Luini A, Gatti G, Ballardini B, Zurrida S, Galimberti V, Veronesi P *et al.* Development of axillary surgery in breast cancer. *Ann Oncol* 2005; **16**: 259–262.

31 Rosen PR, Groshen S, Saigo PE, Kinne DW, Hellman S. A long-term follow-up study of survival in stage I (T1 N0 M0) and stage II (T1 N1 M0) breast carcinoma. *J Clin Oncol* 1989; **7**: 355–366.

32 Cianfrocca M, Goldstein LJ. Prognostic and predictive factors in early-stage breast cancer. *Oncologist* 2004; **9**: 606–616.

33 Francissen CM, Dings PJ, van Dalen T, Strobbe LJ, van Laarhoven HW, de Wilt JH. Axillary recurrence after a tumor-positive sentinel lymph node biopsy without axillary

treatment: a review of the literature. *Ann Surg Oncol* 2012; **19**: 4140–4149.

34 Gentilini O, Veronesi U. Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: Sentinel node *vs* Observation after axillary UltraSouND). *Breast* 2012; **21**: 678–681.

35 Viale G, Zurrida S, Maiorano E, Mazzarol G, Pruneri G, Paganelli G *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.

36 Bevilacqua JL, Kattan MW, Fey JV, Cody HS III, Borgen PI, Van Zee KJ. Doctor, what are my chances of having a positive sentinel node? A validated nomogram for risk estimation. *J Clin Oncol* 2007; **25**: 3670–3679.

37 Mittendorf EA, Hunt KK, Boughey JC, Bassett R, Degnim AC, Harrell R *et al.* Incorporation of sentinel lymph node metastasis size into a nomogram predicting nonsentinel lymph node involvement in breast cancer patients with a positive sentinel lymph node. *Ann Surg* 2012; **255**: 109–115.

38 Meretoja TJ, Heikkilä PS, Mansfield AS, Cserni G, Ambrozay E, Boross G *et al.* A predictive tool to estimate the risk of axillary metastases in breast cancer patients with negative axillary ultrasound. *Ann Surg Oncol* 2014; **21**: 2229–2236.

39 Houssami N, Ciatto S, Turner RM, Cody HS III, Macaskill P. Preoperative ultrasound-guided needle biopsy of axillary nodes in invasive breast cancer: meta-analysis of its accuracy and utility in staging the axilla. *Ann Surg* 2011; **254**: 243–251.

40 Kramer GM, Leenders MW, Schijf LJ, Go HL, van der Ploeg T, van den Tol MP *et al.* Is ultrasound-guided fine-needle aspiration cytology of adequate value in detecting breast cancer patients with three or more positive axillary lymph nodes? *Breast Cancer Res Treat* 2016; **156**: 271–278.

41 Denley H, Pinder SE, Elston CW, Lee AH, Ellis IO. Preoperative assessment of prognostic factors in breast cancer. *J Clin Pathol* 2001; **54**: 20–24.

42 Chen X, Yuan Y, Gu Z, Shen K. Accuracy of estrogen receptor, progesterone receptor, and HER2 status between core needle and open excision biopsy in breast cancer: a meta-analysis. *Breast Cancer Res Treat* 2012; **134**: 957–967.

43 Yoo SH, Park IA, Chung YR, Kim H, Lee K, Noh DY *et al.* A histomorphologic predictive model for axillary lymph node metastasis in preoperative breast cancer core needle biopsy according to intrinsic subtypes. *Hum Pathol* 2015; **46**: 246–254.

44 Harris GC, Denley HE, Pinder SE, Lee AH, Ellis IO, Elston CW *et al.* Correlation of histologic prognostic factors in core biopsies and therapeutic excisions of invasive breast carcinoma. *Am J Surg Pathol* 2003; **27**: 11–15.

45 Pu RT, Schott AF, Sturtz DE, Griffith KA, Kleer CG. Pathologic features of breast cancer associated with complete response to neoadjuvant chemotherapy: importance of tumor necrosis. *Am J Surg Pathol* 2005; **29**: 354–358.

46 Waaijer L, Willems SM, Verkooijen HM, Buck DB, van der Pol CC, van Diest PJ *et al.* Impact of preoperative evaluation of tumour grade by core needle biopsy on clinical risk assessment and patient selection for adjuvant systemic treatment in breast cancer. *Br J Surg* 2015; **102**: 1048–1055.

47 Focke CM, Decker T, van Diest PJ. The reliability of histological grade in breast cancer core needle biopsies depends on biopsy size: a comparative study with subsequent surgical excisions. *Histopathology* 2016; **69**: 1047–1054.

48 Mattes MD, Bhatia JK, Metzger D, Ashamalla H, Katsoulakis E. Breast cancer subtype as a predictor of lymph node metastasis according to the SEER registry. *J Breast Cancer* 2015; **18**: 143–148.

49 Holm-Rasmussen EV, Jensen MB, Balslev E, Kroman N, Tvedskov TF. Reduced risk of axillary lymphatic spread in triple-negative breast cancer. *Breast Cancer Res Treat* 2015; **149**: 229–236.

50 Gangi A, Mirocha J, Leong T, Giuliano AE. Triple-negative breast cancer is not associated with increased likelihood of nodal metastases. *Ann Surg Oncol* 2014; **21**: 4098–4103.

51 Foulkes WD, Grainge MJ, Rakha EA, Green AR, Ellis IO. Tumor size is an unreliable predictor of prognosis in basal-like breast cancers and does not correlate closely with lymph node status. *Breast Cancer Res Treat* 2009; **117**: 199–204.