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Original Article

Validated prediction model for positive resection margins in breast-conserving surgery based exclusively on preoperative data

J. Ellbrant[1,2,*], K. Gulis[2,3], E. Plasgård[4], T. Svensjö[3], P. O. Bendahl[5] and L. Rydén[2,4]

[1]Department of Surgery, Skåne University Hospital, Malmö, Sweden
[2]Department of Clinical Sciences Lund, Division of Surgery, Lund University, Lund, Sweden
[3]Department of Surgery, Kristianstad Central Hospital, Kristianstad, Sweden
[4]Department of Surgery, Skåne University Hospital, Lund, Sweden
[5]Department of Clinical Sciences Lund, Division of Oncology and Pathology, Lund University, Lund, Sweden

Correspondence to: Division of Surgery, Jan Waldenströms gata 11A, Skåne University Hospital, SE-20502 Malmö, Sweden (e-mail: julia.ellbrant@med.lu.se)

Abstract

Background: Positive margins after breast-conserving surgery (BCS) and subsequent second surgery are associated with increased costs and patient discomfort. The aim of this study was to develop a prediction model for positive margins based on risk factors available before surgery.

Methods: Patients undergoing BCS for *in situ* or invasive cancer between 2015 and 2016 at site A formed a development cohort; those operated during 2017 in site A and B formed two validation cohorts. MRI was not used routinely. Preoperative radiographic and tumour characteristics and method of operation were collected from patient charts. Multivariable logistic regression was used to develop a prediction model for positive margins including variables with discriminatory capacity identified in a univariable model. The discrimination and calibration of the prediction model was assessed in the validation cohorts, and a nomogram developed.

Results: There were 432 patients in the development cohort, and 190 and 157 in site A and B validation cohorts respectively. Positive margins were identified in 77 patients (17.8 per cent) in the development cohort. A non-linear transformation of mammographic tumour size and six variables (visible on mammography, ductal carcinoma *in situ*, lobular invasive cancer, distance from nipple–areola complex, calcification, and type of surgery) were included in the final prediction model, which had an area under the curve of 0.80 (95 per cent c.i. 0.75 to 0.85). The discrimination and calibration of the prediction model was assessed in the validation cohorts, and a nomogram developed.

Conclusion: The prediction model showed good ability to predict positive margins after BCS and might, after further validation, be used before surgery in centres without the routine use of preoperative MRI.

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Introduction

Breast-conserving surgery (BCS) is the surgical procedure of choice for most patients with breast cancer. Combined with adjuvant radiotherapy, BCS is associated with overall survival rates equivalent[1–3] or even superior[4] to those of mastectomy. Increased use of oncoplastic BCS (OBCS) has also allowed breast-conserving cancer surgery for larger tumours, with satisfactory aesthetics and safe oncological outcomes[5–9]. BCS is associated with the risk of involved, or close, margins after the first procedure with or without OBCS[5–8,10,11]. The reported proportions of patients requiring re-excision owing to positive resection margins after BCS vary extensively between surgical centres, ranging from less than 10 per cent to greater than 30 per cent[5–8,10–16]. Positive margins are most often treated with a second surgical procedure. However, this has negative implications regarding cosmetic outcomes, postoperative complications, quality of life, healthcare costs, and delayed start to adjuvant therapy[10,17]. Therefore, preoperative planning of BCS must focus on keeping positive resection margins to a minimum.

Early studies of the predictors of positive margins often evaluated tumour characteristics from postoperative pathology reports, such as lobular cancer[11–13], ductal carcinoma *in situ* (DCIS)[11,12], and multifocality[11,12,14,17]. Identifying patient and tumour characteristics associated with involved and close margins that are available before operation would enable improved patient counselling and allow the surgeon to make preoperative decisions ahead of the first procedure. Recent studies have tried to develop predictive nomograms to identify low- and high-risk patients for positive margins[15,16,18,19] based on patient age, disease stage at diagnosis, tumour characteristics including

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histopathological and molecular subtype, and mammographic and MRI features[15,16,18,19]. Areas under the curve (AUCs) have ranged from 0.69 to 0.82[15,16,18,19], and external validation of existing nomograms has shown poor discrimination (low AUC values)[20,21]; some nomograms have not been validated externally at all[16,19]. Importantly, Pleijhuis and colleagues[15], who presented one of the best performing models, used postoperative tumour data only, because preoperative core needle biopsy was not routinely performed in the centre. Some of the nomograms included MRI predictors[15,18]. The inclusion criteria in the models reported have varied. Pan *et al.*[19] included patients treated with neoadjuvant therapy and used intraoperative frozen-section analysis, whereas Barentsz and co-workers[16] focused on non-palpable tumours. For these reasons, and because MRI is not available as a standard preoperative procedure in all centres, development of a validated prediction model that does not involve MRI variables is required.

The aim of the present study was to develop a prediction model for positive margins after BCS based exclusively on predictors that are easily available before surgery from centres without access to MRI for routine diagnostic work-up. Another aim was to validate the prediction model in two cohorts, one being external. Furthermore, the intention was to develop a nomogram, based on the model, to predict positive surgical resection margins and facilitate patient counselling and surgical decision-making ahead of BCS.

Methods

Study design and patient cohorts

This study was designed as a retrospective observational study and was performed in accordance with STROBE guidelines[22]. All patients undergoing primary BCS at a university hospital in Sweden from 2015 to 2016 (site A) formed the development cohort. Inclusion criteria were *in situ* or invasive cancer as the final postoperative pathological diagnosis; exclusion criteria comprised male sex, neoadjuvant therapy, or benign final diagnosis. Two additional cohorts with the same inclusion and exclusion criteria were created to validate the prediction model: a temporal cohort from the same hospital as the development cohort (site A) and an external cohort from a regional hospital in Sweden (site B), both from 2017 (*Fig. 1*).

Approval was obtained from the Regional Ethical Review Board at Lund University, Sweden (2018/622), and this study was conducted in accordance with the Declaration of Helsinki. No patient consent was required to use the retrospective database. The study was preregistered in the ISRCTN Registry (ISRCTN32164784).

Data collection

All data were pseudonymized and compiled in a database. Patient identification was from operational records (Orbit®, version 5.10.7; TietoEVRY, Kristianstad, Sweden) with the registration of ICD-10 code HAB40. A predefined clinical report form (CRF) was used to enable extraction of data from patients' records and auxiliary services databases regarding preoperative tumour, radiological, and surgical characteristics, such as mammography, ultrasonography, and pathology data. The data extraction was completed by two specialist surgeons, one medical student, and a research nurse. Data from every 10th patient was monitored by a senior investigator.

The definition of positive margins was defined by the National Swedish Guidelines as tumour identified on inked margins for invasive cancer, and margins less than 2 mm for DCIS. These guidelines remained unchanged between 2015 and 2017[23].

Age, menopausal status, BMI, breast size, side, and history of previous breast cancer or breast operations was retrieved from the patients' medical records. Tumour characteristics and data on surgical procedures were preprocessed to form the list of preoperative variables shown in *Tables 1*, *S1*, and *S2*. The main type of oncoplastic procedures in the centres were basic volume displacement techniques. Perioperative specimen imaging (mammography and ultrasonography) was performed routinely with the standard of a minimum of 10 mm as a clear radiological margin. Perioperative and postoperative variables were collected from the same sources (*Table S3*). Microcalcification on mammography in the external validation cohort was found to be evaluated differently by radiologists at site B compared with the consistent evaluation criteria used at site A. At site B, calcifications were documented only if regarded as malignant. The distance from the nipple–areola complex (NAC) was documented based on mammographic imaging. Missing data for distance from NAC and tumour size on mammography were retrieved retrospectively from operation records, and tumour size was validated by mammographic assessment by a breast radiologist.

Core needle biopsy was used routinely for preoperative diagnosis at both study centres. Preoperative core needle biopsy diagnosis was defined by the most malignant finding, so an *in situ* diagnosis refers to tumours without invasive components. Preoperative hormone receptor status was not analysed during this time interval in patients undergoing primary surgery, so this item was not included in the model. Tumours that were not visible on mammography or ultrasonography were coded as having tumour size 0, and a dummy variable was added to the data sets to identify this feature. Tumour size was categorized as not visible, T1 (less than 2 cm), T2 (2–5 cm), or T3 (greater than 5 cm).

Statistical analysis

The primary outcome of the study was positive resection margins after BCS. Univariable logistic regression analysis was used to estimate unadjusted odds ratios with 95 per cent confidence intervals for a selected set of clinically relevant or potentially relevant candidate predictors, and multivariable logistic regression analysis was used to develop the final prediction model. The variable benign preoperative tumour was not included in the predictive model because intended margins for diagnostic resection were kept to a minimum as the procedure is performed to achieve a final histopathological diagnosis. Tumour size on ultrasonography was also not included in the final model because it was closely associated with the included variable DCIS on core needle biopsy. Stepwise backward variable selection with an Akaike information criterion-based method for the threshold for exclusion ($P > 0.157$) was combined with multivariable fractional polynomials; the latter allowed for a non-linear effect of mammographic tumour size. Calcification on mammography was dropped at the last step of the automatic variable selection process, with a P value just above the chosen threshold, but retained in the final model according to its clinical relevance. The model size and number of patients with positive resections margins in the development cohort were evaluated in accordance with the minimum number of events per variable (EPV) criterion (EPV = 10), suggested by Steyerberg and Vergouwe[24].

Model performance was evaluated with respect to discrimination in all three cohorts using AUCs for receiver–operating characteristic (ROC) curves, and regarding calibration in the two validation cohorts. Hosmer–Lemeshow graphs of observed *versus*

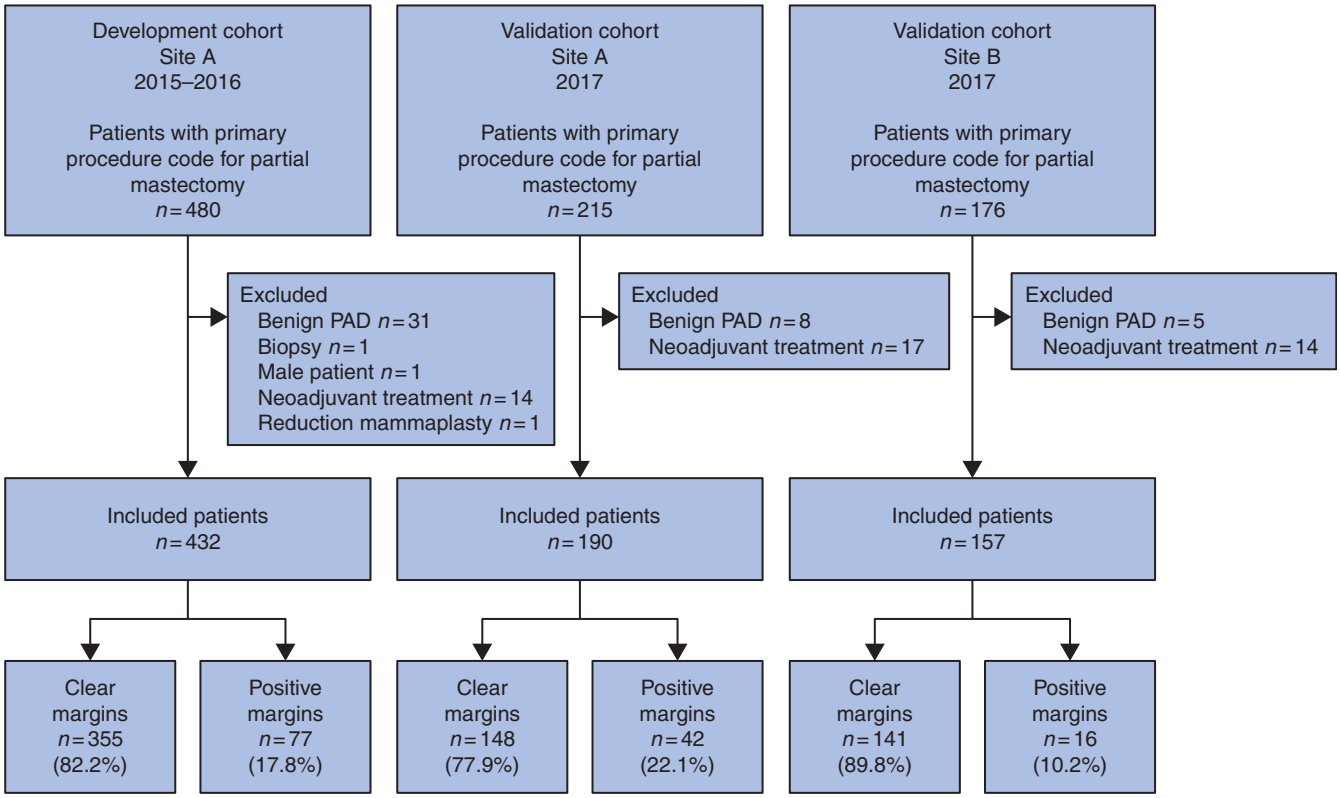

Fig. 1 Study flow chart showing patients in development cohort and validation cohorts.

mean predicted probabilities of positive resection margins in deciles of the latter were used to visualize the calibration and the corresponding Hosmer–Lemeshow test to evaluate goodness of fit. Calibration in the validation cohorts was assessed by means of the calibration slope and by comparing the mean predicted probability of the outcome and the corresponding observed fraction. The final model is presented in both tabular form and as a nomogram.

Statistical analyses were performed using SPSS® version 24.0 (IBM, Armonk, NY, USA) and Stata® version 16.1 (StataCorp, College Station, TX, USA).

Results

Patient demographics

A total of 480 patients at site A underwent primary BCS from 2015 to 2016, of whom 432 were eligible for inclusion in the development cohort (*Fig. 1*). The temporal validation cohort from site A included 190 patients, and there were 157 patients in the external validation cohort from site B. Baseline patient and tumour characteristics were largely comparable in the three cohorts, with some exceptions (*Tables 1*, *S1*, and *S2*). Positive margins were more common in the development cohort and in the temporal validation cohort from site A than in the cohort from site B. Mammographic microcalcification was more common in the validation cohort from site A and less common in the validation cohort from site B compared with the development cohort. However, some of the observed difference in the fraction of reported patients with microcalcifications in external validation cohort B was due to variable reporting, as explained in the methods section. Because oncoplastic techniques have become more common, fewer patients underwent standard partial mastectomy in the cohorts from 2017 from site A and site B than in the development cohort.

Prediction modelling

Univariable analysis

Univariable logistic regression analysis was used to study associations between each of the potential predictors in the development set and the binary outcome, positive resection margins. The results are summarized in *Table 1*. Strong associations were found for mammographic tumour size for visible tumours and for mammographic tumour size categorized into four groups: tumour not visible on mammography, T1, T2 and T3 +. With the most prevalent group, T1, as the reference category, a strong predictive effect was seen for T2 *versus* T1, and a more modest effect for tumour not visible on mammography *versus* T1. Ultrasonographic tumour size was also a strong predictor of positive resection margins. Furthermore, predictive effects were seen for the presence of mammographic microcalcifications, tumours less than 5 cm from the NAC, and histological type on diagnostic core needle biopsy. With the most prevalent histology, invasive ductal cancer, as the reference category, strong predictive effects were seen for invasive lobular cancer (ILC), pure DCIS, and benign biopsy. Several variables, such as patient age, BMI, tumour palpability, tumour location in the breast, and axillary status had no statistically significant predictive value in the development cohort (*Table 1*).

Multivariable analysis

Histological type was recoded as two dummy variables, comparing ILC and DCIS with all other histological types. These variables, with distance to the NAC (less than 5 cm *versus* greater than or equal to 5 cm), method of operation, and mammographic tumour size, were selected by the backward elimination modelling procedure. Microcalcification was a predictor of positive margins

Table 1 Baseline and preoperative characteristics of development cohort, including univariable logistic regression analyses of positive resection margins

	All patients ($n = 432$)	Clear margins ($n = 355$)	Positive margins ($n = 77$)	Odds ratio*	*P*
Demographic characteristics					
Age (years)					
< 50	77 (17.8)	59 (77)	18 (23)	1.89 (0.90, 3.98)	0.095
50–59	92 (21.3)	80 (87)	12 (13)	0.93 (0.42, 2.08)	0.856
60–69	148 (34.3)	117 (79.1)	31 (20.9)	1.64 (0.85, 3.17)	0.142
≥ 70	115 (26.6)	99 (86.1)	16 (13.9)	1.00 (reference)	
BMI (kg/m^2)					
< 22.0	58 (13.4)	45 (78)	13 (22)	1.00 (reference)	
22.0–24.9	115 (26.6)	100 (87.0)	15 (13.0)	0.52 (0.23, 1.18)	0.118
25.0–29.9	156 (36.1)	128 (82.1)	28 (17.9)	0.76 (0.36, 1.59)	0.462
≥ 30.0	103 (23.8)	82 (79.6)	21 (20.4)	0.89 (0.41, 1.94)	0.763
Previous ipsilateral breast surgery					
Yes	28 (6.5)	21 (75)	7 (25)	1.59 (0.65, 3.89)	0.309
No	404 (93.5)	334 (82.7)	70 (17.3)	1.00 (reference)	
Breast side					
Left	228 (52.8)	183 (80.3)	45 (19.7)	1.00 (reference)	
Right	204 (47.2)	172 (84.3)	32 (15.7)	0.76 (0.46, 1.25)	0.273
Breast size (ml)					
< 500	123 (36.8)	102 (82.9)	21 (17.1)	0.88 (0.49, 1.58)	0.667
≥ 500	211 (63.2)	171 (81.0)	40 (19.0)	1.00 (reference)	
Unknown†	98				
Radiological features					
Mode of detection					
Symptomatic	146 (33.8)	120 (82.2)	26 (17.8)	1.00 (0.59, 1.68)	0.995
Mammographic screening	286 (66.2)	235 (82.2)	51 (17.8)	1.00 (reference)	
Visibility on mammography					
Visible	404 (93.5)	335 (82.9)	69 (17.1)	1.00 (reference)	
Not visible	28 (6.5)	20 (71)	8 (29)	1.94 (0.82, 4.59)	0.130
Mammographic tumour size					
All visible tumours (risk per mm)	404 (93.5)	335 (82.9)	69 (17.1)	1.05 (1.02, 1.07)	< 0.001
Mammographic tumour size (mm)‡					
≤ 20 (T1)	338 (78.2)	291 (86.1)	47 (13.9)	1.00 (reference)	
21–50 (T2)	61 (14.1)	41 (67)	20 (33)	3.02 (1.63, 5.60)	< 0.001
> 50 (T3)	5 (1.2)	3 (60)	2 (40)	4.13 (0.63, 25.36)	0.126
Not visible	28 (6.5)	20 (71)	8 (29)	2.48 (1.03, 5.95)	0.042
Absent mass on ultrasonography					
No	390 (90.3)	329 (84.4)	61 (15.6)	1.00 (reference)	
Yes	42 (9.7)	26 (62)	16 (38)	3.32 (1.68, 6.55)	0.001
Ultrasonographic tumour size (mm)‡					
≤ 20 (T1)	322 (80.1)	282 (87.6)	40 (12.4)	1.00 (reference)	
21–50 (T2)	37 (9.2)	25 (68)	12 (32)	3.38 (1.58, 7.26)	0.002
> 50 (T3)	1 (0.2)	1 (100)	0 (0)	–	
Not visible	42 (10.4)	26 (62)	16 (38)	4.34 (2.14, 8.78)	< 0.001
Unknown†	30				
Mammographic calcifications					
Yes	115 (26.6)	82 (71.3)	33 (28.7)	2.50 (1.49, 4.18)	< 0.001
No	317 (73.4)	273 (86.1)	44 (13.9)	1.00 (reference)	
Radiographic multifocality					
Yes	37 (8.6)	28 (78)	8 (22)	1.30 (0.57, 2.97)	0.529
No	395 (91.4)	326 (82.5)	69 (17.5)	1.00 (reference)	
Clinical findings and biopsy diagnosis					
Palpability					
Palpable	227 (52.5)	189 (83.3)	38 (16.7)	1.00 (reference)	
Non-palpable	205 (47.5)	166 (81.0)	39 (19.0)	1.17 (0.71, 1.91)	0.536
Tumour location					
Superior medial quadrant	72 (16.7)	54 (75)	18 (25)	1.00 (reference)	
Superior lateral quadrant	206 (47.7)	173 (84.0)	33 (16.0)	0.57 (0.30, 1.10)	0.093
Inferior lateral quadrant	95 (22.0)	79 (83)	16 (17)	0.61 (0.29, 1.30)	0.197
Inferior medial quadrant	51 (11.8)	42 (82)	9 (18)	0.64 (0.26, 1.58)	0.334
Retromammillary	8 (1.9)	7 (88)	1 (13)	0.43 (0.05, 3.72)	0.442
Distance from nipple–areola complex (cm)					
< 5	109 (25.2)	79 (72.5)	30 (27.5)	2.23 (1.32, 3.76)	0.003
≥ 5	323 (74.8)	276 (85.4)	47 (14.6)	1.00 (reference)	
Core-needle biopsy histological type					
IDC	221 (51.2)	201 (91.0)	20 (9.0)	1.00 (reference)	
ILC	49 (11.3)	30 (61)	19 (39)	6.37 (3.05, 13.29)	< 0.001
Other types of IC	91 (21.1)	81 (89)	10 (11)	1.24 (0.56, 2.77)	0.598
DCIS	48 (11.1)	28 (58)	20 (42)	7.18 (3.44, 14.97)	< 0.001
LCIS and other types of *in situ* cancer	6 (1.4)	4 (67)	2 (33)	5.03 (0.87, 29.16)	0.072

(continued)

Table 1. (continued)

	All patients ($n = 432$)	Clear margins ($n = 355$)	Positive margins ($n = 77$)	Odds ratio*	*P*
Benign	16 (3.7)	10 (63)	6 (38)	6.03 (1.98, 18.33)	0.002
Atypia, suspected malignancy	1 (0.2)	1 (100)	0 (0)	–	,
Type of operation					
Partial mastectomy	309 (71.5)	249 (80.6)	60 (19.4)	1.00 (reference)	
Oncoplastic partial mastectomy	123 (28.5)	106 (86.2)	17 (13.8)	0.67 (0.37, 1.19)	0.172

Values in parentheses are parentheses unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. †Data not recorded in the medical records. ‡T1–T3: tumour stage. IDC, invasive ductal cancer; ILC, invasive lobular cancer; IC, invasive cancer; DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*.

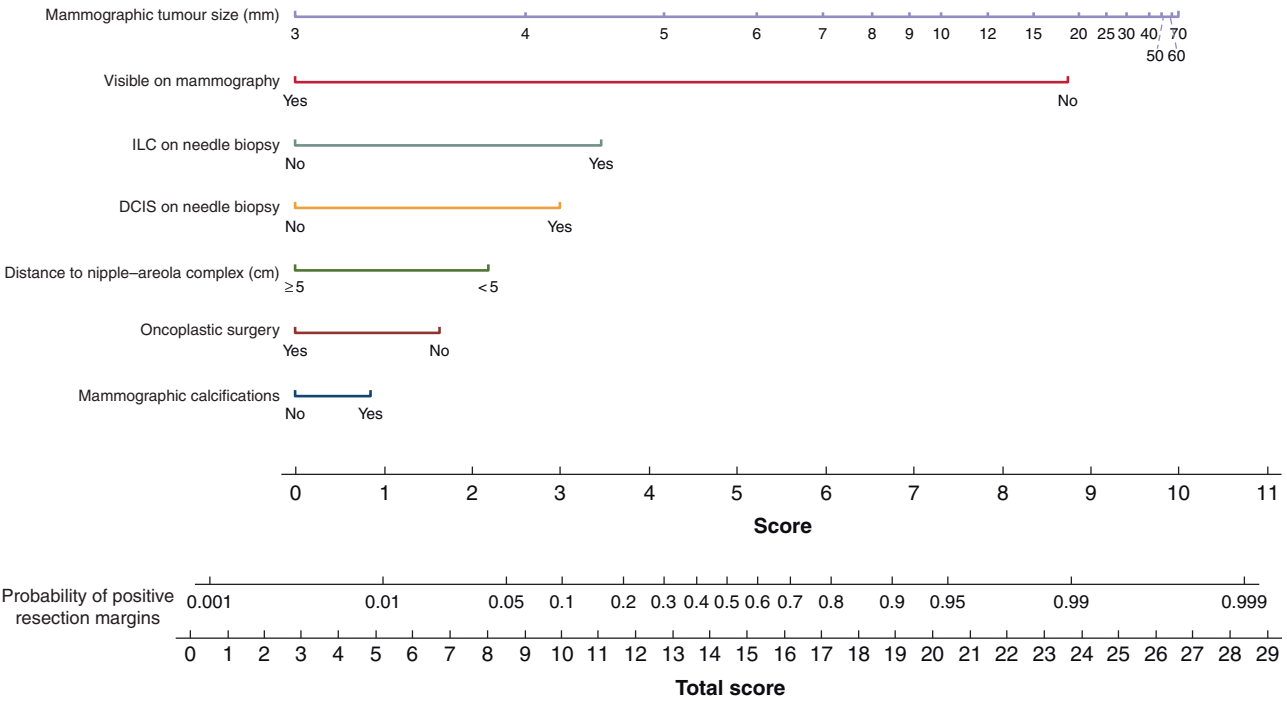

Fig. 2 Nomogram for predicting positive resection margins based on available data before surgery

The nomogram is used as follows. Mark the values for the patient for each of the seven predictors, then read off and sum the individual scores. Finally, mark the total score on the axis at the bottom of the graph and read off the corresponding estimated probability of positive resection margins. Note the non-linear reversed scale for mammographic tumour size. ILC, invasive lobular cancer; DCIS, ductal carcinoma *in situ*.

in other studies[15,18]. In this study, it neared the threshold for automatic selection, so it was decided to retain microcalcification in the final model. Stepwise fractional polynomial modelling revealed that inverse tumour size in millimetres and a dummy variable for detectability on mammography were superior to both modelling of tumour size in millimetres on a linear scale and the same dummy variable for detectability, as well as mammographic tumour size categorized into the three groups, not detectable, T1, and T2+. AUC values for the three models, differing only in the method of modelling mammographic tumour size, were 0.80, 0.79, and 0.78, respectively.

The final model is presented in *Table 2* and *Fig. 2*. The best discriminator between positive and negative resection margins, as measured by *P* values in the multivariable logistic regression model, was ILC, followed by DCIS and distance to the NAC. Mammographic tumour size and type of operation contributed significantly to the discrimination, whereas the presence of microcalcification was less important in the development cohort (*Table 2*). The corresponding ROC curve, with an AUC of 0.80 (95 per cent c.i. 0.75 to 0.85), is shown in *Fig. 3*. With 77 patients with positive resections margins included in the development cohort, the model size was in accordance with the minimum number of events per EPV criterion, EPV = 10[24].

Validation

Baseline characteristics and associations with outcome for the two validation cohorts are summarized in *Tables S1* and *S2*. There were differences in associations with outcomes between the validation cohorts and the development cohort. In the temporal validation cohort from site A, ILC showed no association with positive margins. In the external validation cohort at site B, neither microcalcification nor distance from the NAC predicted positive margins.

The prediction model presented in *Table 2* discriminated between positive and negative resection margins in the two validation cohorts, but the discrimination, measured by AUC, was lower in both the temporal validation cohort from site A and the external validation cohort from site B (*Fig. 4a,b*). Hosmer–Lemeshow graphs showing calibration of the model in the two validation cohorts are presented in *Fig. 4c,d*. The evidence against perfect calibration was stronger for the validation cohort from site A than for the validation cohort from site B, and both calibration slopes were less than

Table 2 Multivariable logistic regression model for predicting positive resection margins based on preoperative characteristics in the development cohort (432 patients)

	Odds ratio	P
−30/(mammographic tumour size, mm)*	1.68 (1.21, 2.32)	0.002
Visible on mammography		
Yes	1.00 (reference)	
No	2.33 (0.72, 7.60)	0.160
ILC on needle biopsy		
No	1.00 (reference)	
Yes	5.59 (2.71, 11.50)	< 0.001
DCIS on needle biopsy		
No	1.00 (reference)	
Yes	4.44 (2.00, 9.83)	< 0.001
Distance from nipple–areola complex ≥5 cm		
Yes	1.00 (reference)	
No	2.96 (1.63, 5.40)	< 0.001
Oncoplastic surgery		
Yes	1.00 (reference)	
No	2.25 (1.17, 4.32)	0.015
Mammographic calcifications		
No	1.00 (reference)	
Yes	1.52 (0.80, 2.89)	0.205
Constant	0.06 (0.02, 0.19)	

Values in parentheses are 95 per cent confidence intervals. *Inverted mammographic tumour size was multiplied by −30 to simplify interpretation of the corresponding odds ratio. As an example, consider two patients with tumour sizes of 10 and 15 mm respectively. Because −30/10 is −3, and −30/15 is −2, these two tumours will have a 1-unit difference on the scale of X = −30/(mammographic tumour size, mm). Hence, according to this model, the odds of a positive resection margin are 68 per cent higher for the patient with the larger of the two tumours, after adjustment for all other predictors in the model. The inverted tumour size was set to 0 if the tumour was not visible on mammography. Hence, these tumours are given the same weight for the variable, X, as infinitely large tumours, but this is corrected for by the dummy variable, visible on mammography. ILC, invasive lobular cancer; DCIS, ductal carcinoma *in situ*.

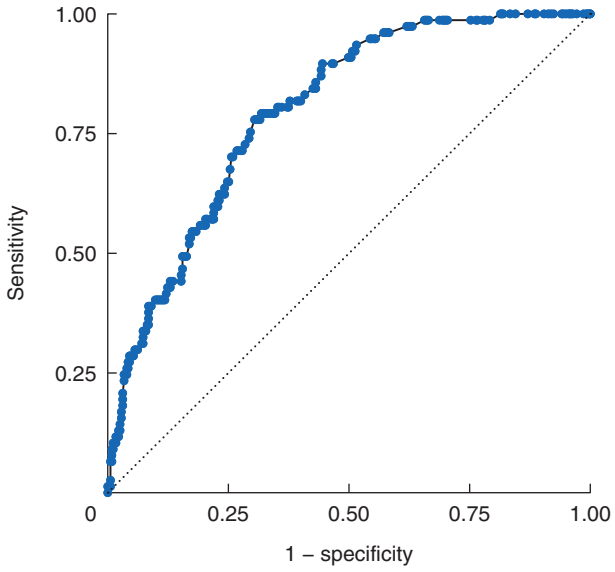

Fig. 3 Receiver–operating characteristic curve for the prediction model in the development cohort

The discrimination of the model is summarized as the area under the curve, which has a value of 0.80.

1.00, indicating some overfitting. The model appeared to underestimate the probability of positive resection margins for patients with a low risk of positive margins in the validation cohort from site A and, conversely, to overestimate this risk in the validation cohort from site B. However, the mean observed proportion of patients with positive resection margins in the decile with the highest predicted probabilities was higher than the corresponding proportions for the other nine deciles in both validation cohorts (*Fig. 4c,d*), suggesting that the model can robustly identify patients at high risk of positive resection margins.

Discussion

A validated prediction model for positive resection margins after initial BCS has been developed. The model includes seven characteristics available before operation and, therefore, could be clinically helpful for breast surgeons in the preoperative evaluation of individual patients in centres without MRI assessment for surgical guidance. All the predictors are routinely available in centres using core needle biopsies, and the model can potentially decrease the proportion of patients requiring multiple surgical procedures. To facilitate its use, the model is presented as a nomogram to identify patients at low and high risk of re-excision.

In this study, preoperative factors associated with positive resection margins were mammographic tumour size, a diagnosis of ILC, microscopic calcifications or DCIS on core needle biopsy, and tumour distance from the NAC. These findings confirm previously published results showing that central tumours[11,25], ILC[8,12,25–33], DCIS[12,15,16,26,32], tumour size[14–16,28,29,31,33], and microscopic calcifications on mammography[15,16] are associated with suspected residual disease. In contrast, there was no association between positive margins and tumour palpability and clinical node positivity. Importantly, a histopathological diagnosis of DCIS or ILC on preoperative core needle biopsy was strongly predictive of positive margins, regardless of the final pathological report.

Recent studies of the predictors of positive margins in BCS have focused on factors that are available before operation for their potential clinical value in preoperative decision-making, and a few predictive nomograms have been developed[15,16,18,19]. The results of the present study are comparable to those of other preoperative prediction models, which have AUC values ranging from 0.70[15] to 0.82[18] (including MRI indicators) in the corresponding development cohorts. However, these nomograms have varied in performance upon validation[16,18,20,21,34,35]. The performance of the present model upon external validation was at least as good as that of previous validation studies and similar to the results of Shin and colleagues[18]. The internal validation of Shin and co-workers' model indicated very good discrimination (AUC 0.85), but a later external validation was not successful, and further refinement of the model has been proposed[34,35]. The nomogram reported by Pleijhuis *et al.*[15] is still in need of further external validation after diverging validation results in external cohorts (AUC 0.47–0.62)[16,21].

The present prediction model did not include radiographic variables other than mammographic tumour size, visibility of the tumour mass, and the presence of microcalcifications, whereas other studies[14,18,26,28] have included a variety of MRI features. The importance of MRI for predicting positive resection margins was inconclusive in larger studies[36,37]. Patients in the present study, as in many institutions, did not routinely undergo preoperative MRI.

In the present study, the scheduled method of operation was chosen for inclusion as a clinically important variable in the prediction model, even though the evidence for an association between this predictor and outcomes was weak in the validation cohort. Several other studies[5–7,9,38] have indicated that OBCS is

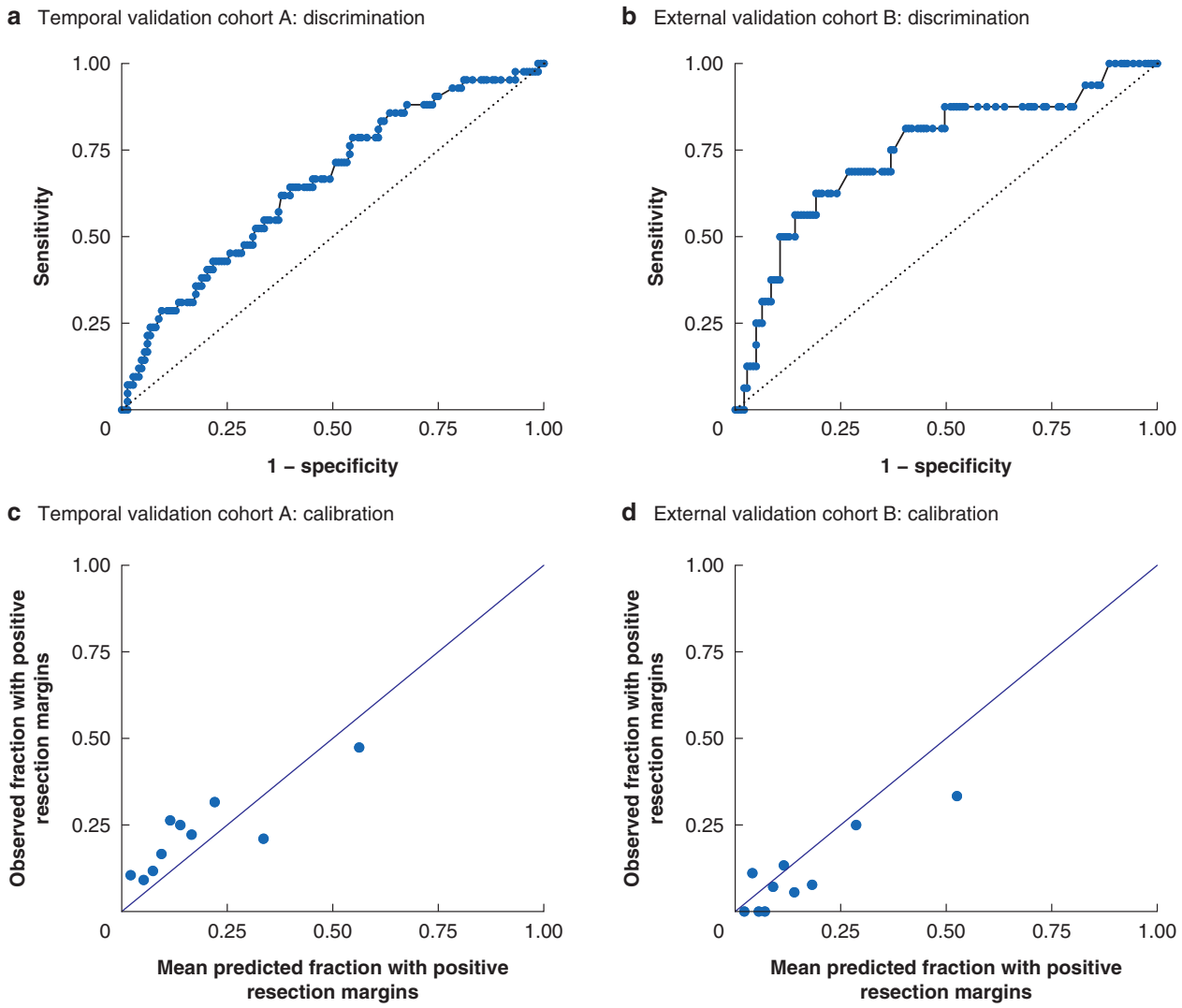

Fig. 4 Discrimination and calibration plots for the temporal validation cohort at site A and the external validation cohort at site B

Receiver operating characteristic curves showing discrimination of the prediction model in **a** temporal validation cohort at site A (area under the curve (AUC) and **b** external validation cohort at site B (AUC 0.75). Corresponding calibration curves for the model are presented in **c** and **d** respectively, as Hosmer–Lemeshow graphs. Calibration by Hosmer–Lemeshow test results is shown as observed (O) and expected (E) fractions of positive resection margins and calibration slopes. **c** O = 22.1 per cent, E = 17.7 per cent, calibration slope 0.47, Hosmer–Lemeshow $P = 0.019$; **d** O = 10.2 per cent, E = 14.9 per cent, calibration slope 0.75, Hosmer–Lemeshow $P = 0.324$.

equal to or even superior to standard BCS regarding oncological safety. Positive margins after OBCS have ranged from approximately 2 to 20 per cent[20,38,39]. The present results indicated that planned OBCS had a negative association with positive margins, similar to previous findings[38].

In this multicentre study, the variability in re-excision rates from 10 to 21 per cent is just a small reflection of the vast variability worldwide[27,32,40–45]. Several factors could have an appreciable impact on positive margins, such as pathology and auxiliary service evaluations and routines, proportion of total primary mastectomies, criteria for positive resection margins, and surgical performance.

The main strength of the prediction model is its pragmatic simplicity, involving only seven preoperative variables that are readily obtainable at most breast centres. Another strength is the ability of the model to identify patients at high risk of positive margins, not only in the development cohort but also in the validation cohorts. Patients would benefit greatly from a tool predicting positive margins before surgery, which would enable wider excision margins and oncoplastic surgery. However, the model somewhat underestimated the risk of positive margins for patients at low risk. The clinical implication of this is less important because patients at low risk of positive margins could undergo routine BCS without the need to consider wider margins.

The retrospective design is a limitation of the study. However, to optimize and standardize data collection, a predefined CRF was used to extract data from patients' records. In addition, all available data in the patients' records had been registered prospectively. Data on breast density were not available at any of the centres, so this variable could not be included in the model. Further limitations include reporting of the presence of mammographic calcification, which at site B was documented only if considered malignant. However, the strong AUC value for the validation cohort from site B indicates that the nomogram is applicable externally.

This novel predictive nomogram could provide clinical and surgical guidance to identify low- and high-risk patients requiring re-excision in settings where MRI is not available, but further

external validation of the model is encouraged. The nomogram could be used to ensure that patients are fully aware of the risk of positive resection margins and that a surgical approach is advised to match the level of risk.

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Supplementary material

Supplementary material is available at *BJS Open* online.

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