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Original article

A validated web-based nomogram for predicting positive surgical margins following breast-conserving surgery as a preoperative tool for clinical decision-making

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ABSTRACT

Background: Breast-conserving therapy, consisting of lumpectomy and adjuvant radiotherapy, is considered standard treatment for early-stage breast cancer. One of the most important risk factors of local recurrence is the presence of positive surgical margins following lumpectomy. We aimed to develop and validate a predictive model (nomogram) to predict for positive margins following the first attempt at lumpectomy as a preoperative tool for clinical decision-making.

Methods: Patients with clinical $T_{1-2}N_{0-1}M_{x-0}$ histology-proven invasive breast carcinoma who underwent BCT throughout the North-East region of The Netherlands between June 2008 and July 2009 were selected from the Netherlands Cancer Registry ($n = 1185$). Results from multivariate logistic regression analyses served as the basis for development of the nomogram. Nomogram calibration and discrimination were assessed graphically and by calculation of a concordance index, respectively. Nomogram performance was validated on an external independent dataset ($n = 331$) from the University Medical Center Groningen.

Results: The final multivariate regression model included clinical, radiological, and pathological variables. Concordance indices were calculated of 0.70 (95% CI: 0.66–0.74) and 0.69 (95% CI: 0.63–0.76) for the modeling and the validation group, respectively. Calibration of the model was considered adequate in both groups. A nomogram was developed as a graphical representation of the model. Moreover, a web-based application (http://www.breastconservation.com) was build to facilitate the use of our nomogram in a clinical setting.

Conclusion: We developed and validated a nomogram that enables estimation of the preoperative risk of positive margins in breast-conserving surgery. Our nomogram provides a valuable tool for identifying high-risk patients who might benefit from preoperative MRI and/or oncoplastic surgery.

Introduction

Breast-conserving therapy (BCT), consisting of lumpectomy and adjuvant radiotherapy, is considered standard treatment for early-stage breast cancer.[1,2] The presence of a positive (surgical) margin, usually defined as tumor cells being present at the inked margin of the lumpectomy specimen, has been reported to be the most consistent risk factor for local recurrence (LR) following BCT.[3,4] The percentage of patients with positive margins following the first attempt at lumpectomy ranges from 20 to 40% in the majority of studies.[5] To reduce the risk of LR in the case of positive margins, additional surgery and/or radiotherapy are required with adverse affects on cosmesis, psychological distress, and health costs.[6]

Previous studies reported large tumor size, lobular histological type, positive N-stage, multifocal disease, lymphovascular invasion, co-existing ductal carcinoma in situ (DCIS), microcalcifications on mammography, and young age to be independent risk factors associated with positive margins following lumpectomy (Supplemental

Abbreviations: AUROC, area under the receiver-operating characteristic curve; BCT, breast-conserving therapy; CNB, core needle biopsy; LR, local recurrence; MVA, multivariate regression analysis; OR, odds ratio.

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Table 1). To allow for simultaneous consideration of multiple risk factors, statistical tools can be applied to calculate the overall probability of a specific outcome.[7] These so-called nomograms are tailored to the profile of an individual patient.[8] User-friendly graphical interfaces and web-based calculators can facilitate the use of nomograms in clinical practice.

Several nomograms have been developed in the field of breast cancer, including one for predicting the risk of positive surgical margins after BCT.[9] However, this study was based and validated on single-center data, which might impair generalizability of the model. The aims of the current study were: i) to develop a user-friendly graphical and web-based nomogram based on multicenter data to predict individual probability of positive margins following the first attempt at lumpectomy based on clinicopathological variables and ii) to validate the nomogram in an independent dataset.

Methods

Patient population

A modeling and a validation group were constituted for development and validation of the nomogram, respectively. The modeling group consisted of breast cancer patients selected from the Netherlands Cancer Registry (NCR). Based on pathological notification through the PALGA (automated pathology archive) system,[10] trained registration clerks gathered data concerning patient, tumor, and treatment characteristics from the patient files. Additionally, the NCR registered surgical margin status following lumpectomy between June 2008 and July 2009. During this time frame, data was collected from 1495 patients who underwent BCT in one of 24 institutions throughout the North-East region of the Netherlands.

Supplemental radiological and clinical variables were collected retrospectively for 1349 patients from 20 out of 24 institutions. Three institutions were excluded due to a relatively limited contribution to the NCR database (<15 patients). One institution did not participate because of a change in the preoperative work-up during the investigated time frame, which might have influenced surgical outcome. Approval was obtained from the institutional review board of all participating institutions prior to initiation of the study.

Women with clinical $T_{1-2}N_{0-1}M_{x-0}$ histology-proven invasive breast carcinoma who underwent BCT were included in the study. Patients with unconfirmed malignancy prior to surgery, undefined margin status, neo-adjuvant treatment, or absence of reported radiological tumor size were excluded. A total of 1185 out of 1349 patients (88%) were eligible for the modeling group.

The validation group consisted of 439 patients who underwent BCT at the University Medical Center Groningen (UMCG), Groningen, The Netherlands between July 2004 and June 2008 or July 2009 and May 2011. Patients who underwent BCT between June 2008 and July 2009 were assigned to the modeling group as they were part of the NCR database. Inclusion and exclusion criteria were identical to those applied in the modeling group. A total of 331 patients (75%) were eligible for the validation group.

Clinicopathological evaluation

The following variables were incorporated from the NCR database: surgical margin status, age, preoperative N-stage, preoperative T-stage, tumor location, histological type, histological grade, estrogen receptor (ER) status, progesterone receptor (PR) status, Her2/neu receptor status, and presence of co-existing DCIS.

Positive surgical margin status was defined as microscopically confirmed invasive carcinoma (IC) and/or DCIS at the inked margin of the lumpectomy specimen following the first attempt at lumpectomy. Staging was performed according to the fifth edition of the TNM atlas. Preoperative T-stage was based on the maximum tumor diameter as measured on MRI (if available) or ultrasonography. Preoperative N-stage was based on clinical and/or radiological examination as well as preoperative histological examination (if available) of the axillary region. Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O).[11] Grading of invasive carcinoma was scored according to the Nottingham (Elston-Ellis) modification of the Scarf–Bloom–Richardson grading system. Positivity of estrogen and progesterone receptors was defined as at least 10% of immunostained nuclei of tumor cells. HER2/neu status was considered positive in case of Her2/neu 3+ (strong and complete membranous expression in >30% of tumor cells) or Her2/neu 2+ (weak complete membranous expression in >10% of tumor cells) confirmed with positive fluorescence in situ hybridization. Co-existing DCIS was defined as the presence of any DCIS component. All pathological variables were assessed on final pathology due to the fact that no preoperative core needle biopsy (CNB) was routinely performed in the vast majority of patients.

The NCR database was supplemented with data collected from patient files at the participating institutions, including clinical (family history, referral from screening, palpability, breast cup size, and prior surgery to the ipsilateral breast), and radiological variables (BI-RADS classification, suspicion of multifocality, preoperative MRI, microcalcifications, density of the breast, and area of the breast on the preoperative digital mammogram). Family history was recorded as negative, first-degree (FDR), or second-degree relatives (SDR). Tumors were classified as non-palpable if a needle-localization procedure was required for excision. BI-RADS classification was recorded according to the fourth edition of the Breast Imaging Reporting and Data System.[12] Suspicion of multifocality was defined as the presence of two or more tumor foci within the same quadrant of the ipsilateral breast as assessed on MRI (if available) or radiography. The presence of microcalcifications was assessed on mammography and reported as present or absent. Density of the breast was assessed on mammograms and reported as one out of four BI-RADS categories: mostly fatty (0–25% dense), scattered fibroglandular tissue (25–50% dense), heterogeneously dense (50–75% dense), and extremely dense (75–100% dense).[12] Area of the breast was determined in square millimeters by manually delineating the breast on the lateral projection of the preoperative digital mammogram. Calculations were performed using the default radiological software package available at each hospital. Last, postoperative variables were scored for the purpose of describing patient and tumor characteristics, including postoperative T-stage, postoperative N-stage, weight of the excised lump, and tumor-to-lump index (defined as the maximum tumor diameter in millimeters divided by the weight of the excised lump in grams).

Within the validation group, clinicopathological variables were collected from patient files in the UMCG database. Variables were scored identically to those in the modeling group.

Statistical analysis

The primary outcome for this study was the proportion of positive surgical margins following lumpectomy. Multivariate logistic regression analysis (MVA) was used to test the association between clinicopathological variables and the likelihood of positive margins. Stepwise backward variable selection was performed to determine informative variables based on the corrected Akaike's Information Criterion (AIC_c).[13] The nested model with the lowest AIC_c value was used to construct a graphical nomogram. A corresponding web-based calculator was developed. Moreover, a second calculator was developed including solely clinical and radiological

variables, which can be applied in the absence of a preoperative CNB.

Model performance was quantified in both the modeling group and the validation group with respect to discrimination and calibration. Discrimination was assessed by calculating the area under the receiver-operating characteristic (AUROC) curve, resulting in a so-called concordance index (*c*-index). Calibration was studied graphically after grouping patients into deciles with respect to their predicted probabilities and plotting the mean predicted probabilities against the mean observed probabilities. Bootstrapping was applied to calculate 95% confidence intervals. Overall fit of the model was evaluated using the Hosmer–Lemeshow goodness-of-fit test. Reported *P*-values are two-sided with alpha 5%.

Statistical analyses were performed using the statistical packages SPSS (SPSS for Windows, version 18.0.3, SPSS Inc., Chicago, IL) and STATA Software, version 10.0 (StataCorp, College Station, TX). Graphs were created using GraphPad Prism (GraphPad Prism for Windows, version 5.00, GraphPad Software, San Diego, CA).

Results

Patient and tumor characteristics of the modeling and the validation group are listed in Table 1.

Positive margins in BCT were present in 19.7% and 24.5% of the patients in the modeling and validation group, respectively (Supplemental Table 2). Marked differences between the modeling and the validation group were observed with respect to age, weight of the excised lump, tumor location, pN-stage, prior surgery to the breast, family history, BI-RADS classification, and presence of DCIS.

Margin positivity ranged from 11% to 38% throughout the 20 institutions that constituted the modeling group. No difference was observed between positive surgical margin rates from university-affiliated and community hospitals ($P = 0.883$). Moreover, no significant difference in the occurrence of positive margins was observed between individual hospitals when evaluated using MVA ($P = 0.282$). Of the 233 patients with positive margins in the modeling group, 92 (39.5%) patients had a relumpectomy with clear margins, 2 (0.9%) patients had a second lumpectomy with persistent positive margins, 16 (6.9%) patients underwent mastectomy, and 123 (52.8%) patients had no further surgery despite positive margins. Data on further surgical management were available for all 233 (100%) patients.

Data on breast cup size was available for only 101 out of 1185 patients (8.5%) in the modeling group and 45 out of 331 patients (13.6%) in the validation group (data not shown). We therefore used the area of the breast on the digital mammogram to substitute for cup size, as the correlation between both variables was strong (Spearman's rho: 0.893, $P < 0.0001$).

MRI was performed in 122 patients (10.3%) in the model group for preoperative tumor assessment. Ultrasonography was performed in the remaining 1064 patients (89.7%). In the validation group, preoperative MRI was performed in 31 patients (9.4%), while the remaining 300 patients (90.6%) had ultrasonography. Sentinel lymph node biopsy was performed in the vast majority of patients, including 1113 (93.9%) patients from the modeling group and 307 (92.7%) from the validation group. Axillary lymph node dissection (ALND) was performed in 293 (24.7%) and 87 patients (26.3%), respectively. A total of 221 (18.6%) and 63 (19.0%) patients received an ALND in addition to an SLNB procedure.

Multivariate analysis

The nested MVA model with the lowest AIC_c (959.6) was selected. Clinicopathological variables constituting the final model were microcalcifications, preoperative MRI, suspicion of multifocality,

Table 1
Patient and tumor characteristics for the modeling and the validation group.

Characteristic	Modeling group		Validation group		*P*-value
	No.	%	No.	%	
No. of patients	1185	100	331	100	
Age (years)					
Mean (±SE)	59.8 (±0.31)		56.5 (±0.63)		<0.001[a]
Median	60.3		56.0		
Range	27–95		26–91		<0.001[b]
≤40	39	3.3	28	8.5	
41–69	919	77.6	255	77.0	
≥70	227	19.2	48	14.5	
Tumor size (mm)					
Mean (±SE)	15.6 (±0.22)		15.2 (±0.48)		0.107[c]
Median	14.0		13.0		
Range	1.5–58.5		2.1–57.9		0.087
pT_{1a}	54	4.6	22	6.6	
pT_{1b}	243	20.5	81	24.5	
pT_{1c}	599	50.5	164	49.5	
pT_2	284	24.0	62	18.7	
pT_3	5	0.4	2	0.6	
Area on mammogram (mm^2)					
Mean (±SE)	17,916 (±6807)		17,575 (±6937)		0.617
Median	17,163		16,498		
Range	3551–46,895		5212–50,619		0.396
≤15000	450	38.0	138	42.4	
15,000–25,000	554	46.8	142	44.7	
≥25,000	181	15.3	45	13.8	
Weight excised lump (g)					
Mean (±SE)	62.5 (±39.7)		56.3 (±40.0)		0.027
Median	53.0		47.0		
Range	6–277		6–299		0.044
≤50	270	44.5	167	51.0	
51–99	172	28.3	78	23.9	
≥100	165	27.2	82	25.1	
Tumor-to-lump index					
Mean (±SE)	0.338 (±0.012)		0.354 (±0.020)		0.503
Median	0.266		0.288		
Range	0.02–3.67		0.02–4.41		0.132
≤0.25	278	45.8	121	39.2	
0.25–0.50	228	37.6	135	43.7	
≥0.50	101	16.6	53	17.2	
Palpability					0.104
Palpable	637	53.8	195	58.9	
Non-palpable	548	46.2	136	41.1	
Tumor location					<0.001
LOQ	122	10.3	42	12.7	
UOQ	535	45.1	170	51.4	
UIQ	189	15.9	50	15.1	
LIQ	150	12.7	26	7.9	
Central	103	8.7	6	1.8	
Histological type					0.062
Ductal	957	80.8	286	86.4	
Lobular	119	10.0	23	6.9	
Specified[d]	109	9.2	22	6.6	
Histological grade					0.214
Grade I	330	28.1	107	32.8	
Grade II	531	45.2	133	40.7	
Grade III	313	26.6	86	26.5	
ER status					0.661
Positive	1002	85.3	276	84.4	
Negative	172	14.7	51	15.6	
PR status					0.443
Positive	750	71.4	226	69.1	
Negative	300	28.5	101	30.9	
Her2/*neu* receptor status					0.486
Positive	125	10.7	40	12.3	
Negative	1041	89.3	290	87.7	
Multifocal disease					0.170
Yes	47	4.0	19	5.7	
No	1138	96.0	312	94.3	
pN-stage					0.004
Positive	310	26.2	113	34.4	
Negative	875	73.8	218	65.6	
Prior surgery to the breast					<0.001
Yes	46	3.9	34	10.3	

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Modeling group		Validation group		*P*-value
	No.	%	No.	%	
No	1139	96.1	297	89.7	
Family history					<0.001
FDR	91	8.9	75	22.8	
SDR	188	18.2	56	17.0	
Negative	749	72.9	199	60.2	
Referred from screening					0.755
Yes	578	49.1	158	47.7	
No	601	50.9	172	52.3	
BI-RADS classification					0.001
II[e]	3	0.3	8	2.5	
III	93	8.1	31	9.7	
IV	611	52.9	155	48.3	
V	447	38.7	127	39.5	
Preoperative MRI					0.680
Yes	122	10.3	31	9.4	
No	1063	89.7	300	90.6	
Microcalcifications					
Yes	245	20.8	74	22.4	0.542
No	937	79.2	257	77.6	
DCIS component present					<0.001
Yes	529	44.6	188	56.8	
No	656	55.4	143	43.2	
Breast density					0.816
0–25%	323	31.0	101	31.2	
25–50%	467	44.9	146	45.0	
50–75%	217	20.8	70	21.6	
75–100%	34	3.3	7	2.2	
Institution					–
University-affiliated	642	54.2	331	100	
Community hospital	543	45.8	–	–	

Abbreviations: ER, estrogen receptor; FDR, first-degree relative; LIQ, lower inner quadrant; LOQ, lower outer quadrant; MRI, magnetic resonance imaging; PR, progesterone receptor; SDR, second-degree relative; UIQ, upper inner quadrant; UOQ, upper outer quadrant.

[a] Independent-samples *t*-test.

[b] Fisher's exact test.

[c] Independent-samples *t*-test following logarithmic transformation to promote data normality.

[d] Specified histological types included mucinous, medullary, tubular, and papillary carcinomas.

[e] BI-RADS classification II with malignancy proven by fine needle aspiration or core needle biopsy.

palpability, preoperative N-stage, preoperative T-stage, density of the breast, histological type, histological grade, ER status and presence of DCIS. Corresponding odds ratios are listed in Table 2. Non-significant variables were included if they improved accuracy of the model.

Table 2
Preoperative clinical, radiological, and pathological variables included in the final model.

Predictor	Odds ratio	95% CI	*P*-value
Suspicion of multifocal disease (vs. unifocal)	2.81	1.30–6.06	0.008
Preoperative MRI scan absent (vs. available)	1.80	1.02–3.18	0.043
Positive preoperative N-stage (vs. negative)	1.73	0.97–3.07	0.062
Non-palpable tumor (vs. palpable)	1.51	1.07–2.13	0.020
Microcalcifications on mammogram (vs. none)	1.37	0.95–2.00	0.094
Preoperative T_2 stage (vs. T_1)	1.33	0.87–2.02	0.185
Breast density on mammogram	1.22	1.00–1.49	0.053
Presence of DCIS component (vs. absence)	3.11	2.19–4.42	<0.001
Lobular histological type (vs. other)	2.90	1.71–4.91	<0.001
Positive ER status (vs. negative)	1.80	1.04–3.13	0.037
Elston III grade (vs. Elston I/II)	1.44	0.96–2.16	0.082

Reported odds ratios indicate a ratio of the probability of positive margins following lumpectomy versus the probability of negative margins.

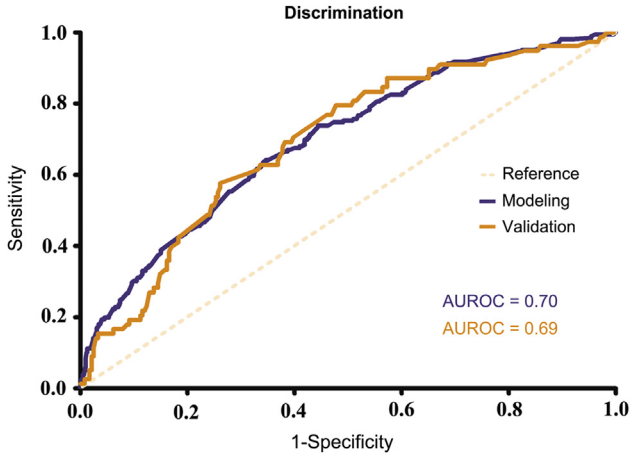

Fig. 1. Discrimination of the final model for the modeling and validation group. The area under the receiver-operating characteristic (AUROC) curve, comparable to the concordance index, indicates the discriminative power of the model. The reference line indicates an AUROC value of 0.5, for which the probability of positive surgical margins is equal to the toss of a coin. An AUROC value of 1.0 would resemble perfect discrimination.

Evaluation of the model

The model fitted the data according to the Hosmer–Lemeshow goodness-of-fit test ($\chi^2 = 2.733$, 8 degrees of freedom, $P = 0.950$). Discrimination (Fig. 1) and calibration (Fig. 2) were first assessed for the modeling group. The *c*-index was calculated to be 0.70 (95% CI 0.66–0.74, $P < 0.001$). Calibration was considered adequate. External validation on the UMCG dataset resulted in a *c*-index of 0.69 (95% CI 0.63–0.76, $P < 0.001$; Fig. 1). Calibration was considered acceptable (Fig. 2).

Nomogram and web-based calculators

A graphical nomogram was developed based on the results of MVA (Fig. 3). The underlying statistical formula was also implemented in a web-based calculator, accessible at http://www.breastconservation.com. Additionally, a second web-based

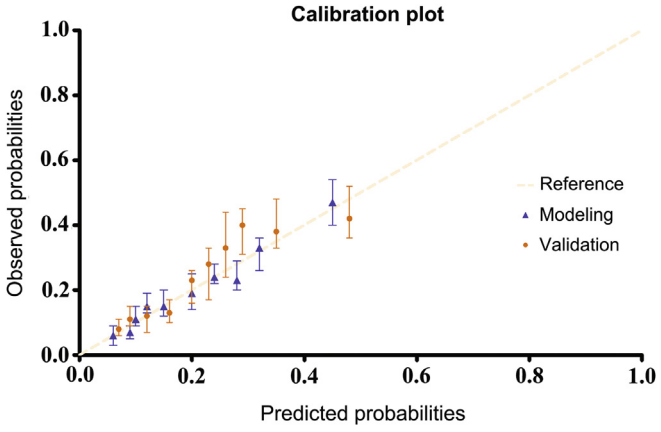

Fig. 2. Calibration of the final model in the modeling and validation group. All patients were grouped into deciles (blue triangles and orange dots) based on their predicted probabilities. Mean predicted probabilities were plotted against the actual incidence of positive margins for each decile. Moreover, 95% confidence intervals are shown for both groups. The reference line represents perfect equality of observed frequencies and predicted probabilities. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

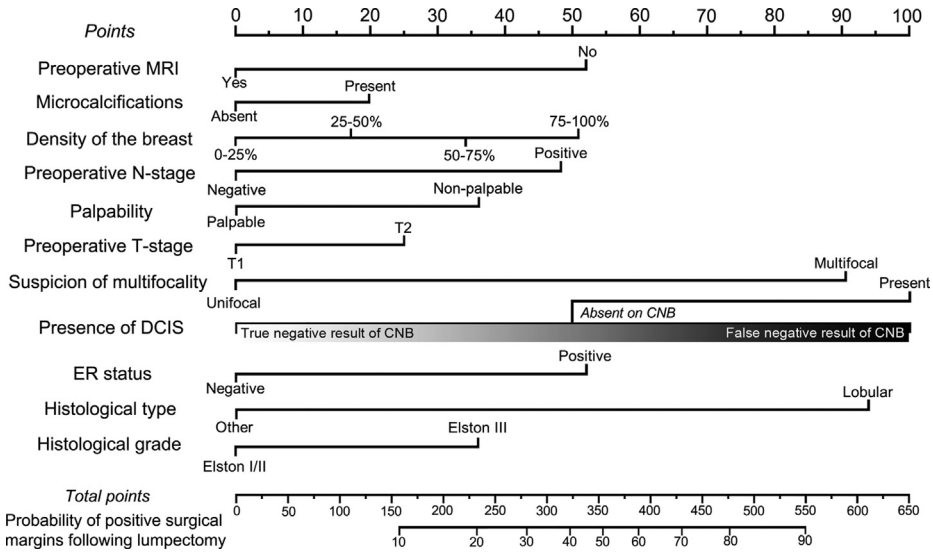

Fig. 3. Nomogram including clinical, radiological, and pathological variables for predicting positive surgical margins following the first attempt at lumpectomy. *Instructions for use*: Locate the patient's status on the 'preoperative MRI' axis. Draw a line straight upward to the 'points' axis to determine how many points are assigned to the individual patient. Repeat this process for the axes below. Sum the points achieved for each variable and locate this sum on the 'total points' axis. From here, draw a line straight downward to obtain the probability of positive surgical margins following lumpectomy for the individual patient. *Note*: Due to the relatively high frequency of false negative findings when assessing the presence of co-existing DCIS in a core needle biopsy (CNB), absence of DCIS should be interpreted with caution. We therefore recommend to determine a suitable probability interval by calculating the probability of positive surgical margins for both true and false negative outcomes. A user-friendly web-based version of the nomogram is available at www.breastconservation.com.

calculator was developed including solely clinical and radiological variables that can be used in the absence of a preoperative CNB. Discrimination of this model ranged from 0.62 to 0.64 for the modeling and validation group, respectively (Supplemental Figure 1). Calibration was considered acceptable for both groups (Supplemental Figure 2). Both calculators provide the user with a patient-tailored estimation of the preoperative risk of positive margins, stratified as low (<15%), intermediate (15–25%), or high (>25%) risk. The calculators support Internet Explorer, Safari, Firefox, and Google Chrome. An example on how to use the online nomogram is provided on the website.

Discussion

We developed a nomogram and corresponding web-based calculators to estimate the risk of positive margins following lumpectomy using clinicopathological variables. Variables predicting for positive surgical margins on MVA included microcalcifications on mammogram (OR 1.37, $P = 0.094$), absence of preoperative MRI (OR 1.80, $P = 0.043$), suspicion of multifocality (OR 2.81, $P = 0.008$), non-palpable tumor (OR 1.51, $P = 0.020$), positive preoperative N-stage (OR 1.73, $P = 0.062$), large tumor size (OR 1.33, $P = 0.185$), high density of the breast (OR 1.22, $P = 0.053$), lobular histological type (OR 2.90, $P < 0.001$), high histological grade (OR 1.44, $P = 0.082$), positive ER status (OR 1.80, $P = 0.037$) and presence of DCIS (OR 3.11, $P < 0.001$). In the absence of preoperative pathological variables (e.g. no CNB available), a second online calculator is available at http://www.breastconservation.com that solely includes clinical and radiological variables.

Assessment of pathological variables in the current study was based on final pathology due to the fact that fine needle aspiration biopsy instead of CNB was performed in the vast majority of patients. Nonetheless, CNB may provide important information on preoperative prognostic factors and shows good correlation with findings on final pathology.[14] Histological type can be accurately predicted on CNB and is reported to be concordant with the subsequent surgical specimen in 93–100% of the cases.[15] For ER status, reported concordance rates between CNB and the surgical specimen range from 86% to 100%.[16–18] Current evidence shows that histological grade can be assessed on CNB and is concordant with final pathology in approximately 75% of the cases.[19] The highest level of agreement is achieved in high-grade carcinomas, with an associated concordance rate of 84%.[14] The presence of co-existing DCIS can also be assessed on CNB and is associated with an increased risk of positive margins.[20–22] However, false negative findings reported in the literature range from 36% to 54%, indicating that the absence of DCIS in the CNB should be interpreted with caution.[21,23] The risk for false negative results of CNB can be minimized by accurate targeting, sufficient biopsy size, and obtaining a larger number of cores.[20] Jimenez et al.[21] reported that CNB predicts the presence of co-existing DCIS in the subsequent surgical specimen with a sensitivity and specificity of 54% and 92%, respectively. The corresponding negative and positive predictive values were 70% and 85%. To account for the relatively high-risk of false negative findings, we recommend determining a suitable probability interval by calculating the probability of positive margins for both true and false negative outcomes when using our nomogram (Fig. 3). The web-based calculator will automatically provide the user with such a probability interval if applicable.

The ability to estimate the preoperative risk of positive margins following lumpectomy could support clinicians in counseling patients regarding the likelihood of requiring further surgery, allowing for a more patient-tailored approach. Although broadly supported for positive margins, some authors have also reported an increased risk for LR in the case of close surgical margins.[4,24] However, the importance of close margins is still a matter of debate.[25,26] Moreover, consensus over what is the most appropriate margin is lacking, with definitions of close margins ranging from <1 mm to <5 mm distance to the inked margin.[27] Because the clinical implications of close margins are uncertain, they were not taken into account in the current study.

In patients identified as high-risk (>25%), we advise to perform a preoperative MRI to assist the clinician in defining the extent of local disease and detect areas of co-existing high-grade DCIS that

are occult on mammography. Indeed, preoperative MRI was reported to reduce the risk of inadequate tumor excision.[28] In the current study, MRI was performed in those patients with preoperative suspicion of multifocal disease or with BRCA1 of BRCA2 mutations. Despite correction for these factors, MRI was found to significantly decrease the risk of positive margins ($P = 0.043$; Table 2). However, the true value of MRI in reducing the risk of inadequate tumor excision in patients preoperatively identified as high-risk needs to be assessed in future studies.

In addition, high-risk patients might benefit from a more extensive surgical excision. Lovrics et al.[29] reported the amount of breast parenchyma excised during BCS to be inversely correlated with the likelihood of positive margins. In the current study, we also found a significant association between low tumor-to-lump index (i.e. relatively small lump compared to size of the tumor) and positive surgical margins ($P = 0.002$). However, although excising relatively voluminous specimens is more accurate in predicting margin status than any predictive model, it has profound repercussions on cosmesis. To allow for relatively extensive excisions while maintaining adequate cosmetic results, oncoplastic surgery was suggested as a technique to minimize breast deformities by immediate reconstruction of large resection defects.[30] The technique might be of particular value for those patients identified as high-risk with our nomogram, although further studies are needed to address this topic.

The rate of positive margins observed in the modeling (19.7%, range: 11–38%) and the validation group (24.5%) are in line with positivity rates reported in the literature.[5] The slightly higher positive margin rate in the validation group can partially be explained by the high rate of co-existing DCIS (56.8% vs. 44.6% in the modeling group, $P < 0.001$), which is known to increase the risk of positive margins.[31]

Very recently, Shin et al.[9] reported on a nomogram for predicting positive surgical margins after BCT. The nomogram was based on retrospective single-center data derived from 1034 Korean breast cancer patients with invasive or in situ breast carcinoma. MVA indicated microcalcifications (OR 1.57, $P = 0.034$), dense breasts (OR 4.52, $P = 0.005$), 0.5 cm difference in tumor size between MRI and ultrasonography (OR 10.00, $P < 0.001$), presence of DCIS (OR 1.58, $P = 0.044$), and lobular histological type (OR 3.99, $P = 0.015$) to be independent predictors for positive surgical margins. Validation was performed on an independent cohort of 563 patients. The concordance indices of the modeling and the validation groups were reported to be 0.82 (95% CI: 0.79–0.86) and 0.85 (95% CI: 0.80–0.89), respectively. Although the reported concordance indices are relatively high when compared to the current multicenter study, this difference may partly be explained by the relative lack of heterogeneity in single-institution data, impairing generalizability of the model.[8] Our nomogram was constructed based on multicenter data derived from 20 institutions, including community-based and university-affiliated hospitals. Validation was performed in an independent dataset that showed marked differences when compared to the modeling group, providing sufficient data heterogeneity to assess generalizability of the nomogram.

Several other nomograms are available in the field of breast cancer, including nomograms for predicting the likelihood of cancer spread to the sentinel lymph nodes,[32] cancer spread to non-sentinel lymph nodes,[33] and the benefit of systemic adjuvant therapy (Adjuvant! Online).[34] Moreover, Rudloff et al.[35] developed a nomogram (*c*-index: 0.704) for predicting the 5- and 10-year probability for ipsilateral breast tumor recurrence after BCT for ductal carcinoma in situ. The nomogram was developed on the basis of unicenter data derived from 1681 patients and included ten clinical, pathological, and treatment variables (age at diagnosis, family history, initial presentation, radiation, adjuvant endocrine therapy, nuclear grade, necrosis, margins, number of excisions, and year of surgery). Sanghani et al.[36] constructed a web-based nomogram for predicting the probability of ipsilateral breast tumor recurrence after BCT. Data was derived from 7811 patients and included both clinical and pathological variables (adjuvant RT or endocrine therapy, age, margin status, number of excisions, and treatment time period). Werkhoven et al.[37] developed a comparable nomogram (*c*-index: 0.68) based on data from 1603 patients. Rouzier et al.[38] developed several nomograms that can be applied to predict the probability of successful BCT in patients who underwent neo-adjuvant treatment.

We acknowledge that there are certain limitations to our study. First, our study is subject to limitations that are inherent to retrospective data collection. Second, as discussed earlier, pathological variables were obtained on final pathology due to the fact that preoperative CNB was not routinely performed in the vast majority of patients. We were therefore unable to evaluate the concordance between pathological variables as assessed on CNB and final pathology. However, numerous studies have evaluated this topic with the majority of studies reporting good concordance rates. Third, we used surgical margin status after the first lumpectomy attempt as a primary endpoint. Although information on positive margin rate after a second lumpectomy might be of particular clinical interest, the absolute number of patients with positive surgical margins after a second lumpectomy in our study was considered insufficient to obtain adequate sample size for nomogram development. Larger patient cohorts are therefore needed to address this topic. Last, our nomogram is based on female Dutch inhabitants, who are primarily Caucasian women. We therefore advise caution against extrapolation of the nomogram to different populations.

Conclusion

We developed and validated a nomogram to predict the probability of positive surgical margins following lumpectomy using clinicopathological variables. Our nomogram could support clinicians in identifying high-risk patients who might benefit from preoperative MRI and/or oncoplastic surgery.

Authorship

R.G.P., A.B.K., G.M.D., and S.S. designed the study protocol. R.G.P, A.B.K., and R.L. collected the data. R.G.P and A.B.K. analyzed the data and developed the nomogram. S.S., G.M.D., and T.W. supervised the project. R.G.P., A.B.K., G.M.D., S.S., T.W., J.B., L.J., J.V., and R.L. interpreted data and wrote the manuscript.

Role of the funding source

No external funding was used for this study.

Conflict of interest statement

All authors declare to have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence (bias) their work.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.breast.2013.01.010.

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