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Prediction of positive resection margins in patients with non-palpable breast cancer

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Abstract

Background: In patients undergoing breast conserving surgery for non-palpable breast cancer, obtaining tumour free resection margins is important to prevent reexcision and local recurrence. We developed a model to predict positive resection margins in patients undergoing breast conserving surgery for non-palpable invasive breast cancer.

Methods: A total of 576 patients with non-palpable invasive breast cancer underwent breast conserving surgery in five hospitals in the Netherlands. A prediction model for positive resection margins was developed using multivariate logistic regression. Calibration and discrimination of the model were assessed and the model was internally validated by bootstrapping.

Results: Positive resection margins were present in 69/576 (12%) patients. Factors independently associated with positive resection margins included mammographic microcalcifications (OR 2.14, 1.22–3.77), tumour size (OR 1.75, 1.20–2.56), presence of DCIS (OR 2.61, 1.41–4.82), Bloom and Richardson grade 2/3 (OR 1.82, 1.05–3.14), and caudal location of the lesion (OR 2.4, 1.35–4.27). The model was well calibrated and moderately able to discriminate between patients with positive versus negative resection margins (AUC 0.70, 95% CI, 0.63–0.77, and 0.69 after internal validation).

Conclusion: The presented prediction model is moderately able to differentiate between women with high versus low risk of positive margins, and may be useful for surgical planning and preoperative patient counselling.

Keywords: Breast cancer; Non-palpable lesions; Tumour margins; Prediction model

Introduction

In breast conserving surgery, obtaining tumour free resection margins is essential for local control.[1] Patients with tumour positive margins often need to undergo subsequent surgery. In the literature, reoperation rates range

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from 10.6 to 48%.[1–4] Risk factors for positive margins include lobular histology, larger tumour size, presence of ductal carcinoma *in situ* (DCIS), lymphovascular invasion, non-palpability, multifocality, and presence of mammographic microcalcifications.[5–9] These risk factors can be used to create a prediction model or nomogram (i.e. graphical presentation of a prediction model)[10] which calculates individual probabilities for positive resection margins. Several prediction models have been developed for T_{1-2} breast cancer.[7,11] These models include different prognostic variables and have moderate to good discriminative abilities (area under the ROC curve of 0.70[7] and 0.823.[11]

Since the introduction of population-based screening programs, early stage invasive breast cancer frequently presents as small and non-palpable lesions, which are particularly amenable to breast conserving surgery combined with radiotherapy. Non-palpable tumours are more likely to be resected with positive margins than palpable tumours (OR 1.51)[7] and incomplete excisions are seen in up to 60% of patients.[12–15] Until now, no model has been developed specifically for women with non-palpable invasive breast cancer.

The aim of this study was to develop a prediction model for predicting positive resection margins after breast conserving surgery in patients with non-palpable invasive breast cancer and provide a short overview of the literature.

Patients and methods

Study population

Two prospectively acquired cohorts were used for analysis. The ethical principles of the Helsinki Declaration were followed and approval was obtained from the local ethics committees.

The first cohort consisted of patients recruited in the context of a multicentre trial (ROLL trial) between December 2007 and April 2011 at four sites in the Netherlands; one university medical centre and three large community hospitals.[16] Some 318 women (>18 years) with biopsy proven non-palpable breast cancer were randomized to either guidewire localization (GWL) or radioguided occult lesion localization (ROLL).[16] In this randomized controlled multicentre trial, positive resection margins (*in situ* or invasive) were seen in 12.6% of patients.

The second cohort was a hospital-based cohort from a large community hospital in the Netherlands and consisted of 1430 patients diagnosed with invasive breast cancer between 1999 and 2010. Some 258 patients had non-palpable histologically proven invasive breast cancer and were treated with breast conserving surgery.[12] In this hospital based cohort, 29/258 (11.2%) patients had an incomplete tumour resection with invasive or *in situ* carcinoma present in the resection margins.

Variables

The following variables were prospectively recorded: demographics, medical history, tumour location, palpability, type of surgery, data on perioperative procedures (e.g. method of localization, lymphoscintigraphy), tumour characteristics (i.e. modified Bloom and Richardson grade,[17] hormonal receptor status, HER2 status since 2005 and histological subtype) and margin status. Additional data on radiological characteristics and missing histological information was collected through review of the original radiology and pathology reports. Breast density was scored visually by a dedicated breast radiologist. The main outcome measure of the study, i.e. resection margins after first breast conserving surgery, was defined as positive when invasive or *in situ* tumour cells were touching the inked surface of the resected specimen (e.g. focally positive margins were considered positive).

Statistical analysis

External validation existing nomogram

Before model building, a recently published nomogram for predicting positive surgical margins after BCS was validated.[7] All patients were entered in the model and the predicted probabilities of positive margins were calculated. A receiver operating characteristic (ROC) curve was fitted and the area under the curve (AUC) was obtained.

Model building

Missing data analysis was performed to evaluate the amount and pattern of missingness (Supplement 1). Single conditional mean imputation was used for imputing missing values if values were missing at random (MAR) or missing not at random (MNAR) (instead of missing completely at random; MCAR).[18] The association between the variables of interest and the outcome (positive resection margins) was univariately evaluated. Categorical variables were compared with the Chi square test. Normally distributed continuous variables were compared with independent *t*-tests, not-normally continuous variables with the Mann–Whitney *U* test. All diagnostic variables with a *p*-value <0.20 in univariate analyses were entered in a logistic regression model. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Manual stepwise backward elimination of variables was performed and the optimal model fit was based on Akaike's Information Criterion.

Calibration of the final model was tested with the Hosmer–Lemeshow test. Predicted probabilities were calculated and a corresponding ROC curve was derived. Discrimination of the model was calculated by the AUC.

Model validation

A bootstrap resampling procedure using 100 iterations was used to correct overfitting of the model (i.e. internal validation). Corrected coefficients were calculated by