The Breast 22 (2013) 773–779

Contents lists available at SciVerse ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

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

Rick G. Pleijhuis [a], Annemiek B.G. Kwast [b], Liesbeth Jansen [a], Jakob de Vries [a], Rosanne Lanting [a], Joost Bart [c], Theo Wiggers [a], Gooitzen M. van Dam [a,*], Sabine Siesling [b,d]

[a] Department of Surgery, University Medical Center Groningen, Groningen, The Netherlands
[b] Comprehensive Cancer Center the Netherlands, Groningen, The Netherlands
[c] Department of Pathology and Laboratory Medicine, University Medical Center Groningen, Groningen, The Netherlands
[d] Health Technology and Services Research, Twente University, Enschede, The Netherlands

ARTICLE INFO

Article history:
Received 6 September 2012
Received in revised form
8 January 2013
Accepted 19 January 2013

Keywords:
Breast-conserving surgery
Surgical margin status
Nomogram
Breast cancer

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.

* Corresponding author. Tel.: +31 50 3612283; fax: +31 50 3614873.
E-mail address: g.m.van.dam@umcg.nl (G.M. van Dam).

0960-9776/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.breast.2013.01.010

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