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Original article

Prediction of positive margins following breast conserving surgery

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ABSTRACT

Introduction: Positive margins after breast conserving surgery frequently warrant reoperation. Our objective was to evaluate predictors of positive surgical margins after breast conserving surgery (BCS), including a previously validated online calculator/nomogram. Use of reoperation was also evaluated.
Methods: Patients with clinical T1-2N0-1Mx-0 primary breast cancer who received standard BCS from 2006 to 2012 were selected ($N = 292$). Exact Pearson Chi-square test was performed for clinical factors and non-parametric tests were used to evaluate the predictive value of the nomogram for positive margins and re-excision. Spearman's correlation analysis was used to compare actual events vs. nomogram calculations. Multivariate logistic regressions were conducted for multiple variables.
Results: Tumor multi-focality ($p = 0.09$) and non-ductal histology ($p = 0.05$), were associated with re-excision; suspicious calcifications ($p = 0.08$) were associated with positive margins, although no p-value reached statistical significance. The nomogram predicted a median positive margin risk of 20% for cases with and without positive margins. Spearman's correlation analysis for positive margins vs. nomogram calculated positive margin risk was 0.091 ($p = 0.121$.)
Conclusions: The Breast Conservation nomogram includes several factors associated with positive margins or reoperation, but none of the variables tested were statistically significant on univariate or multivariate analyses. The nomogram's value could not be confirmed, as there was no significant correlation between the calculated risk values and the presence of positive surgical margins.

Introduction

Positive surgical margins have demonstrated a strong association with local recurrence in breast cancer patients who have received breast-conserving therapy (lumpectomy with adjuvant radiotherapy) as treatment [1]. Identification of patients at increased risk for positive surgical margins may enhance clinical pre-op decision-making. To aid in the identification of high-risk patients, clinicians are increasingly turning to web-based statistical calculators, known as nomograms. Due to their wide availability, ease of use, and predictive power, these online applications are an increasingly useful tool in breast cancer care and treatment.

Nomograms employing clinical or pathologic data are frequently used to predict clinical risk in breast cancer patients. These tools use a patient's clinical and pathologic data to provide an individualized prediction of specific risk. Some of these tools, such as the Gail model, have been extensively validated and accepted [2–5]. These tools have seen great use in providing supplemental information for clinical decision-making. While the Gail model is useful for predicting a patient's lifetime cancer risk, it does not apply to women who have a cancer diagnosis. More recent nomograms attempt to predict positive sentinel nodes and additional sentinel nodes [6,7], however, these do not have a function to determine a patient's risk of positive surgical margins after receiving breast conservation therapy (BCT).

With the recent focus on reoperation and margin status in breast conserving surgery [8], as well as the rising rate of mastectomy [9], the availability of a validated preoperative tool to estimate risk of positive margins may significantly impact surgical decision making for early-stage breast cancer. The nomogram evaluated in this study was developed by the Comprehensive Cancer Center of

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the Netherlands in collaboration with the University Medical Center Groningen (UCMG). This online calculator uses a multi-factor approach to generate an individualized evaluation of a patient's post-op risk for positive surgical margins after receiving BCT. It was developed using a study population of 1185 patients selected from the Netherlands Cancer Registry. A further validation study of 439 women who received BCT at UCMG was also performed [10].

The authors of the original development study have acknowledged that their patient population was limited to primarily Caucasian women treated in the Netherlands. As such, conclusions using the nomogram may not reliably extend to patients of other demographics or treated in other health systems. Our primary goal for this study was to evaluate predictors of positive margins or re-excision after breast conserving surgery and to evaluate the *Breast Conservation* nomogram (www.breastconservation.com) for predictive accuracy in an independent patient population. Due to ongoing discussions regarding the impact of margins and reoperation, we elected to evaluate both positive margins as well as reoperation in this study, especially given the potential differences in practice among European and American surgical practices. The ultimate goal of this study was to determine the predictive power of specific preoperative clinical markers as well as the existing nomogram in identifying patients at high risk for positive surgical margins or reoperation after breast conserving surgery.

Methods

After institutional review board approval, a consecutive series of breast conservation patients was prospectively identified from a single-institution, breast cancer database. Women who received a primary breast conserving operation between 2006 and 2012 for clinical T1-2N0-1Mx-0 were identified for review. All patients had histologically-confirmed invasive breast cancer. Patients with bilateral breast cancer, neoadjuvant therapy, previous breast irradiation, or those who received systemic treatment for a prior malignancy were excluded. Women diagnosed on excisional biopsy or presented after an initial extirpative operation were also excluded.

All patients treated at our institution undergo preoperative multidisciplinary review of films and slides by breast-specific providers, and breast cancer operations are performed by fellowship-trained breast surgeons. Surgical specimens containing localizing wires are radiographed for confirmation of the biopsy clip and intact wire intraoperatively. All gross pathologic breast cancer specimens are inked, serially sectioned, and reviewed intraoperatively by the pathologist, but no frozen sections or cytologic evaluations are performed for breast margin assessment at the time of surgery. Postoperatively, the surgical pathology is reviewed by the same multidisciplinary tumor board, and histologic slides of positive or close margins are reviewed by the group. The decision to perform re-excision is generally made by a consensus of the surgeons and radiation oncologists involved in the pathologic review. At our institution, positive margins are defined as tumor on ink; close margins have tumor within 2 mm of any inked surface.

Patient charts were reviewed for clinical, operative, and pathologic data. The variables collected from patient charts included use of pre-operative MRI status, pre-operative T-stage, pre-operative N-stage, presence of microcalcifications, tumor density, tumor palpability, tumor multi-focality, estrogen receptor status, presence of DCIS, tumor histological type, and tumor grade. MRI status was a categorical yes/no depending on whether the patient received an MRI as part of the initial workup for their breast cancer. Pre-operative T stage was determined based on MRI, mammography, sonography, and physical examination in that order of preference. Pre-operative N stage was determined based on clinical examination as well as biopsy proven evaluation of lymph node tissue (if performed) from the axilla. The presence of suspicious micro-calcifications and tumor multi-focality were determined with evaluation of ultrasonography or mammography. Multi-focality was defined as the presence of two or more tumor foci within the same quadrant of the ipsilateral breast on imaging.

Breast density was reported using the Breast Imaging-Reporting Data System (BI-RADS) for radiological evaluation of mammography, 4th edition. Breast tissue composition fell into four categories: Almost entirely fatty (0–25% density, (BIRADS 1), Scattered fibroglandular densities (25–50% density BIRADS 2), Heterogenously dense (50–75% density, BIRADS 3) Extremely dense (75–100% density, BIRADS 4). It is important to note that BIRADS breast density scoring is different than the BIRADS score used in evaluation of mammographic abnormalities. Clinical tumor palpability was determined based on preoperative history and physical examination.

In addition to clinical data, pathologic data was determined from evaluation of the patient's core-needle biopsy specimens obtained for the initial cancer diagnosis. Tumor grade was assigned using the Nottingham Histologic Score System (the Elston-Ellis modification of the Scarf-Bloom-Richardson grading system. ER/PR status was determined using immunohistochemistry and HER2neu status was determined using fluorescence in situ hybridization (FISH). Histology was classified as ductal, lobular or other; cases with mixed histology were also classified as other.

For evaluation of the online calculator, appropriate patient data was entered into the online predictive nomogram to obtain an estimated positive margin risk. Cases with missing variables were excluded from the series. The Breast Conservation! model includes a basic and advanced calculator. Applicable clinical data was entered for both the advanced and basic calculators for each patient, however, for statistical evaluation of the calculator as a predictor of risk, the basic calculator generated scores were used. The basic calculator generated a discrete number for a percent risk of positive margins for each case; however, many cases were given a range for percent risk of positive margins using the Advanced calculator, despite incorporating all requested clinical datapoints. The variables required by the basic calculator included pre-operative MRI, presence of suspicious microcalcifications, pre-operative T-stage, pre-operative N-stage, tumor palpability, tumor density, tumor multi-focality. Each patient's clinical variables were entered into the software and the resulting output data was recorded. Because nomogram-generated data do not follow normal distribution, Kruskal Wallis test and Wilcoxon rank-sum test were performed to evaluate the value difference of the online tool compared to 1) surgical margin status (negative, close, or positive), and 2) use of reoperation, respectively.

Exact Pearson Chi-square test was performed to assess the association between clinical variables used by the nomogram and surgical margin positivity, as well as use of re-excision, to incorporate two-factor cross tabulation. The estimated positive margin risk was derived from the online basic calculator using 7 clinical factors including pre-operative MRI, presence of suspicious microcalcifications, pre-operative T-stage, pre-operative N-stage, tumor palpability, tumor density, and tumor multi-focality. Multivariate logistic regression models with three variables, the estimated positive margin risk, tumor grade, and ER receptor status, were used to predict positive margin and re-operation.

Results

Positive surgical margins: Of the 405 consecutive charts reviewed, 292 were eligible for inclusion into the validation group. Of this population, 235 were Caucasian, 26 African-American, 21