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Original article

Positive margins prediction in breast cancer conservative surgery: Assessment of a preoperative web-based nomogram

Lídia Alves-Ribeiro [a, *], Fernando Osório [a, b], Isabel Amendoeira [c, d], José Luís Fougo [a, b]

[a] Medical Faculty of Porto University, Alameda Prof. Hernâni Monteiro, Porto 4200 – 319, Portugal
[b] Breast Center, São João University Hospital, Alameda Prof. Hernâni Monteiro, Porto 4200 – 319, Portugal
[c] Pathology Department, São João University Hospital, Alameda Prof. Hernâni Monteiro, Porto 4200 – 319, Portugal
[d] Institute of Molecular Pathology and Immunology of the University of Porto, Rua Júlio Amaral de Carvalho, 45, Porto 4200-135, Portugal

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ABSTRACT

Margin status of the surgical specimen has been shown to be a prognostic and risk factor for local recurrence in breast cancer surgery. It has been studied as a topic of intervention to diminish reoperation rates and reduce the probability of local recurrence in breast conservative surgery (BCS).

This study aims to validate the Dutch **BreastConservation! nomogram,** created by *Pleijhus* et al., which predicts preoperative probability of positive margins in BCS.

Patients with diagnosis of breast cancer stages cT1-2, who underwent BCS at the Breast Center of São João University Hospital (BC-CHSJ) in 2013–2014, were included. Association and correlation were evaluated for clinical, radiological, pathological and surgical variables. Multivariable logistic regression and ROC curves were used to assess nomogram parameters and discrimination.

In our series of 253 patients, no associations were found between margin status and other studied variables (such as age or family history of breast cancer), except for weight (p-value = 0.045) and volume (p-value = 0.012) of the surgical specimen.

Regarding the nomogram, a statistically significant association was shown between cN1 status and positive margins (p-value = 0.014). No differences were registered between the scores of patients with positive versus negative margins. Discrimination analysis showed an AUC of 0.474 for the basic and 0.508 for the expanded models.

We cannot assume its external validation or its applicability to our cohort. Further studies are needed to determine the validity of this nomogram and achieve a broader view of currently available tools.

Introduction

Breast conservative surgery (BCS) plus adjuvant radiotherapy has become the standard treatment of early stage invasive breast cancer, with survival rates no different from mastectomy, even in young patients [1–3]. Ipsilateral breast tumor recurrence rates at 10 years of follow-up are not superior to 5–10% of BCS cases (with series of results reporting 8% at 12 years and approximately 15% at 20 years) [4–6].

Local recurrence of breast cancer is influenced by several factors, including age of the patient, tumor biology and molecular subtype, availability ofpersonalized systemic therapy and extent of local surgical excision [7]. Although local control is not the only important factor, margin evaluation has been studied as a factor of intervention, with rates of local recurrence after BCS declining over the years [7]. However, it is important to mention that negative margins do not exclude residual disease and that positive margins do not assure its presence [8].

Houssami et al. indicate margin status as a prognostic factor in BCS; however, it is also added that the increase of the distance threshold for negative margins has no significant effect on local recurrence, with no additional benefit for local control [9,10]. The "Consensus Guideline on Margins for BCS with whole-breast

Abbreviations: AUC, area under the curve; BC-CHSJ, Breast Center of São João University Hospital; BCS, breast conservative surgery; BI-RADS, breast imaging reporting and data system; CHSJ, São João University Hospital; CNB, core-needle biopsy; DCIS, ductal carcinoma *in situ*; FMUP, Medical Faculty of Porto University; MRI, magnetic resonance imaging; NST, invasive breast carcinoma of no special type; OBS, oncoplastic breast surgery; OR, odds ratio; ROC curves, receiver operator characteristic curves; SD, standard deviation; WHO, World Health Organization.

* Corresponding author.
E-mail address: mimed10142@med.up.pt (L. Alves-Ribeiro).

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irradiation in stages I and II invasive breast cancer" states that wider than "no ink on tumor" margins do not have a significant decrease on ipsilateral breast tumor recurrence [11]. This meta-analysis, which included 33 studies, identified a positive margin rate of 21.9% [11].

The focus on margins in BCS prompted the creation of several nomograms of presurgical application, in order to predict a positive surgical margin [12,13]. However, these nomograms have few reports of external validity and lack studies of comparison between them [14].

Particularly regarding the **BreastConservation! nomogram**, *Pleijhuis* et al. considered both radiological variables and core-needle biopsy (CNB) as important factors for predicting a positive margin [13]. Its application has shown opposite results in two published studies [15–17].

The application of these nomograms may be useful in clinical decision-making by identifying high-risk patients who may benefit from treatment options other than BCS [13]. Further evaluation of the nomogram in different populations may be important to clarify its applicability, since there is a lack of consensus on its validity. A report of 331 patients from The Netherlands (similar to the one which the nomogram is based on) supported its use, but another study in a sample of 292 Florida patients did not confirm this finding [13,15–17].

The aim of this study is the validation of the referred web-based nomogram as a preoperative tool to predict the probability of positive margins in a sample of Portuguese patients with invasive early stage breast cancer submitted to BCS in the BC-CHSJ.

Material and methods

Patient population

The study population includes patients with preoperative diagnosis of invasive breast cancer of stages T1-2 (cT1-T2) who underwent BCS (including conventional BCS and different techniques of OBS) at the BC-CHSJ between January 2013 and December 2014. Patients who had diagnosis of cTis or bilateral breast cancer, subjected to neoadjuvant medical therapy, personal history of breast cancer or undetermined surgical margin status (Rx) were excluded.

Study design, variable collection and management

This is a retrospective cohort study. Online patient charts were consulted in order to complete clinical, surgical, pathological and radiological variables.

Clinical variables included age at diagnosis, gender, history of breast surgery, family history of breast cancer, reference source (screening program versus clinical detection), tumor laterality and quadrant localization, palpability, clinical dimension on physical examination and preoperative TNM staging [18].

Surgical variables included surgical procedures on the contralateral breast, intraoperative margin enlargement and type of nodal surgery (sentinel node biopsy, node sampling or axillary clearance).

Pathological variables included histologic type (classified as no special type, lobular or other, according to the WHO classification [19]), histologic grade [according to the Nottingham (Elston–Ellis) modification of the Scarf–Bloom–Richardson grading Score System [20]], estrogen receptor status (determined by immunochemistry) and presence of extratumoral DCIS in the preoperative CNB. Regarding histology, cancers classified as NST were analyzed as ductal for nomogram evaluation, due to the recent reclassification of histology types of breast cancer [19]. We also recorded the specimen margin status (considered positive as "tumor on ink" and dividing into negative margins – R0 – and positive margins – R1), specimen weight, dimensions and volume (calculated by the formula: $4/3\pi \times ½a \times ½b \times ½c$, with a, b and c representing specimen dimensions, assuming an elliptical shape of the specimen) [17], diameter of invasive tumor and presence and diameter of DCIS.

Radiological variables included characterization of the tumor and nodal status (using mammography, ultrasonography, MRI and axillary lymph node biopsy), existence of preoperative MRI, multifocality/multicentricity, presence of microcalcifications, breast density (using BI-RADS density scoring [21]) and BI-RADS evaluation of mammographic abnormalities (0–6) [21].

Surgical procedure

In BC-CHSJ, BCS was performed under perioperative ultrasound guidance, followed by X-ray of the specimen in the operating room, in order to maximize margin adequacy. The surgical specimens were immediately inked (one color for each radial margin), either by the surgeon or by the pathologist. Macroscopic assessment of tumor margins was performed intraoperatively. If a positive margin was identified, the surgeon proceeded to its enlargement in the same operative time.

Nomogram evaluation

The online tool (available at *www.breastconservation.com*) was used for evaluation for the nomogram. Both **basic** (which comprises: existence of preoperative MRI, presence of microcalcifications in the mammogram, preoperative T and N stage, breast density, tumor palpability and suspicion of multifocality) and **expanded** (which adds pathological variables from the CNB, namely: estrogen receptor status, presence of DCIS, histologic type and histologic grade) scores were calculated.

Statistical analysis

Descriptive statistics were used to characterize the sample. Groups of positive and negative margins were compared in all assessed variables. Comparison was tested using independent samples T-Test and non-parametric Mann–Whitney U. Multivariable analysis, by binomial logistic regression, assessed all nomogram variables from both the basic and expanded models. ROC curves of both nomogram models were computed in order to assess AUC – c-index – and discrimination.

All p-values inferior to 0.05 (α) were considered statistically significant. All reported p-values were two-sided. Data analysis was performed using IBM SPSS Statistics version 23.0.0.0 (SPSS Inc., Chicago, IL, USA).

Results

From a total of 287 patients who underwent BCS in BC-CHSJ between January 2013 and December 2014, 35 cases were excluded for the following reasons: preoperative diagnosis of Tis (six), synchronous bilateral disease (one), neoadjuvant chemotherapy (nineteen), previous history of breast carcinoma (eight) and undetermined margin status (one).

From the final sample of 252 patients, all were women, with a mean age of 58.79 years (SD 12.41). The characterization of the validation sample is resumed in Appendix A. No statistically significant associations were found between margin status and the majority of studied variables (such as age at diagnosis, family history of breast cancer, personal history of breast surgery, reference source, tumor laterality and quadrant localization and BI-RADS classification). However, there were statistical differences for