European Journal of Surgical Oncology xxx (2018) 1–8

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Validation and update of a lymph node metastasis prediction model for breast cancer

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ARTICLE INFO

Article history:
Accepted 21 December 2017
Available online xxx

Keywords:
Breast cancer
Axillary lymph node metastasis
Model
Prediction model
Axillary surgery omission

ABSTRACT

Purpose: This study aimed to validate and update a model for predicting the risk of axillary lymph node (ALN) metastasis for assisting clinical decision-making.
Methods: We included breast cancer patients diagnosed at six Dutch hospitals between 2011 and 2015 to validate the original model which includes six variables: clinical tumor size, tumor grade, estrogen receptor status, lymph node longest axis, cortical thickness and hilum status as detected by ultrasonography. Subsequently, we updated the original model using generalized linear model (GLM) tree analysis and by adjusting its intercept and slope. The area under the receiver operator characteristic curve (AUC) and calibration curve were used to assess the original and updated models. Clinical usefulness of the model was evaluated by false-negative rates (FNRs) at different cut-off points for the predictive probability.
Results: Data from 1416 patients were analyzed. The AUC for the original model was 0.774. Patients were classified into four risk groups by GLM analysis, for which four updated models were created. The AUC for the updated models was 0.812. The calibration curves showed that the updated model predictions were better in agreement with actual observations than the original model predictions. FNRs of the updated models were lower than the preset 10% at all cut-off points when the predictive probability was less than 12.0%.
Conclusions: The original model showed good performance in the Dutch validation population. The updated models resulted in more accurate ALN metastasis prediction and could be useful preoperative tools in selecting low-risk patients for omission of axillary surgery.

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https://doi.org/10.1016/j.ejso.2017.12.008
0748-7983/

Introduction

Axillary lymph node (ALN) status is an important prognostic factor and a major determinant for postoperative treatment decision-making for breast cancer patients [1,2]. ALN staging evolved together with the shift in surgical treatment from the largest tolerable surgery to less invasive surgery. During this process, sentinel lymph node biopsy (SLNB) replaced ALN dissection and has become the standard of care for ALN staging in breast cancer patients with clinically negative ALN for over 10 years. SLNB has significantly reduced the incidence of surgical complications such as upper limb lymphedema and impaired shoulder function, and has improved patients' quality of life without compromising their survival [3–7]. However, the surgical complications from SLNB cannot be ignored. Lymphedema occurs in approximately 5–8% of patients receiving a SLNB and paresthesia in 10–15% [6–12]. In addition, 28–49% of the patients experience shoulder-arm function impairment [11–13]. Notably, 60–70% of the patients receiving a SLNB are shown to have negative SLNs after histopathological analysis and thus do not benefit from the procedure [4,14,15].

Due to early detection through the national screening program, more patients are being diagnosed with early breast cancer and are more often free from ALN metastasis [16]. If patients with a pathologically negative ALN can be preoperatively predicted, omission of axillary surgery could avoid the above-mentioned surgical complications and improve their quality of life, without affecting the postoperative treatment decision-making. Consequently, accurate assessment of the preoperative patients' risk of ALN metastasis is required. However, all currently used imaging modalities have low sensitivity in predicting ALN metastasis, resulting in a false-negative prediction of around 40–70% [17–20]. Therefore, new tools for prediction of preoperative ALN metastasis are urgently needed.

We previously developed a predictive model for ALN metastasis in a Chinese breast cancer population based on clinicopathological features from the primary tumor and axillary ultrasound [21]. The model was based on six independent predictors for ALN metastasis: clinical tumor size, histological tumor grade, estrogen receptor (ER) status, longest axis, cortical thickness and hilum status of the ALN as detected by ultrasonography. The model was validated on an additional set of 234 Chinese patients, generating an area under the receiver operating characteristic curve (AUC) of 0.864[21], indicating a good performance in ALN metastasis prediction.

In this study we validated the performance of the Chinese model for predicting ALN metastasis in a large Dutch breast cancer population. The model was updated using the Dutch and Chinese patient data in order to improve its discriminative performance and predictive accuracy and maintain its generalizability in different ethnic groups.

Methods

Patients

We selected all women with primary breast cancer who underwent breast surgery and axillary staging at six participating Dutch hospitals (one university hospital, two teaching and referral hospitals and three general hospitals) between 2011 and 2015 from the Netherlands Cancer Registry (NCR). The NCR records data on all cancer patients in the Netherlands. The inclusion and exclusion criteria were the same with that used in the initial study which developed the model [21]. Patients with one or more ALN(s) detected by a preoperative ultrasound and receiving either a SLNB or ALN dissection were included in this study, irrespective whether the ALNs were palpable or not. Exclusion criteria were use of primary systemic therapy, ductal carcinoma *in situ* and bilateral breast cancer. Patients with lymph node cortical thickness larger than 2.3 mm as measured by ultrasound received a final needle aspiration cytology (FNAC) according to Dutch guideline [22]. In addition to the Dutch patients, the Chinese patients ($n = 322$) diagnosed at Cancer Hospital of Shantou University Medical College between 2009 and 2014 for developing the model were also used in the present study for updating the original model [21]. This study was approved by all participating hospitals.

Data collection

From the NCR we collected data on age at diagnosis, menopausal status, tumor location, histological grade, ER, progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2) and pathological ALN status. Data on histological grade, ER, PgR and HER2 status were obtained from surgical resection specimens. Data on clinical tumor size of the primary tumor, and longest axis, cortical thickness and hilum status of the ALN were obtained from measurements by high frequency ultrasound (>10 MHz). The ultrasound reports and images were initially checked by one author (M.A.) after receiving training from a radiologist (M.D.D.). In case of uncertainty the image was reviewed by a radiologist of the participating hospital. All researchers involved in the data collection were blinded to the pathological ALN status of the patients.

Staging was coded according to the Tumor, Node and Metastasis (TNM) classification [23]. Tumor grade was scored according to the Nottingham grading system [24]. ER, PgR and HER2 status were categorized as described previously [21]. Both ER and PgR status were divided into four categories: (<10%), + (10–25%), ++ (25–75%) and +++ (>75%) [21]. Since the NCR registered the ER and PgR status in 10% steps (0, 10%, 20%, etc.), we replaced the second cut-off point (25%) with 30% and the third (75%) with 80%. Variables related to ALNs were measured on the most suspicious lymph node detected by ultrasonography, which was defined as the lymph node with the thickest cortex and/or absence of a hilum. A lymph node was defined as positive if macrometastases, micrometastases or isolated tumor cells (ITCs) were identified by histopathological analysis [21].

Statistical analysis

Differences of categorical and continuous variables between groups were analyzed using the Chi-square and Mann-Whitney *U* test, respectively. The clinical value for each predictor in the original model was used to calculate the ALN metastasis probability for each patient in the present study. The AUC was used to evaluate the discriminative performance of the model. For the calibration of the original model, the enrolled Dutch patients were sorted on their predicted probability and grouped into three equally sized groups. For each group, the mean model-predicted probability and the actual percentage (95% confidence interval [CI]) of ALN metastasis were calculated. A calibration plot was drawn showing the mean model-predicted probability against the actual percentage of ALN metastasis, providing information about the predictive accuracy of the model for each group.

To improve its discriminative performance and predictive accuracy, we updated the original model using both the Dutch and the Chinese populations as follows. Generalized linear model (GLM) tree analysis was applied to the Dutch and Chinese patient populations to classify patients into groups with different risk of ALN metastasis based on their clinicopathological characteristics. In each group, the model was updated separately by adjusting the intercept and slope of the original model. Detailed information on GLM tree analysis is provided in the Supplementary Methods. The AUC and calibration plot were used to assess the discriminative performance and

Please cite this article in press as: Qiu S-Q, et al., Validation and update of a lymph node metastasis prediction model for breast cancer, European Journal of Surgical Oncology (2018), https://doi.org/10.1016/j.ejso.2017.12.008