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Original article

Validation of a breast cancer nomogram for predicting nonsentinel node metastases after minimal sentinel node involvement: Validation of the Helsinki breast nomogram

Lobna Ouldamer [a,b,c,*], Flavie Arbion [d], Alexis Balagny [a,c], Florence Fourquet [e], Henri Marret [a,c], Gilles Body [a,c]

[a] Department of Gynecology, CHRU de Tours, Hôpital Bretonneau, 2 Boulevard Tonnelé, 37044 Tours, France
[b] INSERM Unit 1069, Tours, France
[c] François Rabelais University, Tours, France
[d] Department of Pathology, CHRU de Tours, Hôpital Bretonneau, 2 Boulevard Tonnelé, 37044 Tours, France
[e] Department of Biostatistics, CHRU de Tours, Hôpital Bretonneau, 2 Boulevard Tonnelé, 37044 Tours, France

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ABSTRACT

Background: Complete node dissection for tumor-positive sentinel lymph nodes (SLN) is becoming more controversial. Nevertheless, current practice guidelines still recommend complete axillary lymph node dissection (ALND) for breast cancer patients whose SLN contains a metastatic tumor. The Helsinki breast cancer nomogram developed by Meretoja TJ et al. aims to predict the risk of positive non-sentinel lymph nodes in patients with minimal sentinel node involvement, it uses tumor diameter and multifocality. The purpose of this study was to test the accuracy of the nomogram among patients with micrometastatic SLN-positive biopsy findings.
Methods: The Helsinki nomogram was used to calculate risk of metastases for 49 consecutive patients with SLN micrometastases or isolated tumor cells (ITC) who underwent complete ALND. The nomogram was evaluated by calculating the area under the receiver-operator characteristic (ROC) curve.
Results: The area under the ROC curve for the nomogram applied to all patients with micrometastases and ITC was 0.72 (range 0.60–0.85) (0.791 in the original publication).
Conclusions: The Helsinki breast cancer nomogram is a useful tool for patients with minimal sentinel node involvement.

Introduction

Completion axillary lymph node dissection (ALND) has been considered to be the gold standard for cases in which a metastasis is found in the sentinel lymph node (SLN).[1] ALND remains the standard approach for SLN-positive patients recommended by the American Society of Clinical Oncology and the French guidelines. However, approximately 50%–70% of patients with disease-positive SLN have no additional positive nodes, which means that it may be possible to avoid axillary dissection in selected patients.[2–8]

There has been discussion in the literature about whether systematic ALND for patients with positive SLNs is appropriate. In the randomized American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, patients with a positive SLN were randomized into two groups: complete ALND or axillary observation. There was similar outcome in the ALND and SN biopsy-only arms, despite a nonsentinel node involvement rate of 27% in the ALND arm suggesting that complete ALND after positive SN may not improve survival. However, the study closed prematurely due to poor recruitment, so it is unlikely that the number of subjects successfully enrolled in the study will provide adequate power to show a difference in survival, even if any such difference exists.[9] Also, all patients in this trial underwent breast-conserving treatment with whole-breast radiation. So, it is unclear whether these results can be generalized to patients undergoing mastectomy without radiotherapy.

Metastases are found in non-SLNs in approximately 10% of patients with isolated tumor cells (ITC) in the SLN and in 20%–35% of patients with micrometastases in the SLN[10]; complete ALND is routinely performed in these patients.[11]

* Corresponding author. Department of Gynecology, CHU Bretonneau, 2 Boulevard Tonnelé, 37000 Tours, France. Tel.: +33 02 47 47 47 47; fax: +33 02 47 47 38 01.
E-mail address: l.ouldamer@chu-tours.fr (L. Ouldamer).

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Meretoja et al. developed a nomogram to predict the likelihood of finding additional positive nodes on ALND in patients with micrometastasis or ITC in the SLN. The nomogram predicts individual patient risk and was developed from a logistic-regression analysis and included only two statistically significant variables: tumor diameter and multifocality. The receiver-operating characteristic (ROC) curve for this tool was 0.791 indicating good prediction and discrimination.[12]

We therefore decided to apply this nomogram to our SLN-positive series and evaluated its usefulness for the subgroup of patients with micrometastatic SLNs.

Patients and methods

A total of 1283 consecutive cases of SLN biopsy from primary untreated breast cancer patients at the tertiary oncological referral center of Tours (France) were prospectively entered into a multidisciplinary team meeting register between January 2004 and December 2011.

With the authorization of the institutional review board we retrospectively reviewed this prospective database.

We studied a subset of 187 cases that fulfilled the following inclusion criteria: primary invasive breast carcinoma with clinically negative axillary lymph nodes and no prior systemic therapy; successful SLN biopsy and metastatic disease identified by any method (routine histopathology, serial sectioning, staining with hematoxylin and eosin [HE], immunohistochemistry [IHC]); and complete ALND.

Exclusion criteria were: neoadjuvant chemotherapy, inflammatory breast cancer, ductal carcinoma *in situ*, failed SLN mapping, clinically suspicious axillary lymph nodes and bilateral procedures.

Both blue dye (patent blue, Laboratoire Guerbet, Paris, France) and radioisotopes (^{99m}Tc-labeled colloid sulfur, Nanocoll, General Electric Healthcare SA, USA) were used for lymphatic mapping with SLN biopsies.

Static lymphoscintigraphy was performed to visualize the probable localization of SLN, and a hand-held gamma detection probe (Gamma-sup/Clerad/France) was used intraoperatively to identify the most radioactive area. SLN were identified as nodes with blue dye uptake, radiotracer uptake, or both.

Histopathological evaluation

Fresh tissue labeled as SLN was delivered without fixation to the pathology lab. Each lymph node was bisected along its major axis. One half of the nodal tissue was frozen, sliced into 5 μm-thick sections and stained with blue methylene and with hematoxylin and eosin (HE) for intraoperative consultation. In cases with technical limitations, such as incomplete representation of the tissue or folding, additional sections were obtained at the discretion of the consultant pathologist.

Upon completion of the intraoperative consultation, tissue samples were fixed in 10% buffered formalin and then embedded in paraffin. Three slides were prepared: two of sections taken at 200-micron intervals were stained with HE, and a conservative section of a deeper level was studied for pancytokeratin by immunohistochemistry.

Immunohistochemistry for cytokeratin AE1/AE3 was used to confirm suspicious cells in the SLN.

Following the American Joint Committee on cancer recommendations, macrometastases were defined as tumors >2 mm long and micrometastases as tumors between 0.2 and 2 mm long. Tumors <0.2 mm long were regarded as isolated tumor cells.

If a frozen section was positive, ALND was performed during the same surgical intervention. For patients with SLN metastases but that were not identified in interoperative frozen sections, ALND was performed at a later date.

The Helsinki breast cancer nomogram was used to predict the individual risk of non-SLN positivity from patient data. The nomogram was developed a to predict the likelihood of finding additional positive nodes on ALND in patients with micrometastasis or ITC in the SLN. First, univariate analysis was performed to determine factors associated with non SLN metastases, all variables (tumor diameter, multifocality, lymphovascular invasion, and tumor location) with p value less than 0.15 were then included into a logistic regression analysis using backward stepwise method. Variables with p value <0.05 were considered statistically significant in the multivariate analysis. Tumor diameter ($p = 0.002$) and multifocality ($p = 0.039$) were found to be the only statistically significant variables and were included in the final predictive model. With a 10% cutoff value for predicted probability the model had sensitivity of 38.2% and specificity of 85.7% and selects 84.1% of patients to have predicted risk of less than 10% for additional metastases showing good clinical utility.[12] For nomograms, 10% or less cutoff values are considered in the literature to define the subgroup of patients with a low predicted probability of metastatic non-SLN (having a probability of metastatic non-SLN ≤ 10% predicted by nomogram).

Statistical analyzes were performed by R 2.13.1 (http://www.cran.r-project.org/). For numeric data, results are reported as mean and median values ± standard deviation (SD). Numeric data were analyzed with Student's t-test if normally distributed, and the Mann–Whitney test if not. Categorical data were analyzed with the chi-squared test or with Fisher's exact test.

To measure discrimination by the nomogram, a receiver-operating characteristic (ROC) curve was constructed. The ROC curve assesses the relationship between the sensitivity and the false positive rate (1- specificity) of a test across all possible threshold values that define the positivity of a disease or condition.

The overall accuracy of the nomogram is expressed as the area under the ROC curve (AUC).

The AUC can be interpreted as the probability of a correct assignment of disease presence in random pairs of patients, one patient in each pair who has disease and one who does not. It is generally accepted that AUC values of 0.7–0.8 indicate satisfactory discrimination, and that AUC values >0.8 represent good discrimination.

A calibration plot was drawn showing the actual (women who actually had positive non-SNs) versus nomogram-predicted probability.

Results

Between January 2004 and December 2011, metastatic disease was found in 216 patients; 29 (13 isolated tumor cells, 10 micrometastasis and 6 macrometastasis) of these patients did not undergo ALND (presence of co-morbidities or a history of controlateral ALND or patient choice) and were excluded from this analysis.

Thus 187 cases met our inclusion criteria, and they included a subgroup of 49 patients with SLN micrometastases or isolated tumor cells (ITC). Descriptive clinical and histopathological data for the study population are listed in Table 1.

The mean age was 57 years (range, 30–84 years).

The mean pathological tumor size was 15.33 mm (range 4–34 mm).

The mean number of SLN identified was 2.37 (range 1–6), and the mean number of nodes extracted at ALND was 11 (range 1–31).

The characteristics of positive-ALND patients are showed in Table 2.

The nomogram was applied to the micrometastatic SLN and ITC cohort ($n = 49$). The predicted probability of non-sentinel metastases for each patient are showed in Table 3.