The Breast 23 (2014) 453–459

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Prediction of non-sentinel lymph node involvement in breast cancer patients with a positive sentinel lymph node

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ARTICLE INFO

Article history:
Received 18 August 2013
Received in revised form
26 January 2014
Accepted 16 March 2014
Available online 24 April 2014

Keywords:
Breast cancer
Sentinel lymph node
Prediction
Non-sentinel lymph node involvement
External validation

ABSTRACT

Completion axillary lymph node dissection (cALND) is the golden standard if breast cancer involves the sentinel lymph node (SLN). However, most non-sentinel lymph nodes (NSLN) are not involved, cALND has a considerable complication rate and does not improve outcome. We here present and validate our predictive model for positive NSLNs in the cALND if the SLN is positive.

Consecutive early breast cancer patients from one center undergoing cALND for a positive SLN were included. We assessed demographic and clinicopathological variables for NSLN involvement. Uni- and multivariate analysis was performed. A predictive model was built and validated in two external centers.

21.9% of 470 patients had at least one involved NSLN. In univariate analysis, seven variables were significantly correlated with NSLN involvement: tumor size, grade, lymphovascular invasion (LVI), number of positive and negative SLNs, size of SLN metastasis and intraoperative positive SLN. In multivariate analysis, LVI, number of negative SLNs, size of SLN metastasis and intraoperative positive pathological evaluation were independent predictors for NSLN involvement. The calculated risk resulted in an AUC of 0.76. Applied to the external data, the model was accurate and discriminating for one (AUC = 0.75) and less for the other center (AUC = 0.58).

A discriminative predictive model was constructed to calculate the risk of NSLN involvement in case of a positive SLN. External validation of our model reveals differences in performance when applied to data from other institutions concluding that such a predictive model requires validation prior to use.

Introduction

In Europe, breast cancer is the leading cause of cancer death [1]. In primary operable breast cancer, lymph node involvement is the most important prognostic factor [2]. Axillary lymph node dissection (ALND) has been part of breast cancer surgery since the Halsted radical mastectomy was introduced. ALND improves loco-regional control and delivers important prognostic information, but is associated with complications that hamper quality of life [3–5].

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http://dx.doi.org/10.1016/j.breast.2014.03.009
0960-9776/

More than a decade ago, the biopsy of the sentinel lymph node (SLN) has safely replaced ALND for axillary staging in primary operable, clinically lymph node negative breast cancer with much less morbidity [6,7]. If the SLN is histologically free of tumor, patients are considered lymph node negative. [8] In case of SLN involvement, completion axillary lymph node dissection (cALND) remains the golden standard [8,9]. Recent new data challenge this paradigm, because many patients undergoing cALND, seem to lack non-sentinel lymph node (NSLN) involvement [10]. Non-randomized, retrospective studies have previously shown that omitting cALND in highly selected patients with SLN involvement is safe [11,12]. Two prospective randomized trials, one by the American College of Surgeons Oncology Group (ACOSOG) and one by the International Breast Caner Study Group (IBCSG) recently showed that cALND may be safely omitted in some cT1-2 SLN positive tumors [13,14].

In the absence of reliable guidelines on omitting cALND in SLN-positive disease, predictive tools for NSLN involvement remain important since they allow an individual approach to any form of regional treatment. We here present a model to predict NSLN involvement in case of positive SLNs and validate it in two external datasets.

Patients and methods

UHL patient series

Data of 1926 consecutive patients with a primary operable lymph node negative breast cancer who underwent a SLN biopsy at the University Hospitals Leuven (UHL) between July 2003 and December 2010 were entered in the UHL Multidisciplinary Breast Center database. The axilla was considered negative by clinical examination and ultrasound or by fine needle aspiration cytology (FNAC) if suspicious lymph nodes on ultrasound. An axillary lymph node was considered suspicious when one of the following criteria was present: (a) increased short axis resulting in a round shape, (b) hypoechoic aspect with loss of normal distinction between the hypoechoic rim and hyperechoic hilus, (c) cortical thickness more than 2 mm and (d) a focal bulge of normal contour. The 501 (26.0%) patients with a positive SLN (micro- or macrometastasis) were included. We excluded patients without cALND based on comorbidity, age or patient's desire ($n = 19$), patients with bilateral positive SLNs ($n = 10$), a patient with a false positive SLN ($n = 1$) (intraoperative positive SLN but definitive pathological evaluation could not confirm this) and a patient with a suspicious axillary ultrasound without prior preoperative FNAC ($n = 1$). Finally, 470 patients were included in our study. Complete data were available for 451 patients (Fig. 1).

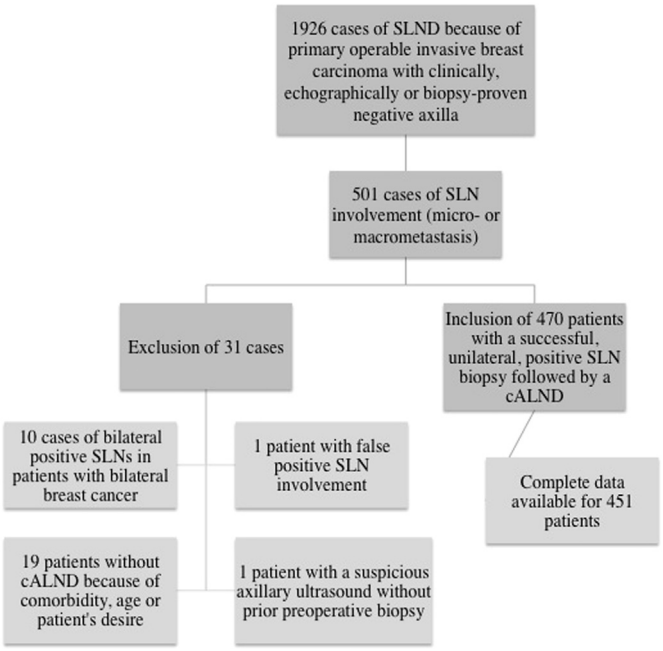

Fig. 1. Patient selection and collection of data for UHL patient series.

External validation patients

Two independent Belgian centers participated for external validation of the UHL predictive model. Each center provided a series of consecutive patients with similar inclusion criteria to the UHL cohort. Center A (General Hospital Groeninge Kortrijk) provided data from 149 patients, operated between 2003 and 2012. Center B (General Hospital Sint-Augustinus Wilrijk) provided complete information on 119 patients who were operated between 2006 and 2011.

SLN identification

At the UHL the SLN was identified using subdermal injection of Technetium-99m-nanocolloid and subareolar patent blue dye. Technetium-99m-nanocolloid injections were performed within 24 h before surgery and were followed by pre-operative lymphoscintigraphy. Patent blue dye was injected following induction of anesthesia.

Dissection of the SLN was guided by a gamma-probe and by blue lymphatics. A SLN was defined as a radio-isotope-hot and/or patent blue coloured lymph node. Suspect lymph nodes by palpation of the axilla were also dissected and sent for intraoperative evaluation.

Center A used a similar technique as UHL for the identification of the SLN but without the use of patent blue. Center B only performed injection with patent blue in case of negative pre-operative lymphoscintigraphy.

Pathological evaluation

At the UHL the intraoperative microscopic evaluation of SLNs was performed by touch imprint cytology, frozen section or both from 2003 to 2007. From 2008, the microscopic screening of SLNs was done by frozen section only. During surgery, every SLN was sectioned in thin slices of ±2 mm. Subsequently, the slices were quickly frozen and cut with a cryostat microtome into 5 μm thick sections. A quick H&E staining was performed and slides were analyzed with a light microscope. Following intraoperative evaluation, the SLNs were fixed in 4% buffered formalin and embedded in paraffin for definitive evaluation by enhanced histopathological evaluation. The protocol used in UHL included: H&E and cytokeratin immunohistochemistry (IHC; prekeratine Ab, clone AE1/AE3 from DAKO) on paired serial sections taken at 0.3 mm interval throughout the block.

Micro- or macrometastasis detected during frozen section (i.e. during surgery) or after enhanced pathological examination resulted in immediate or delayed cALND, respectively. SLNs involved with isolated tumor cells only (≤0.2 mm) were considered as node negative and thus not subjected to cALND. Lymph nodes collected from cALND, were cut in thin slices and examined by H&E; lymph nodes from lobular breast cancers classified as lymph node negative on H&E were additionally stained with epithelial markers.