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Cross-validation of three predictive tools for non-sentinel node metastases in breast cancer patients with micrometastases or isolated tumor cells in the sentinel node

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Abstract

Background: We cross-validated three existing models for the prediction of non-sentinel node metastases in patients with micrometastases or isolated tumor cells (ITC) in the sentinel node, developed in Danish and Finnish cohorts of breast cancer patients, to find the best model to identify patients who might benefit from further axillary treatment.

Material and method: Based on 484 Finnish breast cancer patients with micrometastases or ITC in sentinel node a model has been developed for the prediction of non-sentinel node metastases. Likewise, two separate models have been developed in 1577 Danish patients with micrometastases and 304 Danish patients with ITC, respectively. The models were cross-validated in the opposite cohort.

Results: The Danish model for micrometatases was accurate when tested in the Finnish cohort, with a slight change in AUC from 0.64 to 0.63. The AUC of the Finnish model decreased from 0.68 to 0.58 when tested in the Danish cohort, and the AUC of the Danish model for ITC decreased from 0.73 to 0.52, when tested in the Finnish cohort. The Danish micrometastatic model identified 14–22% of the patients as high-risk patients with over 30% risk of non-sentinel node metastases while less than 1% was identified by the Finish model. In contrast, the Finish model predicted a much larger proportion of patients being in the low-risk group with less than 10% risk of non-sentinel node metastases.

Conclusion: The Danish model for micrometastases worked well in predicting high risk of non-sentinel node metastases and was accurate under external validation.

Keywords: Breast cancer; Sentinel node; Micrometastases; Isolated tumor cells; Non-sentinel node metastases

Introduction

The majority of patients with micrometastases or isolated tumor cells (ITC) in the sentinel node have no further spread beyond the sentinel node and will not benefit from an axillary lymph node dissection (ALND).[1,2] In addition, the recent International Breast Cancer Study Group (IBCSG) 23-01 trial, where breast cancer patients with micrometastases or ITC in the sentinel node were randomized to either ALND or no treatment of the axilla, did not find any difference in disease-free survival between patients, with and without ALND.[3] Accordingly, it is possible that adjuvant systemic treatment together with whole breast irradiation can eliminate low volume axillary metastases left in the axilla in these patients, making an ALND redundant. As a result, ALND is now generally abandoned in patients with only micrometastases or ITC in the sentinel node. Still, studies indicate that a small group of patients with micrometastases exists, with a high risk of non-sentinel node (NSN) metastases,[4,5] and some of these patients might experience an axillary recurrence if further axillary treatment is omitted. This is

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underlined by the results from a recent Dutch study reporting a four-fold increased risk of axillary recurrence in patients with micrometastases in the sentinel node, if the axilla was left untreated.[4] Therefore a tool is needed to identify patients, in whom adjuvant treatment might not be sufficient to eliminate residual axillary metastases, resulting in a high risk of relapse. Such a tool would create a tailor-made treatment of the axilla, and spare the majority from an unnecessary ALND, but still prevent an axillary recurrence in high-risk patients.

Several tools have been developed,[6,7] and validated[7] for patients with macrometastases in the sentinel node, but these tools are not very precise in patients with micrometastases.[8–13] Furthermore, they have a large degree of inter-institutional variation,[13–18] which hampers their direct implementation into clinical use in a new population. Only a few predictive tools have been developed based on patients with only micrometastases or ITC in the sentinel node,[5,12,19] and external validation of these models is sparse.[13,20]

The aim of the present study was to cross-validate three existing models for predicting NSN metastases, developed in two separate populations of breast cancer patients with micrometastases or ITC in the sentinel node. We compare the performance of the models and evaluate their robustness for inter-institutional use.

Material and method

Between 2003 and 2011, 302 Finnish breast cancer patients with micrometastases and 235 with ITC in the sentinel node, have been operated at the Breast surgery unit of Helsinki University Central Hospital. 24 patients with micrometastases and 29 patients with ITC did not undergo a completion ALND. Based on the remaining 484 patients a model has been developed for the prediction of NSN metastases. The model includes tumor size and multifocality as risk factors.[12] The model was internally validated in a separate series of 51 Finnish breast cancer patients with micrometastases or ITC in the sentinel node.

In Denmark, 2137 breast cancer patients with either micrometastases or ITC in the sentinel node were operated between 2002 and 2008 in eighteen different Danish breast surgery departments. Patients were registered prospectively in the Danish Breast Cancer Cooperative Group (DBCG) Database. The DBCG database is a national breast cancer database and has been described in details elsewhere.[21] 256 patients, 147 with micrometastases and 109 with ITC, did not undergo a completion ALND. Based on the remaining 1881 patients, 1577 with micrometastases and 304 with ITC, two models were developed.[5] 61 patients were excluded due to missing information on variables included in the final models. The final DBCG model for prediction of NSN metastases in patients with micrometastases in the sentinel node was based on 1521 patients and included tumor size, lymphovascular invasion, hormone receptor status, location of tumor in the breast and proportion of positive sentinel nodes as risk factors. The final model for prediction of NSN metastases in patients with ITC was based on 299 patients and included tumor size, young age (<40) and proportion of positive sentinel nodes as risk factors. The DBCG model for patients with micrometastases has been validated in an independent cohort of 720 Danish breast cancer patients with micrometastases, operated in 2009 and 2010 and prospectively registered in the DBCG database.[22] Likewise, the DBCG model for patients with ITC has been validated in 180 Danish patients with ITC, operated in 2009 and 2010.[22] Further details on development and internal validation of the three models have been described elsewhere.[5,12]

Micrometastases were, in all cohorts, defined as tumor deposits not larger than 2 mm, and ITC were defined as tumor deposits not larger than 0.2 mm. Additionally, cell count was used to classify metastases in the Danish cohorts. Metastases between 10 and 100 tumor cells were defined as micrometastases, and single cells or cell clusters of less than 10 cells were defined as ITC.[23] Histopathological examination of the sentinel nodes has been described elsewhere.[5,12] Multifocality was defined differently in the two cohorts. In the Danish cohort, multifocality was defined as more than one invasive carcinoma placed more than 2 cm apart. Invasive carcinomas within 2 cm were defined as satellite tumors and not included as multifocal carcinomas. In contrast, the Finnish cohort defined any cancer with more than one invasive focus as multifocal, regardless of distance between the tumors. Preoperative axillary ultrasound was performed in all patients and fine needle aspiration was performed in case of suspicious lymph nodes. A combination of radioactive tracer and blue dye was used to identify sentinel nodes. In the Finnish cohort lymphoscintigraphy was used as a routine, while it was optional in the Danish cohort.[23] Radioactive or stained lymph nodes were removed as sentinel nodes together with any lymph nodes considered suspicious by palpation or inspection.

The cohort for external validation of the Helsinki model consisted of the original cohort of Danish breast cancer patients with micrometastases or ITC in the sentinel node. 43 patients with micrometastases and 7 patients with ITC were excluded due to missing information on either tumor size or focality, leaving 1534 patients for external validation. The cohort used for external validation of the DBCG model for patients with micrometastases consisted of the 278 Finnish patients with micrometastases. The cohort used for external validation of the DBCG model for patients with ITC consisted of the 206 Finnish patients with ITC. Patient, tumor and sentinel node characteristics of the Danish and Finnish cohorts are shown in Table 1.

Statistical analysis

Patient and disease characteristics for the original Danish and Finnish cohorts listed in Table 1 were analyzed by χ^2 test, excluding unknowns. For the multivariate models developed from the original cohorts, discrimination