

# Application of artificial neural networks for predicting presence of non-sentinel lymph node metastases in breast cancer patients with positive sentinel lymph node biopsies

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## Abstract

**Introduction:** The aim of this study was to present a new predictive tool for non-sentinel lymph node (nSLN) metastases.

**Material and methods:** One thousand five hundred eighty-three patients with early-stage breast cancer were subjected to sentinel lymph node biopsy (SLNB) between 2004 and 2012. Metastatic SLNs were found in 348 patients – the retrospective group. Selective axillary lymph node dissection (ALND) was performed in 94% of cases. Involvement of the nSLNs was identified in 32.1% of patients following ALND. The correlation between nSLN involvement and selected epidemiological data, primary tumor features and details of the diagnostic and therapeutic management was examined in metastatic SLN group. Multivariate analysis was performed using an artificial neural network to create a new nomogram. The new test was validated using the overall study population consisting of the prospective group (365 patients – SLNB between 01–07.2013).

**Results:** Accuracy of the new test was calculated using area under the receiver operating characteristics curve (AUC). We obtained AUC coefficient equal to 0.87 (95% confidence interval: 0.81–0.92). Sensitivity amounted to 69%, specificity to 86%, accuracy – 80% (retrospective group) and 77%, 46%, 66% (validation group), respectively. The Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram the calculated AUC value was 0.71, for Stanford – 0.68, for Tenon – 0.67.

**Conclusions:** In the analyzed group only the MSKCC nomogram and the new model showed AUC values exceeding the expected level of 0.70. Our nomogram performs well in prospective validation on patient series. The overall assessment of clinical usefulness of this test will be possible after testing it on different patient populations.

**Key words:** breast cancer, sentinel lymph node biopsy, non-sentinel node metastases, nomogram.

## Introduction

Breast cancer is the most common malignant disease in women in Poland. In 2010, a total of 15,981 new cases were diagnosed in our country [1, 2]. 22.4% of cancer incidence in women was accounted for breast cancer, being the cause of 12.8% of oncological deaths [2]. With regards to women, neoplasm of breast (along with trachea, bronchus and lung) contribute to the highest number of years of life lost [3].

Axillary lymph node conserving treatment considerably reduces the risk of complications of axillary lymphadenectomy [4–6]. This was possible due to wider use of sentinel lymph node biopsy (SLNB) in breast cancer patients without clinically suspicious axillary lymph nodes [4–6].

The involvement of other axillary lymph nodes is expected in about 40% of breast cancer patients with metastatic SLNs [7]. More than half of these patients do not benefit from complementary axillary lymph node dissection (ALND) leading to lymphadenectomy-related complications.

The presence of metastases in non-sentinel lymph nodes (nSLN) mostly depends on the size of metastases (AJCC classification [8]) found in the sentinel lymph node (SLN). In a study by Kohrt *et al.*, if isolated tumor cells (ITC) were present in SLN, metastatic nSLNs were found in 4.7% of patients. In case of SLN micrometastases nSLNs metastases concerned 42% of patients. The size of SLN metastases exceeded 2 mm in 71% of examined patients [9].

The addition of other risk factors led to the development of systems for numerical evaluation of the probability of finding metastases in nSLN. The available scoring scales include clinical data obtained from pre- and post-SLNB records. High clinical value of these systems has been proven in

multiple studies [10–20]. It was also demonstrated that use of these scales may help in the therapeutic decision-making process [21–23].

The methodology of developing the nomograms was based on selection of factors influencing the rate of occurrence of metastases in nSLNs in a statistically significant manner. Different systems use multivariate analysis including different (for each of them) sets of selected data. The Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram includes eight clinical parameters: size of pathology, multifocality, histologic form with histologic tumor grade, involvement of vascular structures, estrogen receptor status, number of resected lymph nodes during SLNB: with and without metastases, and method of detection of metastases in SLN (also available on-line: <http://nomograms.mskcc.org/breast/>) [10]. Other scales evaluate fewer variables – from seven (MOU) [17] to only three (Tenon [18], Stanford [9] and Cambridge [19]).

The aim of this study was to present a new model of predicting the incidence of metastases in nSLNs in early breast cancer patients.

## Material and methods

### Analyzed group

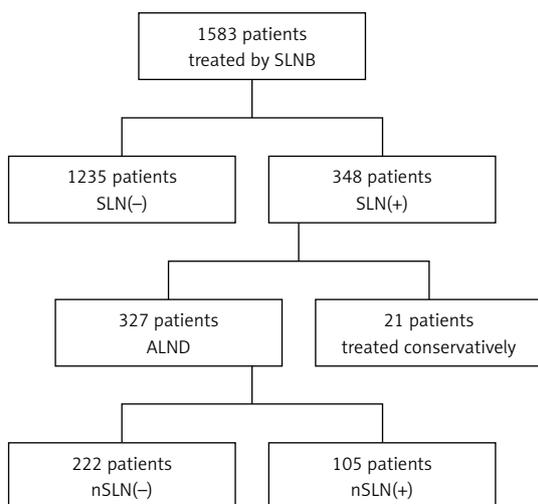
One thousand five hundred eighty-three patients with early-stage breast cancer were scheduled for SLNB between January 2004 and December 2012 in the Bydgoszcz Oncology Center. Metastatic SLNs were found in 348 (22%) patients – SLN(+) patients.

The study included all consecutive patients with pathologically proven early invasive breast cancer without clinically and radiologically suspected lymph nodes (cN0). Patients who underwent neoadjuvant treatment were excluded from the study. Complementary ALND was performed in the majority of SLN(+) patients – 94% ( $n = 327$ ). These patients comprised a study group subjected to a retrospective analysis. Data obtained as a result of the analysis were used for statistical calculations and for creation of a new prognostic model.

Involvement of nSLNs was identified in 32.1% (105/327) of patients following ALND (Figure 1) – nSLN(+) patients.

Prospective evaluation of the new test was based on a group of 365 consecutive patients hospitalized in the Bydgoszcz Oncology Center and subjected to SLNB. SLN metastases were diagnosed in 73 patients and selective ALND was performed in 67. The proportion of nSLN(+) patients was 35.8% (24/67).

The treatment protocol was approved by the Local Bioethical Committee and all patients



**Figure 1.** Patients treated by sentinel lymph node biopsy – nodal metastatic lesions – retrospective group

signed informed consent. The analysis had no influence on therapeutic process (surgical procedures, adjuvant treatment). Collected clinical data were stored with no possibility of patients being identified by third parties.

### Selection of evaluated data

Factors increasing the risk of tumor metastases in nSLN were defined. Obtained results were presented in the form of a nomogram, which was developed by using an artificial neural network for statistical calculations.

The correlation between nSLN involvement and numerous variables including selected epidemiological data (menopausal status, age, carcinoma of contralateral breast, family history and gynecological history), primary tumor features (histological type, size, palpability and multifocality, *comedo* component, suspicious microcalcifications in mammography, grading, estrogen (ER) and progesterone receptor (PR) expression and HER2 status, molecular type of the tumor and Ki-67 index), details of diagnostic and therapeutic management (methods of preoperative tumor diagnostics, need for mastectomy, SLN mode, type of SLN metastasis and method of detection, presence of intravascular tumor emboli, infiltration of lymph node capsule, number of dissected SLNs, number of involved SLNs) were calculated.

### Clinicopathological data acquisition

ER, PR, Ki-67 and HER2 levels were assessed immunohistochemically (IHC). Tumors were deemed positive for these receptors if at least 10% of invasive tumor cells in a section exhibited nuclear staining. Histologic grading was defined according to the Scarff-Bloom-Richardson system. HER2 positivity was defined as a 3+ staining intensity score at immunohistochemical analysis for HER2 protein or for HER2 gene amplification by fluorescence in situ hybridization (FISH).

Based on IHC or FISH findings of ER, PR, HER2, and Ki-67 expression, the study population was divided into five subtypes: luminal A (ER positive and/or PR positive, HER2 negative and Ki-67  $\leq$  14%); luminal B1 (ER positive and/or PR positive, HER2 negative and Ki-67  $>$  14%); luminal B2 – luminal HER2 (ER positive and/or PR positive and HER2 positive, irrespective of Ki-67 expression); HER2-overexpressed (ER negative, PR negative and HER2 positive); and basal-like – triple-negative breast cancer (TNBC: ER negative, PR negative and HER2 negative).

### Statistical analysis

The initial stage of calculations included a univariate analysis of the influence of evaluated clinical parameters on the presence of metastases in

nSLN. The differences between groups were evaluated by the  $\chi^2$  test. It allowed to define factors associated with significantly increased rates of tumor metastases in nSLNs.

Multivariate analysis for creating a new nomogram was done. Unlike former prognostic systems, all the factors (including those not showing a statistically significant influence on the presence of metastases in nSLN) were included. Statistical calculations were performed using an artificial neural network with MLP 40-5-2 structure and BFGS learning algorithm (SOS error function, activation function of the neurons in the hidden layer – logistic function and activation function of the neurons in the output layer – logistic function). Predictive accuracy was assessed by calculating the area under the receiver operating characteristic (ROC) curve (AUC).

SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses. A  $p$ -value below 0.05 was considered statistically significant.

The predictive value of other prognostic systems (MSKCC [10], Tenon [18] and Stanford [9] nomogram) was also assessed in analyzed subjects.

Patients with complete sets of necessary clinical data resulting from the methodology of each test were qualified for calculations.

### Results

Three hundred and twenty-five women and 2 men were included in the retrospective group. Median age was 53 years (range: 23–80 years). Median histopathological size of excised primary invasive carcinoma was 21 mm (range: 4–70 mm). Detailed characteristics of the analyzed patients are presented in Table I.

Median number of harvested SLNs was 2 (range: 1–13, mean: 2.8). Median number of metastatic SLNs was 1 (range: 1–6, mean: 1.4).

Median number of removed lymph nodes at the completion of ALND was 14 (range: 1–37, mean: 15.9). Median number of metastatic non-sentinel lymph nodes was 3 (range: 1–25, mean: 4.3).

For some of the analyzed variables, such as SLN capsule infiltration ( $p < 0.0000001$ ), tumor emboli ( $p < 0.0000001$ ), number of involved SLNs ( $p < 0.000001$ ), size of SLN metastasis ( $p < 0.000014$ ), method of the diagnosis of metastasis ( $p < 0.008$ ), and clinical staging ( $p < 0.008$ ), univariate analysis showed a significant correlation with the presence of metastatic nSLN lesions.

Other analyzed factors did not show a significant correlation ( $p > 0.05$ ).

Based on a subsequent multivariate analysis (using an artificial neural network) including all baseline factors, the variables used in the new prognostic system were defined. Among the data that increased the rate of nSLN(+) patients

**Table I.** Characteristics of patients with metastases in the sentinel lymph node subjected to adjuvant axillary lymph node dissection – retrospective group

Data set	All patients (n = 327)	nSLN(+) (n = 105)	nSLN(-) (n = 222)	P-value
Age – median (range)	53 (23–80)	52 (30–78)	53 (23–80)	0.591892
Menopausal status:				0.577337
Premenopausal patients	106 (32.4%)	37 (35.2%)	69 (31.1%)	
Postmenopausal patients	219 (67.0%)	68 (64.8%)	151 (68.0%)	
Man	2 (0.6%)	0	2 (0.9%)	
Carcinoma of contralateral breast	17 (5.2%)	7 (6.7%)	10 (4.5%)	0.415645
Estrogen hormone therapy	41 (12.5%)	14 (13.3%)	27 (12.2%)	0.775080
No date	3 (0.9%)	1 (1.0%)	2 (0.9%)	
Number of pregnancies – median	2 (0–7)	2 (0–6)	2 (0–7)	0.471348
Familial breast cancer	70 (21.4%)	25 (23.8%)	45 (20.3%)	0.476830
No date	2 (0.6%)	1 (1.0%)	1 (0.5%)	
Localization of tumor:				0.286121
Outer quadrants	246 (75.2%)	85 (81.0%)	161 (72.5%)	
Inner quadrants	55 (16.8%)	13 (12.4%)	42 (19.0%)	
Behind areola (central part)	26 (8.0%)	7 (6.7%)	19 (8.5%)	
Palpability of tumor	261 (79.8%)	85 (81.0%)	176 (79.3%)	0.566708
Size of primary tumor – median [mm] – palpable assessment	21 (8–50)	22 (10–40)	21 (8–50)	0.265277
Classification of clinical stage assessment (cTNM):				0.008064
T1	181 (55.4%)	50 (47.6%)	131 (59.0%)	
T2	143 (43.7%)	52 (49.5%)	91 (41.0%)	
T3	3 (0.9%)	3 (2.9%)	0	
Methods of preoperative tumor diagnostics:				0.667273
FNB	135 (41.3%)	43 (41.0%)	92 (41.4%)	
CNB/VAB	82 (25.1%)	29 (27.6%)	53 (23.9%)	
Surgical biopsy	110 (33.6%)	33 (31.4%)	77 (34.7%)	
Breast conserving treatment	181 (55.4%)	49 (46.7%)	132 (59.5%)	0.518992
Pathological size of primary tumor – median [mm]	21 (4–70)	22 (4–65)	21 (4–70)	0.543701
Histological type of tumor:				0.233699
IDC	289 (88.4%)	94 (89.5%)	195 (87.8%)	
ILC	31 (9.5%)	11 (10.5%)	20 (9.0%)	
Other invasive	7 (2.1%)	0	7 (3.2%)	
Comedo components	26 (8.0%)	11 (10.5%)	15 (6.8%)	0.249918
Grade of histological malignancy:				0.225046
G1	22 (6.7%)	4 (3.8%)	18 (8.1%)	
G2	220 (67.3%)	70 (66.7%)	150 (67.6%)	
G3	79 (24.2%)	31 (29.5%)	48 (21.6%)	
No date	6 (1.8%)	0	6 (2.7%)	
Presence of intravascular tumor emboli	29 (8.9%)	23 (21.9%)	6 (2.7%)	< 0.0000001
Multifocality of tumor	68 (20.8%)	27 (25.7%)	41 (18.5%)	0.135888
ER positive	281 (85.9%)	90 (85.7%)	191 (86.0%)	0.948689
PR positive	243 (74.3%)	73 (69.5%)	170 (76.6%)	0.150501
HER2 positive	48 (14.7%)	18 (17.1%)	30 (13.5%)	0.718430
No date	1 (0.3%)	1 (1.0%)	0	
Number of dissected SLNs	2 (1–13)	2.9 (1–13)	2.7 (1–9)	0.244038
Number of involved SLNs	1.4 (1–6)	1.7 (1–6)	1.3 (1–4)	0.000001

Table I. Cont.

Data set	All patients (n = 327)	nSLN(+) (n = 105)	nSLN(-) (n = 222)	P-value
Number of SLNs without metastases	1.3 (0–11)	1.2 (0–11)	1.4 (0–8)	0.235988
Infiltration of SLN capsule	151 (46.2%)	75 (71.4%)	76 (34.2%)	< 0.0000001
Type of SLN metastasis:				0.000014
Micrometastasis	55 (16.8%)	4 (3.8%)	51 (23.0%)	
Metastasis > 2 mm	272 (83.2%)	101 (96.2%)	171 (77.0%)	
SLN mode:				0.007666
HP	278 (85.0%)	97 (92.4%)	181 (81.5%)	
IHC	49 (15.0%)	8 (7.6%)	41 (18.5%)	
Methods used for SLN metastasis detection:				0.577424
Intraoperative examination	205 (62.7%)	78 (74.3%)	127 (57.2%)	
Final examination	99 (30.3%)	18 (17.1%)	81 (36.5%)	
Without intraoperative examination	23 (7.0%)	9 (8.6%)	14 (6.3%)	
Mean Ki-67 value	21.7 (1–99)	22.8 (1–85)	21.1 (1–99)	0.863708
No date	84 (25.7%)	25 (23.8%)	59 (26.6%)	
Molecular type of breast cancer – St Gallen 2011:				0.867930
Luminal A	94 (28.7%)	27 (25.7%)	67 (30.2%)	
Luminal B1	105 (32.1%)	35 (33.3%)	70 (31.5%)	
Luminal B2 – HER2(+)	35 (10.7%)	13 (12.4%)	22 (9.9%)	
ERBB2(+)	13 (4.0%)	5 (4.8%)	8 (3.6%)	
Basal-like	27 (8.3%)	9 (8.6%)	18 (8.1%)	
No date	53 (16.2%)	16 (15.2%)	37 (16.7%)	

HP – histopathological examination, cTNM – TNM classification of clinical stage assessment, FNB – fine needle biopsy, CNB/VAB – core needle biopsy/vacuum-assisted biopsy, IDC – invasive ductal carcinoma, ILC – invasive lobular carcinoma, G – grade of histological malignancy of tumor, ER – estrogen receptors, PR – progesterone receptors, IHC – immunohistochemical examination, HER2 – status of overexpression/amplification of HER2 receptor, nSLN(+) – non-sentinel lymph nodes metastases, nSLN(-) – non-sentinel lymph node without metastases, p – level of significance p.

Table II. Clinical and epidemiological data used in the new prognostic system

Data set	Factor	Numerical weight of factor
Epidemiological data	Bilateral breast cancer	1.464457
	Familial breast cancer	1.423244
	Estrogen hormone therapy	1.408682
Primary tumor features	Palpability of tumor	1.572449
	HER2 status	1.532806
	Lesion multifocality	1.486024
	Grade of histological malignancy – G	1.439505
	Molecular type of tumor	1.257715
	Comedo components	1.229792
	Localization of tumor	1.210360
	Histological type of tumor	1.116262
	Ki-67 value	1.021498
	ER receptor status	1.000000
PR receptor status	1.000000	
Details of diagnostic and therapeutic management	Infiltration of SLN capsule	2.408308
	Presence of intravascular tumor emboli	2.216140
	Type of SLN metastasis	1.000000

in a statistically significant manner, the developed nomogram included three out of six of the above-mentioned variables (SLN capsule infiltration, size of SLN metastasis, tumor emboli). In the case of the remaining variables, statistical calculations included another 14 analyzed factors – Table II.

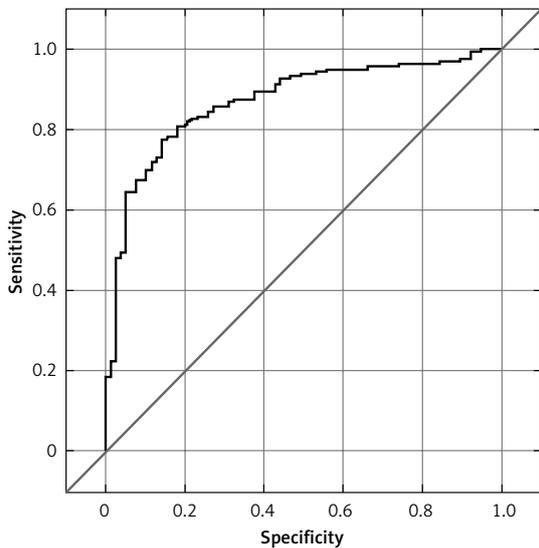
An AUC coefficient of 0.87 was obtained (95% confidence interval (CI): 0.81–0.92). Sensitivity was 69%, specificity 86%, accuracy 80%, positive predictive value (PPV) 70% and negative predictive value (NPV) 15% (retrospective group).

For the MSKCC nomogram, the calculated AUC value was 0.71 (95% CI: 0.65–0.78), for Stanford 0.68 (95% CI: 0.61–0.74), for Tenon 0.67 (95% CI: 0.61–0.73). Figures 2–5 show ROC curves for particular computational models.

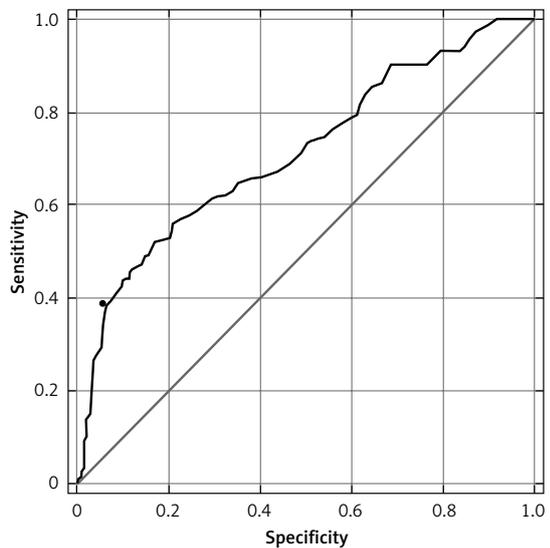
Clinical value of the new system was validated by means of a prospective analysis of a group of patients subjected to SLNB after the system had been developed. Sensitivity was 77%, specificity 46%, accuracy 66%, PPV 72% and NPV 48% (prospective group).

### Discussion

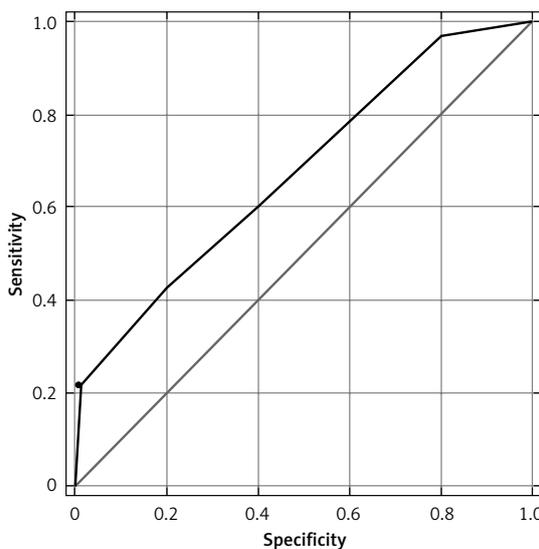
Methods of statistical calculations used to create the previously published prognostic tests were based on a multivariate analysis of some selected variables. Data included in that analysis concerned clinical parameters which significantly increase the rate of finding metastatic lesions in nSLN [9, 10, 17, 24]. However, it seems that using that kind of methodology of calculation could be



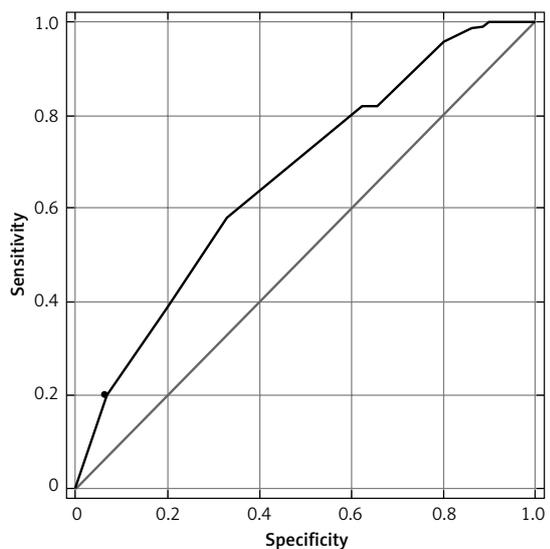
**Figure 2.** ROC curve – new nomogram – BRDA (AUC = 0.879)



**Figure 3.** ROC curve – MSKCC nomogram (AUC = 0.713)



**Figure 4.** ROC curve – Stanford nomogram (AUC = 0.676)



**Figure 5.** ROC curve – Tenon nomogram (AUC = 0.666)

a direct cause of problems with obtaining higher values of the AUC coefficient than the ones already obtained (including limitations concerning sensitivities and specificities of particular nomograms). This was the cause of lack of progress in developing new tests.

Using more sophisticated mathematical methods (artificial neural networks) allowed better results to be achieved, especially concerning the value of the AUC coefficient (and thus, sensitivity and specificity of the developed system).

The observations presented above corroborate the results of probability calculations concerning occurrence of metastatic nSLNs obtained with three other prognostic tools (MSKCC, Tenon, Stanford). In the analyzed group of patients (retrospective group) only the MSKCC nomogram obtained AUC values exceeding the expected level of 0.70. Two other systems scored less satisfactory results.

SLN(+) patients diagnosed with metastases not exceeding 2 mm in size (ITC, micrometastases) do not require ALND as complementary surgery [25, 26]. The results of the randomized ACOSOG Z0011 trial [27] by Giuliano *et al.* and the panel expert recognition for the therapeutic option suggested in that study gained at a conference in St Gallen [25, 28] increased the possibility of axillary conservative treatment of selected patients with SLN micrometastases. Use of nomograms (especially those with the highest prognostic value) can make the choice of further treatment notably easier.

Due to the method used for scoring of evaluated variables and the type of predicted risk of nSLN metastases, this system is considered a nomogram. It was based on multivariate analysis of available clinical data conducted using an artificial neural network. Calculations estimate the probability of occurrence of the predicted event (presence of nSLN metastases) for each individual patient.

Clinical parameters most frequently used in the previously developed statistical tools included the size of the primary tumor and the type of metastatic lesion in SLN [9, 10, 17–24]. In these calculations, both variables showed a statistically significant influence on the probability of finding metastatic nSLNs (univariate analysis). However, among the data evaluated in the new nomogram, only the latter parameter turned out to be decisive, while most of the variables used by the artificial neural network had a *p*-value of less than 0.05.

The expression of estrogen and progesterone receptors and overexpression of HER2 in breast cancer patients are important predictive and prognostic factors [29].

Determination of the ER, PgR, HER2, and Ki-67 status is essential in order to divide invasive breast cancers into biological types [30]. Defining which group the cancer belongs to influences

planning of further treatment. Assumptions concerning mainly the details of systemic treatment were included in generally accepted standards of treatment of patients with breast cancer. Clinical relevance of individual prognostic factors (ER, HER2, histological grading) was also taken into account [25, 28, 30–34].

Molecular type of tumor has been tested by other groups for association with nSLN metastasis [9, 10, 18], but there seems to be no significant correlation between molecular type and metastasis. The Ki-67 index was also evaluated for prediction of nSLN metastasis, but it did not significantly correlate with nSLN metastases [18]. Inclusion of the value of the Ki-67 mitotic index and biological type of breast cancer is therefore an additional measure of innovation of the examined calculation method.

In the group of prospectively analyzed patients (stage of initial clinical evaluation of the new nomogram) the increase in sensitivity and PPV of 77% and 72% vs. 69% and 70%, respectively (for the retrospective group) was observed. Significantly lower specificity (46% vs. 86%) and accuracy (66% vs. 80%) were found. This means that a patient identified with the new computational model as suspicious – nSLN(–) – does not require verification of that diagnosis in an invasive way (surgery). On the other hand, suspected nSLN(+) may be a vicious circle in half of the patients and thus requires further diagnostics (ALND).

The presented assumptions require further verification through use of the new model in a larger group of prospectively studied patients.

Apparent shortcomings of this new prognostic tool – a large number of variables and need for employing an artificial neural network for calculations – are in fact its advantages. They allow for acquiring a high AUC value, which was unprecedented in previous numerical systems. Therefore, the calculated probability of occurrence of nSLN metastasis strongly correlated with the results of postoperative histopathological examination.

However, the complex statistical analyses resulting from the chosen method of data processing will soon be replaced by the on-line calculator available on the site of Bydgoszcz Oncology Center ([www.cobydgoszcz.pl](http://www.cobydgoszcz.pl)). The availability of this tool will facilitate, in our center as well, the use of a scoring system in everyday clinical practice and in prospective studies.

The nomogram, following the example of previous solutions of this type, received its own name – BRDA, which is an acronym for Before Rapid Dissection Answer. The name of the test also refers to the specifics of the geographical location of Bydgoszcz Oncology Center.

In conclusion, in the analyzed group of patients, only the MSKCC nomogram and the new model

for prediction of nSLN involvement exhibited AUC values exceeding the expected value of 0.70. To develop the new test, variables such as biological tumor subtype and Ki-67 index value were used. Both factors are known to be of predictive value for assessment of treatment results among breast cancer patients. However, until now they have not been used to predict the presence of nSLN metastatic lesions.

The BRDA nomogram performs well in prospective validation on patient series. The overall assessment of clinical usefulness of this test will be possible after applying it in prospective studies. It should also be used in other patient populations.

### Conflict of interest

The authors declare no conflict of interest.

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