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RESEARCH

Multi-Institutional Comparison of Non-sentinel Lymph Node Predictive Tools in Breast Cancer Patients with High Predicted Risk of Further Axillary Metastasis

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Abstract Although axillary lymph node dissection (ALND) has been the standard intervention in breast cancer patients with sentinel lymph node (SLN) metastasis, only a small proportion of patients benefit from this operation, because most do not harbor additional metastases in the axilla. Several predictive tools have been constructed to identify patients with low risk of non-SLN metastasis who could be candidates for the omission of ALND. In the present work, predictive nomograms were used to predict a high (>50 %) risk of non-SLN metastasis in order to identify patients who would most probably benefit from further axillary treatment. Data of 1000 breast cancer patients with SLN metastasis and completion ALND from 5 institutions were tested in 4 nomograms. A subset of 313 patients with micrometastatic SLNs were also tested in 3 different nomograms devised for the micrometastatic population (the high risk cut-off being 20 %). Patients with a high predicted risk of non-SLN metastasis had higher rates of

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metastasis in the non-SLNs than patients with low predicted risk. The positive predictive values of the nomograms ranged from 44 % to 64 % with relevant inter-institutional variability. The nomograms for micrometastatic SLNs performed much better in identifying patients with low risk of non-SLN involvement than in high-risk-patients; for the latter, the positive predictive values ranged from 13 % to 20 %. The nomograms show inter-institutional differences in their predictive values and behave differently in different settings. They are worse in identifying high risk patients than low-risk ones, creating a need for new predictive models to identify high-risk patients.

Keywords Sentinel lymph node · Non-sentinel lymph node · Breast cancer · Nomogram · High risk · Axillary lymph node dissection

Introduction

Lymph node status is still considered one of the most important prognosticators of breast cancer [1]. The introduction of lymphatic mapping and sentinel lymph node (SLN) biopsy has completely changed the practice of nodal staging of breast carcinomas, allowing a selective policy and restricting axillary lymph node dissection (ALND) to SLN-positive patients. As the majority of SLN-positive patients harbor no further metastatic lymph nodes in their axilla, the need for a selective approach to routine completion ALND has also been growing. Several predictive tools, including nomograms, scores and others have been created to define a subset of SLN-positive patients with a low risk of further nodal metastasis in the axilla allowing for the omission of completion ALND [2–14]. These predictive tools vary to some extent in the variables entered in their mathematical models, in the variables considered important in predicting non-SLN (NSLN) involvement and the proportion of cases classified as having a low risk of NSNL positivity. Neither of them is perfect, and as assessed by ROC curves, the area under the curve is generally around the range of 0.7 to 0.8 [15].

Owing to the high rate of negative NSLNs following routine completion ALND, several surgeons have abandoned this practice. An analysis of the National Cancer Database suggested that about one fifth of the nearly hundred thousand SLN-positive breast cancer patients had SLN biopsy only [16]. A Survival Epidemiology and End Results based analysis had very similar findings with 16 % of the patients having SLN biopsy alone [17]. The early results of the American College of Surgeons Oncology Group trial Z-0011 have supported this approach: in a well described subset of patients (having breast conserving surgery followed by whole breast irradiation from tangential fields (including the axilla), having limited SLN involvement, and receiving adjuvant systemic therapy in most cases) the addition of completion ALND did not significantly change the 5-year overall survival rates [18]. Although all experts suggest that the results cannot be extrapolated to other subset of patients (e.g. those undergoing mastectomy or neoadjuvant therapies), the need for completion ALND has been questioned in a large subset of breast cancer patients. In the future, at least for a subset of patients, ALND may be considered to be restricted to those with a high risk of NSLN metastasis.

Although in general, predictive tools have been developed to identify the subset of patients with low risk of NSLN involvement, the nomograms can also be used to identify high risk patients, but have seldom been used in this context. In a recent study, we demonstrated that the variables included in the nomograms or scores predicting a low risk of NSLN involvement showed significant inter-institutional variability, and therefore the best predictive tool may be different from institution to institution [19]. In the present analysis we looked at the value of several nomograms in the context of patients at the higher end of the risk scale in a multi-institutional setting.

Materials and Methods

The five participating institutions have submitted data of 200 SLN-positive breast cancer patients with completion ALND as described previously [19]. Briefly, the following variables were collected: tumor size, tumor histological type, tumor nuclear and histological grade, lymphovascular invasion, SLN metastasis size and staging category, method of SLN metastasis detection, extracapsular invasion, number of positive and negative SLNs, number of negative and positive NSLNs.

These data were entered in the following predictive tools: the Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram [2] available on line at http://www.mskcc.org/mskcc/html/15938.cfm, the Stanford nomogram [8] available on line at https://www3-hrpdcc.stanford.edu/nsln-calculator, the MD Anderson nomogram available on line at http://www3.mdanderson.org/app/medcalc/bc_nomogram2/index.cfm?pagename=nsln and the Masaryk nomogram [12].

High risk patients were defined with a predicted risk of NSLN involvement greater than 50 %. The performance of the nomograms in predicting high risk patients was characterized by defining the positive predictive value of the test, although specificity, sensitivity and the false-negative rate (the proportion of patients predicted to have up to 50 % risk of NSLN involvement, but finally found to have metastases on completion ALND among all NSLN positive patients) have also been determined. The area under the empirical

receiver operating characteristic (ROC) curves have been calculated with an on-line calculator developed by the Johns Hopkins University, Baltimore, Maryland (http://www.rad.jhmi.edu/jeng/javarad/roc/JROCFITi.html, last accessed March 25, 2012). Three specific risk percentage defined data subsets were used to obtain all curves: low risk patients (with up to 10 % predicted risk of NSLN metastasis), high risk patients as defined above, and the "grey zone" patients falling in between. Statistical comparisons between the areas under different ROC curves were done with the VassarStats software (Vassar College, Poughkeepsie, NY, USA).

The subset of patients with micrometastasis were analyzed similarly, but with nomograms devised for this low-risk population, i.e. the French micrometastasis nomogram first described by Houvenaeghel et al. [11], the Helsinki micrometastasis nomogram [14] and the revised French nomogram [20]. For these patients the high risk limit was set at above 20 % estimated risk of NSLN metastasis.

All predictive tools have also been characterized by "reverse" positive predictive value, sensitivity, specificity and false-negative rate for the low risk patients. These values take into account that the given nomogram, in the setting of low-risk patients, serves as a test for identifying patients who have no further metastasis, and finding these patients is the positive yield of the test. Therefore a patient with no NSLN metastasis and predicted to have no such metastasis (more precisely having not more than 10 % chance for them) reflects a true positive test (despite a negative ALND nodal status), and a similar patient with a predicted risk above the low-risk cut off value of 10 % is considered to reflect a false-negative test. Because such an interpretation is unusual in the SLN related literature, we preferred to label these statistical values of test performance as "reverse". This method was chosen to allow a direct comparison of the performance of the same nomogram in the low-risk and the high-risk patient group. At the high-risk end, the nomogram is interpreted as a test looking for the identification of patients with positive NSLNs, and a patient with a positive NSLN status and a high (>50 % in general and >20 % for the micrometastatic patients) predicted risk of NSLN involvement reflects a true positive test.

Results

The numbers of cases falling into the low-risk, high-risk and intermediate risk groups for each nomogram and center are shown in Table 1. The proportion of cases falling into the arbitrarily defined high-risk category showed variations both between different nomograms and between institutions using the same nomogram, and ranged from 17 % to 61 %. Although the (reverse) sensitivities of the nomograms for the low-risk setting were much lower than the sensitivities for the high-risk setting, all other parameters assessed were worse for the identification of high-risk patients, including the positive predictive values and the false-negative rates, clinically considered the most important characteristics. There were also relevant inter-institutional fluctuations in the positive predictive values (and other parameters) of each nomogram (Table 1).

Although the overall values suggested that the Masaryk nomogram could be the best among the 4 nomograms tested, with relatively high positive-predictive value and specificity plus a low false-negative rate and an area under the ROC curve of 0.686, this predictive tool requires the size of the SN metastasis as a continuous variable which was not available for all the five datasets. The performance of this nomogram showed the highest differences between the investigated institutions, as shown by significant differences in the areas under the ROC curves (Table 1). Significant inter-institutional differences in the area under the ROC curves were also noted with other nomograms.

On the basis of the validation datasets of identical size, and the positive predictive values the MSKCC nomogram could be the best predictive tool in the high-risk setting for centers A and E, whereas center B would have mostly benefited from the MD Anderson nomogram. Center C had similar positive predictive values for three nomograms, and center D had too low positive predictive values for all the nomograms assessed.

In the micrometastatic setting, few patients had greater than 20 % estimated risk of NSLN positivity. Of the 313 patients with micrometastasis in their SLNs only 4 (1 %) fell into this category with the Helsinki nomogram, 24 (8 %) with the original French micrometastasis nomogram and 65 (21 %) with the revised French nomogram. This is why the analysis concentrated on patients falling outside the low-risk patients (non-low-risk patients with a nomogram based possibility of NSLN involvement greater than10 %).

The comparison of the reverse positive predictive values for the low risk patients and the positive predictive values for the high risk patients demonstrates that the micrometastasis nomograms perform best in the first setting (i.e. low risk patients), as shown in Table 2. For the non-low-risk patients, the positive predictive values are much lower: they range from 0.13 to 0.20 per nomogram when including all institutions together. The predictive values show wider fluctuations when the institutions are looked at individually. These fluctuations are partly related to low case numbers as reflected by the wide 95 % confidence intervals of the proportions of observed NSLN positive cases. The false-negative rates are also rather high for each of the 3 micrometastatic nomograms and the areas under the empirical ROC curves also suggest less than optimal performance of the predictive tools for all the risk spectrum of patients with micrometastatatic SLNS.

Table 1 Characterization of nomograms predicting for NSN status in SN metastatic cases

Predictive tool Center	≤10 % NEG	≤10 % POZ	>10 % ≤50 % NEG	>10 % ≤50 % POS	>50 % NEG	>50 % POS	Prop High risk	Actual proportion of HR POS	LR Reverse SENS	LR Reverse SPEC	LR Reverse PPV	LR Reverse FNR	HR SENS	HR SPEC	HR PPV	HR FNR	Area under ROC curve
MSKCC nomogram																	
A	17	6	90	22	18	47	65/200 (0.33)	47/65 (0.72; 0.60-0.82)	0.14	0.92	0.74	0.86	0.63	0.86	0.72	0.37	0.732*
B	11	1	91	24	43	30	73/200 (0.37)	30/73 (0.41; 0.31-0.53)	0.08	0.98	0.91	0.92	0.55	0.70	0.41	0.46	0.635
C	31	7	89	37	10	26	36/200 (0.18)	26/36 (0.72; 0.56-0.84)	0.24	0.90	0.82	0.76	0.37	0.92	0.72	0.63	0.676
D	33	5	86	33	28	15	43/200 (0.22)	15/43 (0.35; 0.22-0.50)	0.22	0.91	0.87	0.78	0.28	0.81	0.35	0.72	0.588*
E	10	2	107	45	13	23	36/200 (0.18)	23/36 (0.64; 0.48-0.78)	0.08	0.97	0.83	0.92	0.33	0.90	0.64	0.67	0.627
All	102	21	463	161	112	141	253/1000 (0.25)	141/253 (0.56; 0.50-0.62)	0.15	0.93	0.83	0.85	0.44	0.84	0.56	0.56	0.650
Stanford nomogram																	
A	17	2	51	26	53	51	104/200 (0.52)	51/104 (0.49; 0.40-0.59)	0.14	0.98	0.90	0.86	0.65	0.56	0.49	0.35	0.621
B	46	3	57	20	42	32	74/200 (0.37)	32/74 (0.43; 0.33-0.55)	0.32	0.95	0.94	0.68	0.58	0.71	0.43	0.42	0.693
C	34	7	59	25	37	38	75/200 (0.38)	38/75 (0.51; 0.40-0.62)	0.26	0.90	0.83	0.74	0.54	0.72	0.50	0.46	0.653
D	12	1	55	16	80	36	116/200 (0.58)	36/116 (0.31; 0.23-0.40)	0.08	0.98	0.92	0.92	0.68	0.46	0.31	0.32	0.576
E	10	1	56	12	64	57	121/200 (0.61)	57/121 (0.47; 0.38-0.56)	0.08	0.99	0.91	0.92	0.81	0.51	0.47	0.19	0.664
All	119	14	278	99	276	214	490/1000 (0.49)	214/490 (0.44; 0.38-0.49)	0.18	0.96	0.90	0.82	0.65	0.59	0.44	0.35	0.64
Masaryk nomogram																	
A	17	2	82	30	22	47	69/200 (0.35)	47/69 (0.68; 0.56-0.78)	0.14	0.98	0.90	0.86	0.60	0.82	0.68	0.41	0.724*
C	24	6	95	29	11	35	46/200 (0.23)	35/46 (0.76; 0.62-0.86)	0.19	0.91	0.80	0.82	0.50	0.92	0.76	0.50	0.714*
D	4	1	114	32	28	21	49/200 (0.25)	21/49 (0.43; 0.30-0.57)	0.03	0.98	0.80	0.97	0.39	0.81	0.43	0.61	0.599*
All	45	9	291	91	61	103	164/600 (0.27)	103/164 (0.63; 0.55-0.70)	0.11	0.96	0.83	0.89	0.51	0.85	0.63	0.49	0.686
MDA nomogram																	
A	4	0	95	29	22	50	72/200 (0.36)	50/72 (0.69; 0.58-0.79)	0.03	1.00	1.00	0.97	0.63	0.82	0.69	0.37	0.731*
B	28	1	102	28	15	26	41/200 (0.21)	26/41 (0.63; 0.48-0.76)	0.19	0.98	0.97	0.81	0.47	0.90	0.63	0.53	0.727*
C	23	3	98	35	9	32	41/200 (0.21)	32/41 (0.78; 0.63-0.88)	0.18	0.96	0.89	0.82	0.46	0.93	0.78	0.54	0.722*
D	6	3	121	36	20	14	34/200 (0.17)	14/34 (0.41; 0.26-0.58)	0.04	0.94	0.67	0.96	0.27	0.86	0.41	0.74	0.554*
E	10	2	105	49	15	19	34/200 (0.17)	19/34 (0.56; 0.39-0.71)	0.08	0.97	0.83	0.93	0.27	0.89	0.56	0.73	0.593*
All	71	9	521	177	81	141	222/1000 (0.22)	141/222 (0.64; 0.57-0.70)	0.11	0.97	0.89	0.90	0.43	0.88	0.64	0.57	0.673

* Significant differences between at least two of the marked areas under the ROC curves

Table 2 Characterization of the NSN predictive tools for SN micrometastatic cases

Predictive tool Center	≤10 % NEG	≤10 % POS	>10 % ≤20 % NEG	>10 % ≤20 % POS	>20 % NEG	>20 % POS	LR Reverse SENS	LR Reverse SPEC	LR Reverse PPV	LR Reverse FNR	Proportion Non-Low risk	Actual rate of NSLN metastasis in the NON-low risk patients (proportion; 95 % CI)	Non-LR SENS	Non-LR SPEC	Non-LR PPV	Non-LR FNR	Proportion HR	Actual proportion of HR POS	SENS HR	SPEC HR	PPV HR	FNR HR	Area under ROC curve
French micrometastasis nomogram																							
A	22	2	27	6	0	0	0.45	0.75	0.92	0.55	33/57 (0.58)	6/33 (0.18; 0.08-035)	0.75	0.45	0.18	0.25	0/57 (0.00)	0	0.00	1.00	NA	1.00	0.599
B	24	1	49	4	6	1	0.30	0.83	0.96	0.70	60/85 (0.71)	5/60 (0.08; 0.03-0.18)	0.83	0.30	0.08	0.17	7/85 (0.08)	1/7	0.17	0.92	0.14	0.83	0.598
C	20	3	35	5	11	0	0.30	0.63	0.87	0.70	51/74 (0.69)	5/51 (0.10; 0.04-0.21)	0.63	0.30	0.10	0.38	11/74 (0.15)	0/11	0.00	0.83	0.00	1.00	0.411*
D	23	2	31	5	2	0	0.41	0.71	0.92	0.59	38/63 (0.60)	5/38 (0.13; 0.05-0.28)	0.71	0.41	0.13	0.29	2/63 (0.03)	0/2	0.00	0.96	0.00	1.00	0.549
E	9	0	18	3	2	2	0.31	1.00	1.00	0.69	25/34 (0.74)	5/25 (0.20; 0.08-0.40)	1.00	0.31	0.20	0.00	4/34 (0.12)	2/4	0.40	0.93	0.50	0.60	0.758*
All	98	8	160	23	21	3	0.35	0.77	0.93	0.65	207/313 (0.66)	26/207 (0.13; 0.09-0.18)	0.76	0.35	0.13	0.24	24/313 (0.08)	3/24	0.09	0.93	0.13	0.91	0.558
New French nomogram																							
A	23	3	18	3	8	2	0.47	0.63	0.89	0.53	31/57 (0.54)	5/31 (0.16; 0.07-0.33)	0.63	0.47	0.16	0.38	10/57 (0.18)	2/10	0.25	0.84	0.20	0.75	0.562
B	56	3	14	2	9	1	0.71	0.50	0.95	0.29	26/85 (0.31)	3/26 (0.12; 0.03-0.30)	0.50	0.71	0.12	0.50	10/85 (0.12)	1/10	0.17	0.89	0.10	0.83	0.6
C	26	4	21	1	19	3	0.39	0.50	0.87	0.61	44/74 (0.59)	4/44 (0.09, 0.03-0.22)	0.50	0.39	0.09	0.50	22/74 (0.30)	3/22	0.38	0.72	0.14	0.63	0.488
D	25	2	19	4	12	1	0.45	0.71	0.93	0.55	36/63 (0.57)	5/36 (0.14; 0.06-0.29)	0.71	0.45	0.14	0.29	13/63 (0.21)	1/13	0.14	0.79	0.08	0.86	0.543
E	9	0	13	2	7	3	0.31	1.00	1.00	0.69	25/34 (0.74)	5/25 (0.20; 0.08-0.40)	1.00	0.31	0.20	0.00	10/34 (0.29)	3/10	0.60	0.76	0.30	0.40	0.741
All	139	12	85	12	55	10	0.50	0.65	0.92	0.50	162/313 (0.52)	22/162 (0.14; 0.09-0.20)	0.65	0.50	0.14	0.35	65/313 (0.21)	10/65	0.29	0.80	0.15	0.71	0.582
Helsinki nomogram																							
A	43	7	6	1	0	0	0.88	0.13	0.86	0.12	7/57 (0.12)	1/7 (0.14; 0.01-0.53)	0.13	0.88	0.14	0.88	0/57 (0.00)	0	0.00	1.00	NA	1.00	0.501*
B	66	1	13	4	0	1	0.84	0.83	0.99	0.17	18/85 (0.21)	5/18 (0.28; 0.12-0.51)	0.83	0.84	0.28	0.17	1/85 (0.01)	1/1	0.17	1.00	1.00	0.83	0.848*
C	57	7	8	1	1	0	0.86	0.13	0.89	0.14	10/74 (0.14)	1/10 (0.10; 0.00-0.43)	0.13	0.86	0.10	0.88	1/85 (0.01)	0/1	0.00	0.99	0.00	1.00	0.493*
D	40	4	14	3	2	0	0.71	0.43	0.91	0.29	19/63 (0.30)	3/19 (0.16; 0.05-0.38)	0.43	0.71	0.16	0.57	2/63 (0.03)	0/2	0.00	0.96	0.00	1.00	0.563*
E	28	4	1	1	0	0	0.97	0.20	0.88	0.03	2/34 (0.06)	1/2 (0.50; 0.09-0.91)	0.20	0.97	0.50	0.80	0/34 (0.00)	0	0.00	1.00	NA	1.00	0.582
All	234	23	42	10	3	1	0.84	0.32	0.91	0.16	56/313 (0.18)	11/56 (0.20; 0.11-0.32)	0.32	0.84	0.20	0.68	4/313 (0.01)	1/4	0.03	0.99	0.25	0.97	0.581

* Significant differences between at least two of the marked areas under the ROC curves

CI confidence interval, *FNR* false-negative rate, *HR* high-risk, *LR* low-risk, *NEG* negative, *NSLN* non-sentinel lymph node, *POS* positive, *PPV* positive predictive value, *ROC* receiver operating characteristic, *SENS* sensitivity, *SPEC* specificity

Discussion

Because the majority of patients with positive SLNs has no further metastasis in the axilla, routinely performing ALND in these patients results in overtreatment in most such patients. A selective approach has been clearly needed, and predictive tools such as nomograms have been created to identify patients with the lowest risk of NSLN metastasis [2–14, 20]. Many of these tools have been validated either with independent data coming from the institutions creating the predictive model or with completely independent datasets.

In an earlier study we demonstrated significant inter-institutional variations in the values and proportions of variables used in models and predictive tools of NSLN metastasis, suggesting that the models may work differently from institution to institution, and that individual validation could be a good approach for finding the best predictive model available.

Although the models were created to identify patients at low-risk for NSLN metastasis, current trends may create the need for identifying the opposite end of the spectrum and identify patients with a high risk of NSLN involvement as a set of patients who would most likely benefit from completion ALND.

Our results show that the predictive tools have lower positive predictive values to identify patients with more than 50 % risk of NSLN metastasis than to identify patients with up to 10 % risk of NSLN positivity, what may mean that different predictive models might be required for better identifying higher risk patients. There were also relevant inter-institutional fluctuations in the positive predictive values (and other parameters) of each nomogram, suggesting that these predictive tools might also perform differently in different institutions (Table 1), and institutional validation might be of some help in choosing the best performing tool in the given setting.

Patients with micrometastatic SLNs are considered to have low risk of NSLN positivity [21]. However, in a previous single institutional analysis, it was found that patients not included in the group with low predicted risk of NSLN involvement had a rather high rate (0.30; 6/20) of NSLN positivity, although the case numbers were low [22]. This is why it was felt important to test the hypothesis further, and look at the higher risk end of SLN micrometastatic breast cancer patients and see whether there was really a subset with a substantial rate of NSLN metastasis influenced by factors other than the size of the SLN metastasis (e.g. lymphovascular invasion, tumor size etc.). Although the non-low-risk patients had higher rates of NSLN involvement than the low risk patients, altogether their NSLN positivity rate was still low. This finding alone may suggest that SLN micrometastatic patients do not require completion ALND, which is in accordance with the last St Gallen consensus recommendation [23]. On the other hand, an individualized patient centered decision making on ALND taking into account patients' choice and perception of acceptable risks of potential undertreatment and/or overtreatment can also be an option, and in such cases identifying those with higher risk may be important. As the whole micrometastatic group has a low overall rate of NSLN metastasis, the predictive tools seem to perform worse in the higher risk subset, and this is also evidenced by a recent Danish study [24]. Nevertheless, inter-institutional differences were evidenced by different positive predictive values and areas under the ROC curves in this subset too (Table 2).

In summary, this inter-institutional validation of nomograms predicting NSLN status in SLN positive patients at the high risk end of the spectrum shows that the predictive models tested perform better at the low risk end. Inter-institutional variations in the performance of the nomograms exists at the high risk end too, and therefore if one wishes to use a predictive model in the setting of identifying patients with the highest chances of metastasis beyond the SLNs, it is advised to make a retrospective validation of several models and chose the nomogram performing the best in the given institution. The results also support the need to create specific predictive tools to find patients with the highest likelihood of NSLN metastasis.

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