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Research Article

Validation of a Predictive Tool for Assessing the Risk of Non-Sentinel Node Metastases in Breast Cancer Patients with Sentinel Lymph Node Metastasis

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Abstract

Background: An original predictive tool based on the primary tumor's and sentinel node's features able to assess the risk and the extent of nodal metastases into residual axillary lymph nodes after sentinel node biopsy was proposed.

Materials and Methods: A training set of 1,836 breast cancer patients was assessed to select those clinico-pathological factors to be included into a multivariate model that was validated in 201 patients.

Results: T stage category ($P = .018$); histological grading ($P = .048$), and number of metastatic SN ($P = .027$) were included into the predictive model and tested into the validation set (AUC of the ROC curve was .638; $P = .001$). Four categories of patients, based on the individual probability to have one or more additional positive nodes, were identified.

Conclusion: This predictive tool may aid in the decision-making as for completion axillary dissection in breast cancer patients with sentinel node metastasis.

Keywords: Breast Cancer; Sentinel Lymph Node Biopsy; Axillary Dissection

Introduction

Until a few decades ago, Axillary Lymph Node Dissection (ALND) was considered the milestone in the surgical treatment of breast cancer patients. Thanks to the proposal of the Sentinel Lymph Node Biopsy (SLNB) that proved effective first in melanoma and then in breast cancer patients for the pathological staging of regional lymph nodes, the systematic use of ALND has gradually lost its staging and therapeutic role [1-6]. Actually, in 38% to 67% of patients with node-positive disease the only tumor-involved lymph node is the sentinel lymph node (SN) so that most patients would not benefit at all from completion ALND [7-9]. As a matter of fact, the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial has demonstrated that SLNB-alone compared with ALND did not result in inferior loco-regional disease free and overall survival in patients with up to two sentinel lymph nodes (SNs) with metastases, notwithstanding the limitations of this study regarding the failure to achieve the target accrual, possible randomization imbalance favoring the SLND-alone group, and the inclusion of patients undergoing only breast-conserving surgery followed by whole-breast radiotherapy [10-13]. The same lack of therapeutic effectiveness of completion ALND was demonstrated in the IBCSG 23-01 trial in which patients with SN micro metastases only who did not undergo ALND had a very low (1%) incidence of axillary recurrence notwithstanding the rather high rate (13%) of non-sentinel node metastases detected in the ALND arm [14].

Although the therapeutic benefit from completion ALND in SLNB-positive seems at most negligible as for regional disease control, the prognostic information supplied by regional nodal staging might have an impact on the adjuvant treatment planning (chemo- and/or radiation therapy) because patients with four or more axillary lymph node metastases are at high risk of disease relapse, have a worse prognosis, and are more likely to receive additional chemotherapy as well as regional nodal irradiation [15-17].

While waiting for a more widespread consensus as for the need of a completion ALND in patients with SNs metastases, a standardized method to support the decision-making in these patients might be represented by a predictive tool based on the primary tumor's and SNs' features able to assess the risk and the extent of nodal metastases into residual axillary lymph nodes after SLNB (non-sentinel nodes, NSN). Recently, various models have been built up with the aim of predicting this risk but most of them are prone to perform differently in different institution [12,18-30]. For these reasons, a training set of 1,836 consecutive breast cancer patients undergoing surgery at our Breast Unit was assessed in order to select those clinico-pathological factors that could be included into a multivariate model able to predict additional disease into the axilla. This predictive tool was tested into a validation set of 201 patients undergoing SLNB and completion ALND at the same Institution with the aim of verifying its performance and matching it with two other validated predictive tools, that is the Breast Cancer Nomogramof the MD Anderson Cancer Center, and the Breast Cancer Nomogram of the Memorial Sloan Kettering Cancer Center [18-19].

Materials and Methods

Between January 2012 and December 2015, a retrospective assessment of the clinico-pathological features of 1,836 patients with early stage breast cancer, undergoing surgery at the Breast Unit of the IRCCS San Martino-IST Hospital in Genoa – Italy, was performed. A specific database was developed including known risk factors for additional axillary metastases after a tumor-positive SN, such as: i) clinical and histological data of the tumor (size, site, multifocality, histological type, Scarff-Bloom-Richardson (SBR) grade, presence of lymphovascular

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invasion, expression of estrogen and/or progesterone receptor status, Ki67 proliferative index, human epidermal growth factor receptor-2 (c-HER2) status, number of mitoses/mm^2); ii) histology of SNs (size of metastatic foci, that is micro- (> 0.2 mm) and macrometastasis (> 2 mm); extra-capsular extension; number of histologically-positive and -negative SNs; ratio of histologically positive SN to the total number of removed SNs) and NSNs at completion ALND (total number of retrieved lymph nodes, number of histologically-negative and -positive NSN).

As regards SN detection, a standard procedure was adopted, as previously described [5]. An intraoperative examination of the SN was performed in each patient; at frozen section examination, the SN was bisected along its major axis, and five sections cut at 20 μm intervals were obtained from each half. Three of these sections were stained with hematoxylin-eosin (H&E); if they were negative or doubtful, the other two sections were stained with AE1/AE3 antibodies to keratin. The SN was then processed routinely for permanent sections, and at least four additional sections were examined with H&E and immunochemistry (IHC). The ALND specimens were also examined according to the standard departmental protocol: the NSN were identified without clearance of the fat; all lymph node material was processed, stained, and examined; two H&E-stained sections from each half lymph node were examined, and IHC was not used to evaluate these sections. Pathological staging was defined according to the International Union against Cancer (UICC) TNM classifications of malignant tumors [31].

Generation of the Predictive Model

The training set of 1,836 patients was analyzed to test the association between clinico-pathological factors and presence of one or more additional positive NSN by means of Pearson Chi-square tests, Fisher's exact tests, and univariate logistic regressions. A multivariate logistic regression model was then fitted to the data including as covariates patient age, tumor histology, size and histologic grade, site, estrogen/progesterone receptors and HER-2 status, Ki67 activity, number of positive SNs. Initially, all variables were introduced into the model; those not statistically associated (P values greater than .05) with the presence of one or more additional positive NSN were removed by means of a step-down procedure based on the likelihood-ratio test. The logistic regression coefficients estimated for the variables left into the model were then used to compute the individual probability of the presence of one or more additional positive NSN for each patient in the sample.

First, a risk score for each patient was computed with the following formula: risk scorei = exp (b0 + b1x1i + b2x2i … + bnxni), where x1i , x2i ... xni, are the values of the covariates in the individual patient and b0b1 b2 ... bn are the coefficients estimated in the logistic regression model. The individual probability of the each patient to have one or more additional positive NSNs was computed as pi = (risk scorei/1 + risk scorei) x 100.

The individual probabilities were computed for all patients and subdivided by 10-points probability intervals (0-10%, 10-20%, etc.). The goodness-of-fit of the multivariate regression was assessed by the Pearson and the Hosmer-Lemeshow tests. The discrimination power of the model was quantified by the area under the Receiver Operating Characteristic (ROC) curve.

All statistical analyses were two-sided and performed with the SPSS package (version 20 for Windows, SPSS, Inc. Chicago, Ill). P values < .05 were considered significant.

Validation of the Predictive Model

Validation was performed using an independent set of 201 consecutive patients (validation set) undergoing SLNB with one or more metastatic SNs and completion ALND at our Breast Unit from January 2016 to February 2017. The coefficients estimated in the original model were applied to the validation set to determine the probability for each patient to have one or more additional positive NSN. The ability of the model to predict the presence of positive NSN was evaluated by comparing the probabilities estimated by the model with the actual observations in the validation set both at the group level (Pearson and the Hosmer-Lemeshow tests) and at the individual level by means of Receiver Operating Characteristic (ROC) curve.

Results

In the training set of 1836 patients, 556 of them underwent ALND and 265 (46.7%) had additional axillary metastases. Table 1 indicates the clinico-biological features of patients; the variables that were associated with additional metastases in univariate analysis with a P value less than .05 were included into the multivariate logistic model that is: T stage category; multifocality; lymphatic invasion; histological grade; total number of SN harvested, and number of positive SN.

Three variables were finally selected for inclusion into the predictive model, that is: T stage category (P = .018); histological grading (P = .048), and number of metastatic SN (P = .027) (Table 2). The following mathematical model was obtained from the logistic regression analysis in order to predict the presence of additional axillary metastases, with pi indicating the probability of NSN metastases:

risk scorei = exp (b0 + b1x1i + b2x2i + b3x3i)

where x1i = T stage, x2i = histological grade of the primary tumor, and x3i = number of positive SN; b0 is the value of the constant; b1, b2, and b3 are the corresponding coefficients estimated in the logistic regression model. The individual probability of each patient to have one

1oAUC	Std. Error	*P*	95% CI	
			Lower limit	Upper limit
,655	,027	,000	,602	,708

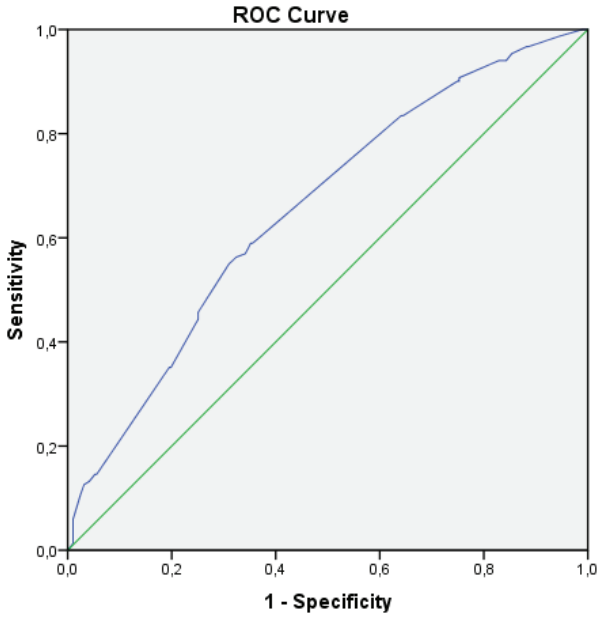

Figure 1: Predicted Probability in the training set of patients (*N* = 1,836).

Table 1: Univariate analysis comparing the clinico-pathological features of the patients undergoing completion ALND with or without additional lymph node metastases.

Clinico-biological features	No additional metastases in ALND (n = 265)	Additional metastases in ALND (n = 265)	All patients	*P*
Patient age (years)				
Mean (range)	60.28 (31-82)	61.56 (34-86)	60.4 (31-86)	0.41
Standard deviation	13.4	11.81	12.1	
T stage of the primary tumor				
Tmic/T1a	15 (5.4%)	5(2.0%)	20 (3.8%)	0.002
T1b	29 (10.4%)	18 (7.2%)	47 (8.9%)	
T1c	153 (55.0%)	98 (39.2%)	251 (47.5%)	
T2	72 (25.9%)	97 (38.8%)	169 (32.0%)	
T3	9 (3.3%)	32 (12.8)	41 (7.8%)	
Multifocality of the primary tumor				
No	231 (80.7%)	209 (77.7%)	440 (78.7%)	0.000
Yes	56 (19.3%)	60 (8.9%)	116 (21.3%)	
Lymphatic invasion in the primary tumor				
No	56 (19.3%)	31 (11.5%)	87 (15.5%)	0.000
Yes	125 (43.1%)	187 (69.3%)	312 (55.7%)	
n.a.	109 (37.6%)	52 (19.3%)	161 (28.8%)	
Vascular invasion in the primary tumor				
No	94 (32.4%)	112 (41.5%)	206 (36.8%)	.068
Yes	5 (1.7%)	6 (2.2%)	11 (2.0%)	
n.a.	191 (65.9%)	152 (56.3%)	343 (61.3%)	
Hormone receptor status				
ER+/PgR+	199 (71.8%)	183 (69.6%)	382 (70.7%)	0.184
ER+/PgR- or ER-/PgR+	35 (12.6%)	47 (17.9%)	82 (15.2%)	
ER-/PgR-	43 (15.5%)	33 (12.5%)	76 (14.1%)	
KI67				
≤15%	119 (42.7%)	110 (42.0%)	229 (42.3%)	0.875
> 15%	160 (57.3%)	152 (58.0%)	312 (57.7%)	
HER-2 status				
Negative	188 (68.4%)	172 (65.4%)	360 (66.9%)	0.462
+/++	52 (18.9%)	61 (23.2%)	113 (21.0%)	
+++	35 (12.7%)	30 (11.4%)	65 (12.1%)	
Histological grade of the primary tumor				
Grade I	32 (11.2%)	12 (4.5%)	44 (7.9%)	0.014
Grade II	177 (61.9%)	176 (65.7%)	353 (63.7%)	
Grade III	77 (26.9%)	80 (29.9%)	157 (28.3%)	
Histology of the primary tumor				
Ductal carcinoma	233 (80.1%)	210 (77.8%)	443 (79.8%)	0.38
Lobular carcinoma	31 (10.6%)	34 (12.6%)	65 (11.5%)	
Other	25 (8.6%)	23 (8.5%)	48 (8.7%)	
Number of sentinel nodes harvested				
Mean (range)	2.1 (1-4)	1.29 (1-3)		0.000
Standard deviation	1.81	1.61		
Number of positive sentinel nodes harvested				
1	190 (65.3%)	115 (43.4%)	305 (54.8%)	0.000
≥ 2	101 (34.7%)	150 (56.6%)	251 (45.2%)	

Legend: n.a., not available; HER-2, Human Epidermal Growth Factor Receptor 2; ER, Estrogen Receptor; ER -, ER ≤ 10%; PgR, Progesteron Receptor Progesteron; PgR -, PgR ≤ 10%.

Citation: Gipponi M, Fregatti P, Depaoli F, Murelli F, Ballestrero A, Guenzi M, et al. Validation of a Predictive Tool for Assessing the Risk of Non-Sentinel Node Metastases in Breast Cancer Patients with Sentinel Lymph Node Metastasis. Int J Surg 2018; 1:104.

Table 2: Odds ratio of the selected variables included into the predictive model.

Variable		B	Odds Ratio	95% CI	*P*
T Stage					0.018
	Tmic/T1a		1 (ref)	-	
	T1b	.325	1.384	0.322-5.952	
	T1c	.690	1.993	0.531-7.480	
	T2	1.326	3.766	0.988-14.352	
	T3	1.152	3.166	0.624-16.067	
Histological Grade					0.048
	1		1 (ref)	-	
	2	.996	2.707	1.079-6.794	
	3	.805	2.237	0.834-6.003	
N. of metastatic sN					0.027
	0		1 (ref)	-	
	1	.477	1.612	0.922-2.818	
	≥ 2	1.076	2.932	1.159-7.421	
Constant	-2.493				

Legend: CI, confidence interval; N, number; SN, sentinel node.

or more additional positive NSN was computed as pi = (risk scorei/1 + risk scorei) x 100.The AUC of the ROC curve for this training set of patients was .655 (P = .000) (Figure 1).

Hence, this predictive model was validated into the following set of 201 patients, and the corresponding AUC of the ROC curve was .638 (P = .001) (Figure 2). Moreover, when two other predictive tools, that is the Breast Cancer Nomogram of the MD Anderson Cancer Center and the Breast Cancer Nomogram of the Memorial Sloan Kettering Cancer Center, were applied to the 201 patients, a similar significant performance (P = .000) was observed with the former while the latter was not statistically significant. Table 3 reports the predictive probabilities of additional axillary lymph node metastases as observed in the validation set. Four categories of patients, based on the individual probability of each patient to have one or more additional positive NSNs, were identified

i) Log Score (LS) < -0.997: this category included 61 patients with 72.1% (44 out of 61) negative (that is, no additional lymph nodes at completion ALND), and 27.9% (17 out of 61) positive cases (that is, one or more additional lymph node metastases at completion ALND);

ii) LS ranging from -0.997 to -0.68: this category included 58 patients with 62.1% (36 out of 58) negative and 37.9% (22 out of 58) positive cases;

iii) LS ranging from -0.68 to -0.34: this category included 26patients with 50.0% (13 out of 26) negative and 50% (13 out of 26) positive cases;

iv) LS >-0.34: this category included 56 patients with 46.4% (26 out of 56) negative and 53.6% (30 out of 56) positive cases.

If only category i) is considered as "low risk", 61 patients could be spared an ALND. If categories i) and ii) were considered as "low risk", 119 patients could be spared an ALND with 67.2% (80 out of 119) true-negative and 32.8% (39 out of 119) false-negative cases. If categories i), ii), and iii) were considered as "low risk", 145 patients who could be spared an ALND with 64.2% (93 out of 145) true-negative and 35.8% (52 out of 145) false-negative cases.

Table 3: Predictive value of the model at the different cut-off levels.

			Axillary Lymph-Node Status at completion ALND			Total
			pN0	pN1	pN2-3	
Category Logscore	<28% (LS<-0.997)	N	44	14	3	61
		% in CatLog score	72,1%	22.9%	4.9%	100,0%
	28-34% (-0.997 to -0.68)	N	36	10	12	58
		% in CatLog score	62,1%	17,2%	20.7%	100,0%
	35-41% (-0.68 to -0.34)	N	13	7	6	26
		% in CatLog score	50,0%	26.9%	23.1%	100,0%
	>41% (LS > -0.34)	N	26	6	24	56
		% in CatLog score	46,4%	10.7%	42.9%	100,0%
Total		N	119	37	45	201
		% in CatLog score	59,2%	18.4%	22.4%	100,0%

Legend: LS, log score.

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AUC	Std Error	*P*	95% CI	
			Lower limit	Upper limit
,638	,040	,001	,560	,716

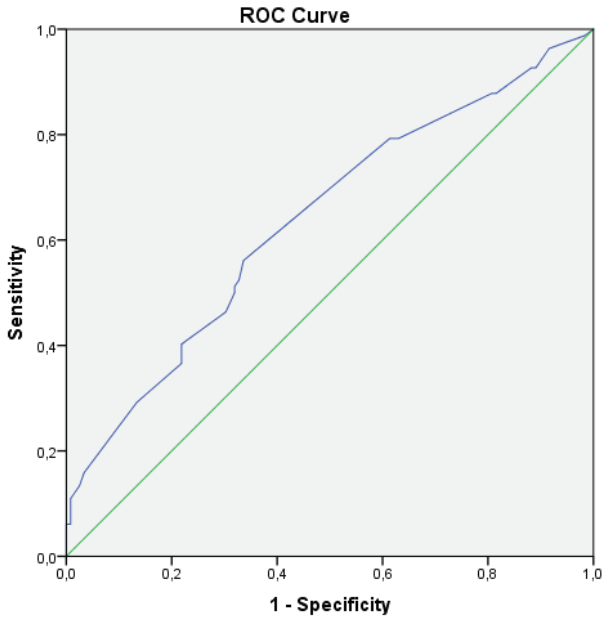

Figure 2: Predicted Probability in the validation set of patients (*N* = 201).

Discussion

Since the pioneering study of Fisher et al [32-33], the therapeutic benefit of ALND has been questioned; actually, the results of the NSABP-04 study excluded any survival benefit due to ALND because, according to the Authors, breast cancer is a systemic disease from its onset so that any treatment aimed at removing nodal metastases is unlikely to affect survival. These findings were confuted by the meta-analysis of Orr [34] of six clinical trials suggesting an average survival benefit from ALND of 5.4%; another meta-analysis of 78 clinical trials indicated that improved loco-regional control in patients with early-stage breast cancer translated into a benefit of survival at 15-year follow-up observation [35]. The question was expected to be solved by SLNB followed by selective ALND that is completion axillary dissection in SN-positive patients only, because this strategy could restrain to patients with a high risk of additional axillary metastatic lymph nodes the therapeutic effect of ALND while sparing the side-effects of the procedure to node-negative patients. However, both in patients with SN micrometastasis and, to a lesser extent, macrometastasis no therapeutic effect of completion ALND could be appreciated [10-14].

As to the former, the clinico-biological reasons may be that: i) SN micrometastases have, at most, a negligible prognostic value in patients undergoing pathological staging by means of SLNB compared with what can be observed in patients staged by ALND, due to the focused analysis of the SN; ii) patients with micrometastatic tumor deposits in the form of pN0 (i+) or pN1mi do not seem to have a worse prognosis compared with SN-negative patients; iii) the risk of additional axillary lymph node metastasis in patients with SN micrometastasis and favorable histopathological features of the primary tumor (well-differentiated, T1 tumors without lympho-vascular invasion) is rather low, if any, and iv) the IBCSG 23-01 randomized clinical trial indicated a lack of therapeutic effectiveness of completion ALND in patients with SN micrometastases undergoing completion ALND notwithstanding the high rate (13%) of NSN metastases detected in the ALND arm [14,36-39].

However, the perspective is less clear in patients with SN macrometastasis because although the results of the ACOSOG Z0011 trial suggested that SLNB-alone compared to ALND did not result in inferior loco-regional disease free and overall survival in patients with up to two SNs with metastases, such findings may be useful in the decision-making of patients undergoing breast-conserving surgery followed by whole-breast radiotherapy only but not to mastectomy; moreover, the limitations of this study are well known, such as the failure to achieve the target accrual, and the possible randomization imbalance favoring the SLND-alone group [10-13].

As a matter of fact, an international consensus as for the need of a completion ALND in patients with SNs macrometastases is still lacking, and the decision-making and counselling of the individual patient might be assisted by the availability of more standardized tools able to predict the risk and the extent of metastases into NSN after a positive SLNB. In this view, several models have been built up with the aim of predicting this risk although most of them are likely to perform differently in different Institutions. Moreover, great variations have been reported as regards: i) the magnitude of the source data for selecting the most predictive parameters; ii) the weigh attributed to these parameters into the predictive model; iii) the clinical features of the study population such as the stage of the disease that influences the prevalence of nodal metastases and, consequently, the predictive performance; iv) the differences in the technique of SLNB, and v) the discrepancy of histology protocols that may determine an over- or understating of nodal disease [12,18-30,40-42]. For all these reasons, available predictive tools have a wide range of performance in a given Institution so that they should be tested and validated at the Institution where they are planned to be used before assisting in decision-making and patient advising.

Our findings allowed to select only three significant parameters (tumor stage, histologic grade, and number of SN-positive) that were included into a logistic equation that could predict the risk and extent of metastases into NSN after a positive SLNB. This greatly simplifies the use of our predictive model as compared with the other available tests that include much more parameters, variably represented and with a different weigh of prediction; moreover, the inclusion of the required parameters into a computerized equation automatically gives the individual predictive score [30]. Worth of noting, these three parameters were selected by analyzing a large training set of breast cancer patients undergoing surgery at the same Breast Unit in a rather short period, thus reducing operator-related variations thanks to the adoption of uniform procedures as regards SLNB detection and histologic examination, avoiding temporal variations related to disease stage at presentation as well. This may explain the constant predictive performance of our test both in the training and validation set, as indicated by the very similar value of the Area under the Curve (AUC) of the ROC curve equal to 0.655 and 0.638, respectively. As a matter of fact, the challenge with other predictive tools, such as the Breast Cancer Nomogram of the MD Anderson Cancer Center and the Breast Cancer Nomogram of the Memorial Sloan Kettering Cancer Center, indicated that it well matched especially with the former (P = .000); moreover, the use of only three variables may greatly enhance the feasibility of its application [18-19].

Our level of predictive performance, although certainly better than tossing a coin and superior to simple clinical judgment, might be regarded at first sight of negligible value because the AUC of the ROC curve was close to the lower value of what is usually regarded as the satisfactory range (0.65 to 0.85) [30,43]. Our findings, however, indicated that our selected cut-off (<28%) would allow to avoid almost one third

of completion ALND (61/201 = 30.3%), and in 72% of these cases (44 out of 61) NSN are expected to be histologically-negative, 22.9% (14 out of 61) to have only one histologically-positive NSN and thus staged as pN1a, while the remaining 4.9% (3 out of 61) would be staged as pN2a or pN3a, due to an overall detection of four or more metastatic lymph nodes as the sum of both SN-positive and NSN-positive lymph nodes.

As regards pN1a patients after completion ALND, current validation studies indicates that the false-negative rate as for the prediction of a low risk of NSN involvement ranges from 0% up to 40%, with even higher rates in external validation series (16% to 74%) [30,43]. Worth of note, leaving out a residual NSN-positive lymph node in less than 23% of patients should have no therapeutic effect as for regional control; as a matter of fact, the rate of NSN metastases detected in patients undergoing ALND in the ACOSOG Z0011 clinical trial was 27.3%(= 97/355) and, due to the randomization procedure, this rate should be similar in patients in the SLNB-alone arm of treatment who had not a worse outcome. Moreover, the detection of one more pathologic NSN at completion ALND would not modify the disease stage (pN1a) even in a patient with two SN-positive, thus avoiding any implication as regards the adjuvant treatment planning.

The staging of pN2a-pN3a after completion ALND represents the real target of a tailored adjuvant treatment planning because such an extensive nodal involvement is the major parameter to recommend adjuvant chemotherapy in Luminal A or B breast cancers subtypes [44]. So, whether ALND would be omitted in SN-positive patients as suggested by Giuliano et al [13], a 22% risk of medical under-treatment could be anticipated in SN-positive patients (that is, 45 out of 201 patients) which roughly corresponds to the 7% of the entire breast cancer population, if one assumes a mean rate of SN-positivity close to 30% [13]. Such an axillary pathological under-staging seems clearly unacceptable but the adoption of our cut-off score would allow to miss only 3 (1.5%) pN2-3 pathological stages out of 201 SN-positive patients, which corresponds to the 0.45% of the entire breast cancer population. Notably, the potential benefit of adjuvant chemotherapy would be relevant only in pN2-3 stages with a Luminal A or B subtype that is only in 2 out of 201 SN-positive patients, or the 0.3% of the entire breast cancer population. So, a down-staging risk of this magnitude seems clearly negligible as compared to the post-operative complications of a systematic ANLD performed in each SN-positive patient.

As for the selection of patients for regional nodal irradiation, the knowledge of pN2 a status might properly address these patients to an extended regimen of irradiation. Several studies have demonstrated the advantage offered by radiotherapy (RT) extended to lymph node stations both in patients who had breast-conserving surgery and mastectomy; the indication is established in high-risk patients with metastasis in 4 or more lymph nodes although, more recently, it has also been extended to patients with a limited number of metastatic lymph nodes in the presence of other risk factors, such as: age ≤ 40-45 years, tumor size ≥ 3.5-4 cm, ER/PgR negative receptor status, lympho-vascular invasion, extracapsular extension in lymph node metastasis, histologic high-grade, and nodal rate of metastasis > 20-25%. So, the EBCTCG meta-analysis demonstrated in patients with 4 or more positive lymph nodes an advantage in local recurrence, cancer-specific survival and overall survival (with a 20-year benefit of 7.6% from published data in 2014) obtained with post-mastectomy irradiation, regardless of the use of adjuvant chemotherapy [45]. Similarly, in the 2011 EBCTCG meta-analysis evaluating adjuvant RT after conservative surgery, a disease-free survival benefit of 21.7% at 10 years in patients with 4 or more positive lymph nodes was observed [46]. Therefore, the main available guidelines are currently recommending the irradiation of lymph node drainage stations in addition to chest wall or breast RT after conservative surgery in patients with metastasis in 4 or more lymph nodes (pN2a) [47-50].

For these reasons, the adoption of the proposed cut-off score of 28% would imply a false-negative rate < 5% in selecting patients with four or more metastatic lymph nodes, and this should have a negligible impact as for the planning of these adjuvant combined regimens.

Conclusion

A simple and ready available predictive tool for estimating the risk and extent of NSN involvement in patients with positive SNs was developed and validated at the same Institution, with a very fine performance in predicting in high-risk patients with four or more metastatic lymph nodes who should be eligible to adjuvant regimens of chemo- and radiation therapy. This predictive tool may aid in the decision-making in breast cancer patients with SNs metastasis while waiting for a definitive position regarding the therapeutic role of completion ALND.

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