

Non-sentinel lymph node metastases in breast cancer patients with a positive sentinel lymph node: validation of five nomograms and development of a new predictive model

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ABSTRACT

Aims and background. Discordance of intraoperative analysis with definitive histology of the sentinel lymph node in breast cancer leads to completion axillary lymph node dissection, which only in 35-50% shows additional nodal metastases. The aim of the study was to identify individual patient risk for non-sentinel lymph node metastases by validating several statistical methods present in the recent literature and by developing a new tool with the final goal of avoiding unnecessary completion axillary lymph node dissection.

Methods. We retrospectively evaluated 593 primary breast cancer patients. Completion axillary lymph node dissection was performed in 139 with a positive sentinel lymph node. The predictive accuracy of five published nomograms (MSKCC, Tenon, Cambridge, Stanford and Gur) was measured by the area under the receiver operating characteristic curve. We then developed a new logistic regression model to compare performance. Our model was validated by the leave-one-out cross-validation method.

Results. In 53 cases (38%), we found at least one metastatic non-sentinel lymph node. All the selected nomograms showed values greater than the 0.70 threshold, and our model reported a value of 0.77 (confidence interval = 0.69-0.86 and error rate = 0.28) and 0.72 (confidence interval = 0.63-0.81, error rate = 0.28) after the validation. With a 5% cutoff value, sensitivity was 98% and specificity 9%, for a cutoff of 10%, 96% and 2%, respectively.

Conclusions. All the nomograms were good discriminators, but the alternative developed model showed the best predictive accuracy in this Italian breast cancer sample. We still confirm that these models, very accurate in the institution of origin, require a new validation if used on other populations of patients.

Introduction

Sentinel lymph node (SLN) biopsy is today the gold standard to clinically stage axillary-negative breast cancer patients. Completion axillary lymph node dissection (CALND) is the recommended procedure in case of a positive SLN.

The standard procedure to evaluate intraoperative SLN is based on frozen section and hematoxylin-eosin staining, followed by a definitive, postoperative enhanced immunohistochemical evaluation of the remaining tissue, which is fixed in formalin and embedded in paraffin. It is therefore frequent to classify as negative a SLN by frozen section and then detect a metastases, mainly micrometastases, by postoperative immunohistochemistry. This finding lead to a reoperation to clear the axilla, but in 35-

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

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50% there was no residual disease in the non-SLN. This complementary ALND due to the discordance of intra-operative frozen section with definitive histology of SLN lead to upstaging in 6% of cases, adjusting postsurgical treatment in even fewer cases¹.

Starting with the Memorial Sloan Kettering Cancer Center (MSKCC)², many institutions have proposed statistical methods to identify patients at low risk of non-SLN metastases in order to avoid CALND. Initially, we used the MSKCC nomogram retrospectively on our case series and obtained a good discrimination. The area under the receiver operating characteristic (ROC) curve, the test most widely used to validate a nomogram like this, was 0.75, above the threshold of 0.70³. We then tested four other methods: a French approach from the Tenon Hospital of Paris⁴, an American approach from Stanford University⁵, a British approach from Cambridge⁶, and the last one, more recent, derived by a multicentric study in Turkey⁷. All these methods in our experience showed a sufficiently high performance, but they were not powerful enough to influence our clinical decisions. We therefore continued to perform CALND in positive SLN patients, with an incidence of 61.48% of negative non-SLN.

Many studies have confirmed the goodness of the statistical approach, but the conclusions were always the same: the nomograms to predict non-SLN metastasis in breast cancer patients with positive SLN should be used with caution when exported to a different institution from that in which the nomogram itself was developed⁸.

On the other hand, recent works show the underuse of CALND for the management of breast cancer patients with metastatic SLN, reporting only 60% correct axillary staging in America in case of micrometastatic SLN, with an estimated understage in about 21% of cases⁹. Finally, the real prognostic impact of this understaging is not clear if we consider the study of Bilimoria *et al.*¹⁰, who concluded that in patients with microscopic nodal metastases there is no significant differences in axillary recurrence or survival for patients who have undergone SLN biopsy alone *versus* CALND.

Thus, how do we break this chain between a complex statistical analysis and the clinical sense? Specht *et al.*¹¹ attempted to compare their statistical tool with the experience of a group of breast cancer specialists and concluded that the predicting model outperforms experts, but clinicians nonetheless do not change their decisions.

Waiting for an ideal, reliable tool to predict non-SLN metastasis in breast cancer patients with a positive SLN, after analysis of the most frequently used ones, we decided to determine the variables on non-SLN metastases in our positive SLN patients and to develop our own nomogram, comparing the results considering also the high variability of the samples used for the published tools.

Patients and methods

We retrospectively evaluated 593 consecutive patients with primary infiltrating breast cancer who underwent SLN biopsy at the Breast Unit of the Sant'Andrea Hospital of Rome. Of these, 151 (25%) had a positive biopsy but only 140 underwent CALND: in 11 cases the patients refused a new surgical procedure. In 36 (6%) cases of isolated tumor cells, CALND was not performed (Table 1).

All the biopsies were radioguided using a ⁹⁹Tc technique and were performed by the same surgical team. Frozen section was possible in 539 (91%) patients (not performed on 54 patients for SLN <1 cm in diameter or massive adipose involution).

Table 2 reports the principal characteristics of the 139 positive SLN patients who underwent CALND. On these patients we determined the probability of metastatic non-SLN by five published nomograms using, if possible, the Internet resources (MSKCC at www.mskcc.org/nomograms and Stanford at <https://www3-hrpdc.stanford.edu/nslncalculator/>) or using the reported method (Tenon) or formulas (Cambridge and Gur). The area under the ROC curve (AUC) was used to describe the performance of the diagnostic value of each nomogram. Values higher than 0.70 were considered a sign of good discrimination.

The AUC represents the likelihood that the output of the model calculated for a patient, selected casually in the group of the ill ones, is higher than the same value for an individual selected casually from healthy individuals. For this reason, it is the most significant index of the attitude of a model to correctly discriminate between sane and ill subjects.

On the same sample we developed a nomogram with the aim of estimating the likelihood of having at least one metastatic non-SLN.

Table 1 - Descriptive characteristics of study population by five published nomograms (MSKCC, Tenon, Cambridge, Stanford and Gur)

	MSKCC	Tenon	Cambridge	Stanford	Gur
No.	702	81	118	285	607
% positive SLN/ total SLN biopsies	22.4	24	nd	36.4	nd
% age <50 yr	41.3	~30	nd	nd	58
SLN per patient	2.9	2.03	2	1.91	2
% T <10 mm	22.1	33.4	nd	10.9	nd
% Grade I	3.1	52.7	20.3	31.9	6.8
% Lobular type	12	11.6	7.6	9.5	12.2
% LVI	40.5	14	25.4	33.3	53.8
% Multifocality	28.1	nd	10.2	nd	21
% ER+ status	80.8	93.3	85.6	68.1	73.2
% SLN μ metast	nd	37	nd	70.2	17.6
AUC	0.77	nd	0.84	0.83	0.80

AUC, area under the ROC curve; LVI, lymphovascular invasion; nd, not declared; ROC, receiver operating characteristic; SLN, sentinel lymph node.

Table 2 - Patient and tumor characteristics of the study group (n = 139)

Characteristic	No. patients	%
Age, yr		
≤50	66	47.5
>50	73	52.5
Tumor size		
T1 microinfiltrating	1	0.7
T1a	6	4.3
T1b	17	12.2
T1c	69	49.6
T2	46	33.1
Tumor type		
Ductal	116	83.5
Lobular	23	16.5
Grading		
G1	22	15.8
G2	55	39.6
G3	62	44.6
LVI		
Yes	16	11.5
No	123	88.5
Estrogen receptor status		
Positive	89	64.0
Negative	50	36.0
Metastases size		
Micrometastases	54	38.8
Macrometastases	85	61.2

LVI, lymphovascular invasion

Statistical analysis

We first evaluated the performances of the five published nomograms through the estimated values of the AUC, as well as the confidence intervals (CI) at the level of 95% and of the error rate (ER). The ER is defined as the proportion of errors coming from an incorrect classification, i.e., the model discriminates a patient as sane when the predicted likelihood is lower than 0.5 and as sick when it is greater than 0.5. Low ER values and high AUC values imply a good capacity of the model to correctly discriminate between sick and healthy patients.

Our analysis starts fitting a regression model that allows individual and breast cancer characteristics to predict the likelihood of non-SLN metastasis in patients with a positive SLN biopsy. Clinical data were collected for each patient. Univariate analysis of a set of individual, clinical and pathological variables was conducted to select the clinically meaningful, even though not always statistically significant predictors. We finally selected cancer grade, histological type, SLN status (micrometastases or macrometastases), proportion of positive SLN, and tumor size (in mm). We estimated the model considering the logistic specification. Estimates of the model are obtained by the bayespplr function contained in the *Arm* package (Gelman *et al.*¹²) in the Free Software R (<http://cran.r-project.org/>). In the logistic regression model, the output of a non-SNL is treated as a dichotomous variable, status of non-SNL

positive or negative. Figure 1 summarizes the estimated coefficients for the breast cancer patients characteristics and their relative standard errors. Their associated *P* values are listed in the footnote.

Without an independent study population, the model is validated by a re-sampling technique, the leave-one-out cross-validation¹³, which uses the same individuals on which the model has been estimated. This technique consists in separating the sample into two subgroups: the training set and the test set. The training sub-sample consists of *n*-1 units, on which the model is estimated; the remaining units belong to the test sub-sample. The model is estimated on the latter sub-sample. This operation is repeated iteratively *n* times. Following this procedure, we have an estimated value for each patient, obtained by a model whose parameters are estimated on a subgroup of units, a model that does not involve the unit for which the likelihood of detecting metastatic non-SLN is estimated.

Based on the estimated model, we developed a new mono-institutional predictive tool that we compared with the most popular available nomograms.

Results

We recorded in the 139 positive SLN patients who underwent CALND a mean tumor size of 20 mm (± 10, range, 2-50) *versus* 13 mm (± 7, range, 1-42) in the remaining negative SLN patients. Multifocality was described by the pathologist in 26 cases (19% *vs* 10% of N0 patients).

The SLN number per patient was 1.56 (± 0.88, range, 1-10) and the mean number of dissected lymph nodes was 19. The mean overall metastatic size, the largest size of SLN metastasis in millimeters) was 4 mm (± 4, range, 0.2-20).

In 53 cases (38%), we found at least one metastatic non-SLN, and in 24 of these (45%) there was only one more positive lymph node.

The AUC values for MSKCC and Cambridge tools were 0.76 (CI, 0.67-0.85 and 0.68-0.85, respectively), 0.74 for the new Turkish model (CI, 0.65-0.83) and 0.70 for Tenon and Stanford tools (CI, 0.61-0.80 for both).

Figure 1 reports estimated coefficients of the fitted model. The influence of individual and tumor characteristics on the status of non-SLN is in accord with the main findings in recent literature. The most influenced variable is the proportion of positive SLN and, especially, the size of metastases: the difference between the estimated likelihood of having at least a positive non-SLN for 2 patients with the same characteristics, except for the presence of micro-metastases or macro-metastases in the SLN, could increase to 0.40 only as a consequence of this difference (using the “divide by 4” rule, as suggested in Gelman and Hill¹⁴).

Unlike the MSKCC model, in our series, lobular type was correlated to a minor risk of non-SLN metastases, also *versus* G1/G2 ductal types.

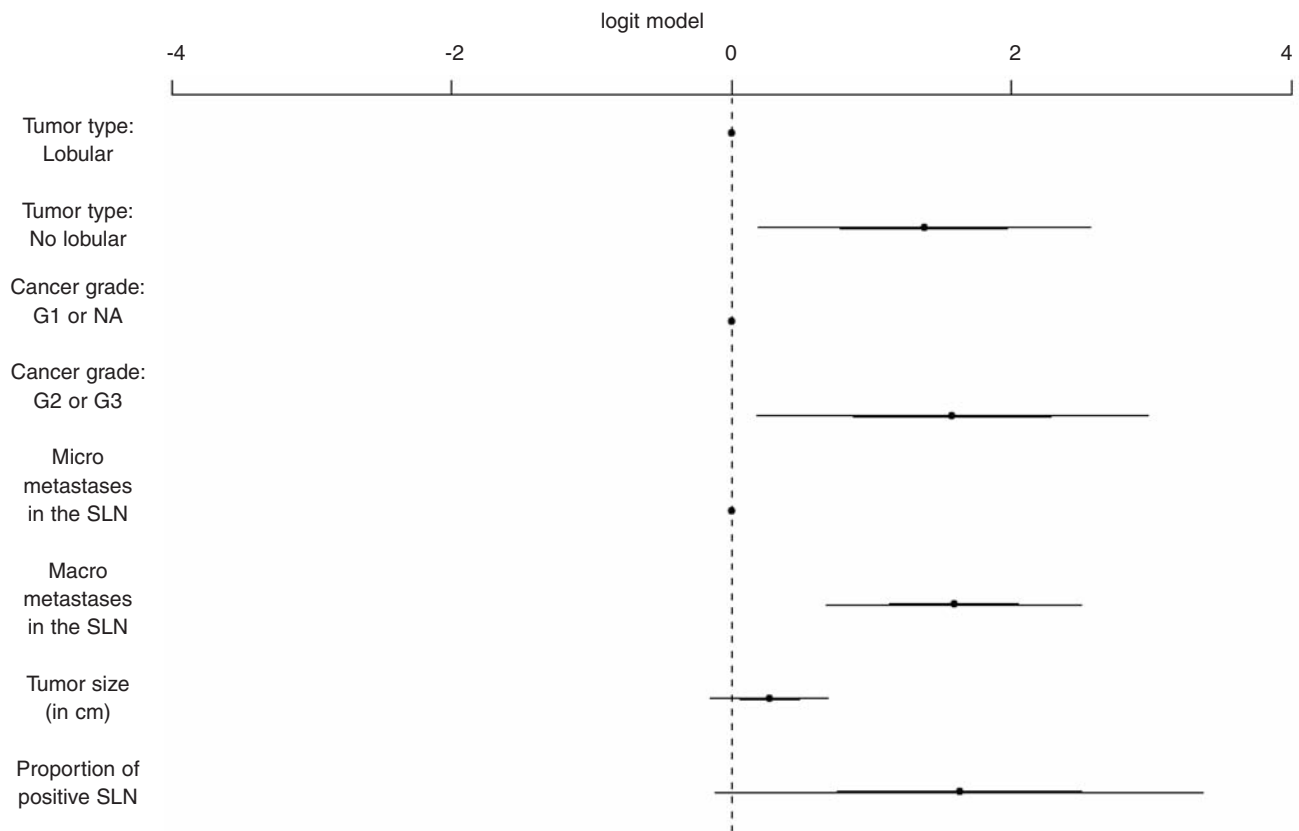


Figure 1 - Estimated coefficients with relative ± 1 and ± 2 standard errors of individual and tumor characteristics in the estimated logistic regression model (P values are equal to 0.021, 0.024, 0.000, 0.200, 0.061, respectively).

The estimated model can be summarized as follows:

$$p = \frac{\exp \{-6.045 + 1.372 \times T + 1.575 \times G + 1.586 \times M + 0.027 \times S + 1.627 \times P\}}{1 + \exp \{-6.045 + 1.372 \times T + 1.575 \times G + 1.586 \times M + 0.027 \times S + 1.627 \times P\}}$$

where p is the probability of positive non-SLN, T is equal to 0 if lobular type and 1 if other, G is equal to 0 in case of G1 tumor and 1 for G2/G3, M values 0 if SLN is micrometastatic and 1 if macro, P is the proportion of positive SLN number among total SLN.

The overall predictive accuracy of the model incorporating the five selected variables, as measured by the AUC, was 0.77, with CI = 0.69-0.86 and ER = 0.28, and its value decreased to 0.72 (with CI = 0.63-0.81 and ER = 0.28) after validation with the leave-one-out cross-validation technique (Figure 2). Nevertheless, among patients with a low predicted probability of non-SLN metastases, the sensitivity was very good. If a cutoff value of 5% was used, sensitivity was 100% and specificity 6%, whereas for a cutoff of 10%, sensitivity was 98% and specificity 21% (Table 3).

Summarizing, the nomogram based on our estimated model (also after the internal validation) presented the best performance especially for low cutoff values, helping physicians to make clinical decisions in uncertain conditions.

Discussion

All the five tools analyzed in our study were above the threshold of predictivity by the AUC, but MSKCC nomogram and the Cambridge model seem more predictive as found in other studies¹⁵⁻¹⁷ and in our previous study¹⁸. The Turkish model (Gur), derived by a multicentric study and not yet validated by other studies, performed as well but not better than the older models. The French model (Tenon, the only one developed as a score) and the Stanford model appeared less predictive on an Italian breast cancer population.

In the five models applied to this population, the AUC values ranged from 0.70 to 0.76, probably due to the high variability of the descriptive characteristics. The mean tumor stage at the operation, the surgical technique of SLN biopsy, and histopathological assessment are the main elements of variability.

For example, the MSKCC model was developed on a lower-stage population than was the Stanford model, as shown by the lower percentage of N-positive patients (22% vs 36%) and the percentage of T <10 mm patients (22% vs 11%). The percentage of micrometastases is another characteristic that represents the mean tumor burden in the sample. For the MSKCC nomogram it is indirectly described by the detection method of SLN

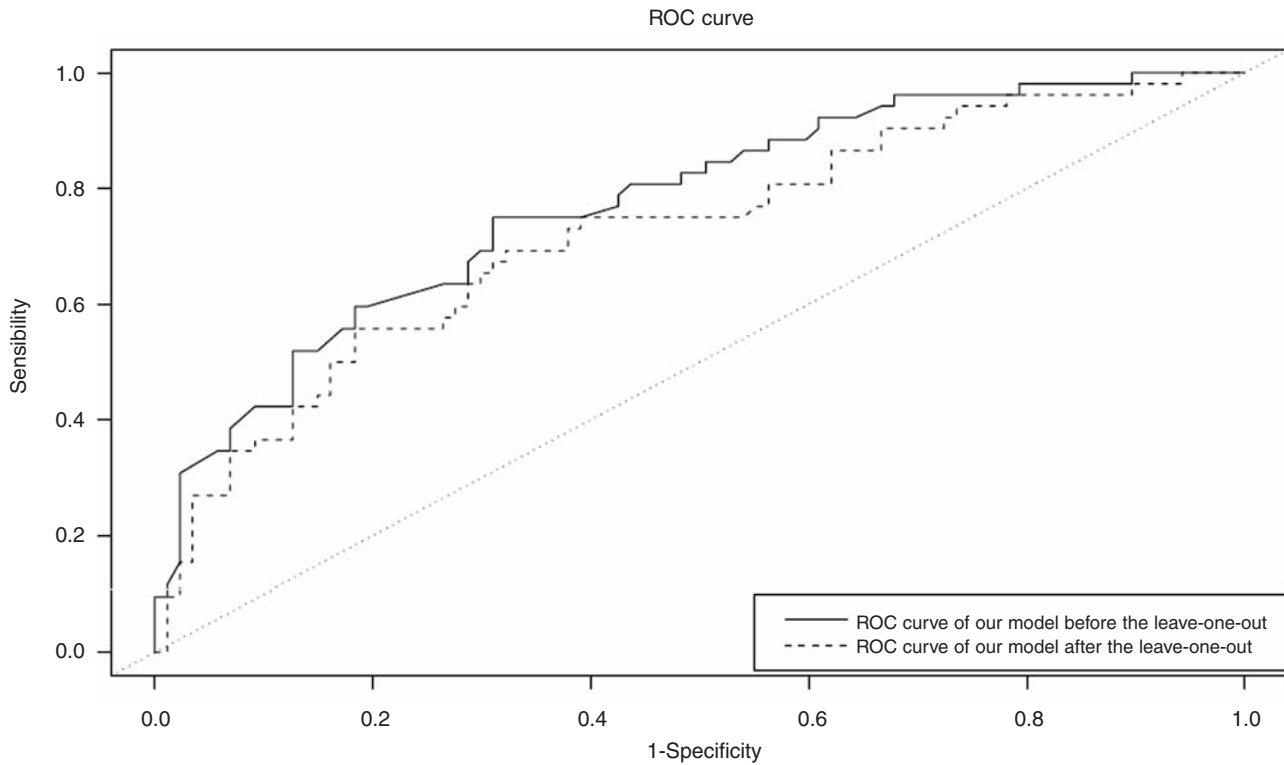


Figure 2 - Discrimination of the estimated model in predicting each individual patient's probability of having positive non-SLN measured by the ROC in the study population of n = 139 patients. The two different areas correspond to the estimated model before and after the leave-one-out cross-validation procedure. ROC, receiver operating characteristic.

Table 3 - Performances of the five published nomograms (MSKCC, Tenon, Cambridge, Stanford and Gur) applied to the study population at 5% and 10% probability cutoff values

	5% Cutoff		10% Cutoff	
	Sensibility	Specificity	Sensibility	Specificity
MSKCC	0.98	0.10	0.90	0.43
Stanford	1.00	0.01	0.96	0.21
Cambridge	1.00	0.00	1.00	0.07
Gur	0.98	0.09	0.65	0.78
Estimated model	1.00	0.06	0.98	0.21
Estimated model, after validation	0.98	0.06	0.961	0.20

(frozen section, hematoxylin-eosin staining, immunohistochemistry) and in the other models ranges from 17 (Gur) to 70% (Stanford). In the Turkish series, this low frequency of micrometastatic SLN justifies the high rate of detection by frozen section. In our experience, and according MSKCC data, frozen section global sensitivity is about 50% (75% in macrometastases detection *vs* only 15% in case of micrometastases). These poor results of frozen section lead to a global reoperation rate of 13% to clear the axilla (about half of SLN metastatic patients).

One of the most significant variables in all studies, as well as in our model and except for the Stanford nomo-

gram, is the proportion of metastatic SLN. Of course this ratio depends on a denominator (total number of SLN harvested) that can vary a lot (the averages ranged from 1.9 to 2.9). The original predictive model presented has been developed with a mean SLN number of 1.5, and this low denominator surely increases the significance of the variable. Such variations depend on the SLN detection method (⁹⁹Tc *vs* blue die or combined) and the surgical technique.

Of the histopathological characteristics, multifocality and estrogen receptor status are constant, whereas tumor grading and lymphovascular invasion vary in the different studies.

Percentage of G1 tumor ranged from 3 to 53% (16% in our series), probably depending on assessment methodology of the pathologist.

Assessment of lymphovascular invasion deserves a separate discussion. Our lowest rate (11%) is probably due to the pathological detection method based on anti-podoplanin monoclonal antibodies, which highlight lymphatic endothelial cells and avoid false positives (neoplastic cells forced into tissue gaps).

Each model therefore emphasizes an aspect, often giving a different weight to the same variable involved in the process of lymph node metastases. The MSKCC nomogram magnifies the overall metastases size through the detection method of the SLN metastases itself: in

case of positive frozen section, the predicted probability of spread to additional lymph nodes is always above the reasonable cutoff of 10% to avoid CALND. Then, the estrogen receptor-positive status, normally considered as a favorable prognostic factor, is correlated to an higher probability of non-SLN metastases. This counterintuitive finding has already been reported in other series¹⁹. The MSKCC tool, the first and more complex model, when applied to other populations does not perform significantly better than the other simpler models.

The Stanford tool emphasizes angiolymphatic invasion, which, as previously reported, has a high variability in the different series maybe for histological technique issues. However, it is the only method that does not consider the proportion of positive SLN, a variable that must be adjusted to the average number of lymph nodes harvested by the biopsy.

The Tenon model is less intuitive to use in practice because it is only a scoring system, and the cutoff of 3.5 points that matches the 97.3% chance of having negative non-SLN appears too high.

The last one, the Turkish model has the great methodological merit of having been generated by a multicentric study, but some considered variables are not standard (for example, the SLN detection method denoting an overall sensibility of 97% of frozen section, very optimistic also in complete absence of micrometastases)²⁰. It is hard to understand, as in that study the MSKCC reached an AUC value of 0.70, considering the highest weight of the variable. On the other hand, in the Turkish study, 47.2% of patients had positive axillary non-SLN *vs* 38% of our study.

In principle, all the analyzed methods tend to overestimate the likelihood of having additional, non-SLN metastases.

These considerations bring us back to the beginning of our work, when, analyzing the published nomograms to predict the non-SLN status, we encountered more and more new models, and the question “which is the ideal model?” was eventually accompanied by another one: “do we need another tool?”. To answer the first question, we developed a new tool implicitly answering the second question. At this time, the methodology of matching our own series with other series of breast cancer patients may have been more important than the results in terms of accuracy of the new nomogram, which must be tested on other populations.

However, the big issue is to convert this accuracy into impact on clinical behavior. These nomograms and algorithms are today mainly used in patient discussions not to make decisions and recommendations about not doing CALND, but rather to achieve informed consent so that the patient understands there is a genuine likelihood that she will undergo a potentially detrimental procedure and still may not have additional lymph node involvement.

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partially answered the question about the real effects of CALND on survival of patients with positive SLN by the recently published multicenter Z0011 trial²¹. Nodal axillary recurrence is confirmed to be a rare event, even in patients with metastatic SLN who have not undergone a complete dissection. Five-year overall and disease-free survival were not different between treatment groups, probably due to radiation and systemic therapies. Thus, the only additional information gained from CALND would be the total number of metastatic lymph nodes, and this information, in most cases, does not change the decision about systemic therapy. The problem is that today in early breast cancer the biological factors (like receptor status) are predominant on staging data for an oncologic treatment plan, and from this point of view, the axillary status *tout-court* could be omitted in the patient management.

The definitive answer will be provided by prospective studies with larger numbers of patients and longer follow-up. We agree with authors who argue that it is not yet possible to know if CALND can safely be omitted in positive SLN patients, but we hope so²².

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