Prediction of nodal staging in breast cancer patients with 1-2 sentinel nodes in the Z0011 era

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Abstract

The aim of this study was to provide an innovative nomogram to predict the risk of >2 positive nodes in patients fulfilling the Z0011 criteria with 1-2 sentinel lymph nodes (SLNs) only retrieved.

From 2007 to 2017, at the Breast Unit of ICS Maugeri Hospital 271 patients with 1-2 macrometastatic SLNs, fulfilling the Z0011 criteria, underwent axillary dissection and were retrospectively reviewed.

A mean of 1.5 SLNs per patient were identified and retrieved. One hundred eighty-seven (69.0%) had 1-2 positive nodes, and 84 (31.0%) had >2 metastatic nodes. Independent predictors of axillary status were: positive SLNs/retrieved SLNs ratio (odds ratio [OR] 10.95, \(P = .001\)), extranodal extension (OR 5.51, \(P = .002\)), and multifocal disease (OR 2.9, \(P = .003\)). A nomogram based on these variables was constructed (area under curve after bootstrap = 0.74).

The proposed nomogram might select those patients fulfilling the Z0011 criteria, with 1-2 SLNs harvested, in whom a high axillary tumor burden is expected, aiding to guide adjuvant treatments.

Abbreviations: ALND = axillary lymph nodes dissection, AUC = area under curve, ENE = extranodal extension, hAB = high axillary burden, SLN = sentinel lymph node, IAB = low axillary burden, LRR = loco-regional recurrence, MSKCC = Memorial-Sloan Kettering Cancer Center, OR = odds ratio, ROC = receiver operating curve.

Keywords: breast cancer, axillary nodal status, nomogram

1. Introduction

Complete axillary lymph nodes dissection (ALND) after a positive sentinel lymph node (SLN) has become much less relevant in the era of multimodal treatment of breast cancer.[1] The American College of Surgeons Oncology Group Z0011 randomized clinical trial showed an excellent loco-regional disease control omitting ALND in patients undergoing breast-conserving surgery with 1-2 macrometastatic SLNs, provided that whole-breast radiotherapy was planned.[2] Long-term outcomes of the Z0011 trial have been recently updated and corroborated previous results.[3] The Z0011 findings have been promptly translated into clinical practice in selected patients who fulfill all the requested criteria.[4] The application of the Z0011 in clinical practice resulted in a significant decrease of ALNDs,[5,6] but a major question arises: how can the surgeon know that only 1-2 nodes are positive, if 1-2 SLNs only are retrieved? This concern is not a collateral issue, because despite few authors report a mean of 3 identified SLNs per patient, the great majority of studies indicate that generally 1 or 2 SLNs are retrieved for each patient.[7] But at least 3 nodes should be removed and analyzed to decide if ALND can be safely omitted, and not surprisingly application of the Z0011 criteria has paradoxically increased the number of harvested SLNs per patient.[8] Moreover, keeping unknown the status of nonsentinel nodes after avoiding ALND in node-positive patients may lead to a “one size fits all” philosophy, widely offering chemotherapy and loco-regional irradiation to strengthen the loco-regional control.[2,9-11] Therefore, if ALND is omitted after a positive SLN but no more than 2 nodes are removed, prediction of nonsentinel nodes status become fundamental to properly escalate or de-escalate systemic treatments if Z0011 is applied.[12] The aims of the present study were:

1. to assess the different clinical and prognostic features of patients with 1-2 vs >2 positive nodes who would not have been discriminated avoiding ALND, according to the Z0011 inclusion criteria;
2. to evaluate the accuracy of currently validated nomograms to predict the non-SLN status;
3. to propose an innovative nomogram to specifically predict the risk of more than 2 positive axillary nodes in patients who fulfill the Z0011 criteria, if 1-2 SLNs only are retrieved.
2. Methods

2.1. Study population

From January 2007 to December 2017, 271 breast cancer patients treated at the Breast Unit of ICS Maugeri Hospital with breast-conserving surgery, clinically node-negative but with 1 or 2 SLNs positive for macrometastasis, were included in the study and received ALND. The study was authorized by the Institutional Review Board and approved by the Ethical Committee of ICS Maugeri Hospital (protocol number 2394/2020). Informed consent to collect retrospective data was obtained from patients. Inclusion criteria were: proven diagnosis of breast cancer by core-biopsy, stage cT1-cT2 breast cancer evaluated on preoperative imaging, stage cN0 evaluated clinically and by axillary ultrasound, indication for breast lumpectomy and SLN biopsy, and planned radiotherapy. Patients who underwent neoadjuvant chemotherapy or total mastectomy were excluded from the study, as well as patients with a clinically positive axillary status, more than 2 positive SLNs or micro-metastatic disease in the SLN, since pNmic status was not an indication for ALND. All selected patients were suitable not to receive ALND according to the American College of Surgeons Oncology Group Z0011 trial.

2.2. SLNs identification and pathological analysis procedures

In all patients a peri-areolar subdermal injection of 0.2 to 0.5 mCi of colloidal human serum albumin labeled with 99m-Tc was performed the day before surgery. During surgery, a gamma probe (Bluetooth Neoprobe Gamma Detection System) was used to localize the SLN. Further nodes with a radioactivity count over 10% of the excised node were considered as other SLNs and removed. All SLNs were sent for intraoperative pathological analysis with standard hematoxylin-eosin, by embedding the sliced lymph node in paraffin wax, taking adjacent sections every 50 micron and staining them with hematoxylin-eosin.

2.3. Study design and endpoints

First, mean number of retrieved SLNs per patient was reported. Based on axillary status evaluated on final histopathology, patients were divided into 2 groups: those who had only 1-2 positive lymph nodes (low axillary burden, lAB), and those who had >2 positive nodes (high axillary burden, hAB). The proportions of IAB and hAB patients after 1 or 2 positive SLNs were assessed to evaluate the risk of axillary under-staging related to Z0011 inclusion criteria. Clinical and pathological variables were compared between the 2 groups, as well as the use of radiotherapy, hormone therapy and chemotherapy, to assess if lAB and hAB patients received different adjuvant treatments after surgery. Then, the crude rates of loco-regional recurrence (LRR) and distant metastases were compared between lAB and hAB patients, to verify a significant prognostic difference between the 2 groups of patients. LRR was defined as the occurrence of ipsilateral breast cancer or nodal disease at axillary, internal mammary or supraclavicular level, proven on core biopsy. Distant metastases was defined as the occurrence of distant lesions with computed tomography and positron emission tomography characteristics suggestive of malignancy.

Five validated nomograms to predict the non-SLN status in case of positive SLN were retrospectively applied to the present study population: Memorial-Sloan Kettering Cancer Center (MSKCC), Mayo, Tenon score, MD Anderson Cancer Center score, and Cambridge formula. In each patient all models were used to calculate the individual risk for non-SLN metastases, based on available variables. The accuracy of these nomograms or scoring systems to discriminate lAB and hAB patients was evaluated by each receiver operating curve (ROC) and the relative area under curve (AUC). For each model, the optimal probability cut-off to better predict >2 positive nodes was determined on ROC, and associated specificity and sensitivity were reported.

All relevant variables which emerged to be possibly related to hAB in descriptive analyses were included in a multivariate analysis with a binomial logistic model to find independent predictors of >2 positive nodes. Correlation of each variable with the outcome was assessed by calculating its odds ratio (OR) and ß coefficient. Calibration was performed by graphical method (Supplementary Fig. S1, http://links.lww.com/MD/E706). To construct the nomogram, the ß coefficient with the higher absolute value selected the relative variable as the “driver variable” on which the model was based, independently from its statistical significance. A score of 0 points was attributed to the lowest value of that variable, and 100 points to the highest value; intermediate values were matched with corresponding points. Then, the other relevant variables possibly related to hAB were included in the model, also in the absence of a statistical significance on multivariate analysis. Each variable was matched with a score based on the ratio between its ß coefficient and ß coefficient of the driver variable. The maximum score was obtained with the subsequent formula:

\[
\text{Maximum score} = \left( \frac{\beta_{\text{variable}}}{\beta_{\text{driver variable}}} \right) \times 100
\]

Once constructed the nomogram, it was applied to each patient of the present study to calculate the individual risk of hAB. A ROC with relative AUC was constructed for the proposed nomogram, based on the predicted probability to have >2 positive nodes, and the optimal cut-off value was determined to discriminate with the maximum accuracy IAB and hAB patients. Finally, an internal validation was performed with bootstrap method. Briefly, the original patient population was re-sampled 500 times and the optimism index (the mean of differences between AUC on bootstrap sample and AUC on original sample) was calculated. Optimism is the amount by which the AUC (or “the apparent prediction accuracy”) overestimates the true prediction accuracy of the model. Then, the corrected AUC after bootstrap was reported.

2.4. Statistical analysis

Variables were reported as means ± standard deviations or as absolute numbers and percentages. Categorical variables were compared using \( \chi^2 \) test, while continuous variables were compared using Student \( T \) test or nonparametric Wilcoxon test in case of nonnormal distribution of the variable. Statistical significance was set at \( P < .05 \) (2 tailed). Data analysis was performed using SAS software (v. 9.4, SAS Institute Inc, Cary, USA) and R software (v. 3.5.1, The R Foundation).

3. Results

3.1. Baseline characteristics in IAB and hAB patients

Mean lesion size on imaging was greater for hAB patients (17.6 ± 10.5 mm vs 14.9 ± 7.1 mm, \( P = .01 \)). Multifocal disease was
observed in 34.5% of hAB cases and in 16.0% of IAB patients ($P=.001$). Lympho-vascular invasion was present in 67.9% of hAB lesions and in 54.0% of IAB tumors ($P=.03$). All the other baseline features were balanced between the two groups, as reported in Table 1.

### 3.2. SLN and axillary status in IAB and hAB patients

One hundred eighty-seven patients (69.0%) had a maximum of 2 positive nodes, and the remaining 84 cases (31.0%) had 3 or more metastatic nodes. A mean of 1.5 ($\pm$0.7) SLNs per patient were identified and retrieved both in IAB and hAB cases ($P=1.000$). IAB patients had a lower mean number of positive SLNs per patient compared to hAB cases (1.1 $\pm$ 0.3 vs 1.3 $\pm$ 0.5, $P<.0001$) and a higher mean number of negative SLNs (respectively 0.4 $\pm$ 0.6 vs 0.2 $\pm$ 0.5, $P=.01$). At final pathology, all 187 IAB patients were staged as pN1, while 42.9% of hAB patients were staged as pN1, 42.9% as pN2 and 14.2% as pN3 ($P<.0001$). Extracapsular extension (ENE) was observed in 6.4% of IAB patients vs 26.2% of hAB cases ($P<.0001$). All these data are reported in Table 1.

### 3.3. Adjuvant treatments and long-term oncologic outcomes

Hormone therapy was administered in 88.2% of IAB cases vs 82.1% of hAB patients ($P=.18$). Locoregional irradiation was offered to 10.7% of IAB patients and to 53.6% of hAB cases, while remaining patients received whole-breast radiotherapy only ($P<.0001$). Chemotherapy was administered in 33.2% of IAB and 26.7% of patients ($P=.11$, Table 2). In particular, an anthracyclines/taxanes-based regimen was proposed in 45.2% of IAB and 66.7% of hAB patients, trastuzumab was received respectively in 12.9% and 6.6% of cases, and other regimens were offered in 41.9% and 26.7% of patients ($P=.06$). Mean follow up was similar between groups, being 52.3 months for IAB and 54.4 months for hAB patients ($P=.65$). No locoregional recurrence was observed among IAB patients, but it was reported in 6.0% of hAB cases (Log-rank test $P=.001$). Distant metastases occurred respectively in 4.3% and 13.1% of patients (Log-rank test $P=.01$). No difference was reported in terms of cancer-related deaths ($P=.11$, Table 2).

### 3.4. Performance of validated nomograms to predict nonsentinel nodal disease

ROC of each nomogram is showed in Fig. 1. The most predictive model applied to our series was the Mayo nomogram (AUC = 0.70), and a probability cut-off of 33% resulted in a sensitivity equal to 65% and a specificity of 71%. The MSKCC nomogram showed an AUC of 0.70 (cut-off 0.36, sensitivity 73%, specificity 55%). The Cambridge formula predicted hAB with an AUC of 0.66, while the Tenon score was associated with an AUC of 0.63 (cut-off 0.34, sensitivity 70%, specificity 47%).

### 3.5. Independent predictive factors of high axillary burden

After multivariate analysis, the only independent predictive factors associated to $>2$ metastatic axillary lymph nodes were a higher ratio of positive SLNs on all retrieved SLNs (OR 10.95, 95% confidence intervals [CI] 2.50–47.93, $P=.001$), ENE (OR 5.51, 95% CI 2.27–13.41, $P=.0002$), and multifocal disease (OR 2.9, 95% CI 1.44–5.84, $P=.003$), as reported in Table 3.

### 3.6. Development and internal validation of a nomogram to predict hAB

Since the higher $b$ coefficient was associated to the positive SLNs/ retrieved SLNs ratio ($b=2.42$), it was considered the “driver
variable" for constructing the nomogram. Based on their ß coefficients, presence of ENE (ß = 1.45) was matched with a score of 60.2 and multifocality (ß = 1.03) with a score of 42.58. Once taken into account all the independent predictors for hAB, a set of nonsignificant variables clinically judged to be relevant for axillary status were included in the model: estrogen receptor, human epidermal growth factor receptor 2status, histological type (invasive ductal vs invasive lobular), lymphovascular invasion and grading (Fig. 2; Supplementary Table S1, http://links.lww.com/MD/E708). Then, the constructed nomogram was applied to each patient: the minimum total score was 26.42 (predicted probability for hAB 4.0%) and the maximum total score was 276.48 points (predicted probability for hAB 90.0%). For each patient the predicted probability with relative confidence intervals was determined and a fitting plot for prediction related to score was constructed (Supplementary Fig. S2, http://links.lww.com/MD/E707) with high goodness of model’s fit (R-squared 0.92), then each interval of probability was associated to a score interval. A ROC based on predicted probability of axillary burden was designed (Fig. 3), and the calculated optimal probability cut-off was 0.31%, which corresponded to a score best cut-off equal to 144.79 points, associated to a sensitivity of 68% and a specificity of 72% for hAB. AUC was equal to 0.76. Finally, an internal validation of model prediction accuracy was performed by bootstrap technique. The optimism index was equal to 0.02, thus the calculated AUC after bootstrap was 0.74. Essentially, we have added a bias correction to the apparent original AUC.

### 4. Discussion

Omission of ALND in the present study would not have correctly discriminated patients with 1-2 metastatic nodes only (69.0% of cases) from hAB patients. This distinction has a prognostic

### Table 2

| Adjuvant treatments and long-term outcomes between lAB and hAB patients. |
|---------------------------------|--------------------------|------------------|------------------|
|                                 | Low axillary burden (n = 187) | High axillary burden (n = 84) | P value |
| Hormone therapy                 |                          |                          |
| Yes                            | 165 (88.2%)              | 69 (82.1%)              | .18 |
| No                             | 22 (11.8%)               | 15 (17.9%)              |     |
| Radiation therapy              |                          |                          |
| Whole breast                   | 167 (89.3%)              | 39 (46.4%)              | .<.0001 |
| Loco-regional                  | 20 (10.7%)               | 45 (53.6%)              |     |
| Chemotherapy                   |                          |                          |
| Yes                            | 62 (33.2%)               | 60 (71.4%)              | .<.0001 |
| No                             | 125 (66.8%)              | 24 (28.6%)              |     |
| Mean follow up (mo)            | 52.3 (±35.5)             | 54.4 (±34.0)            | .65 |
| Loco-regional recurrence       |                          |                          |
| Yes                            | 0 (0.0%)                 | 5 (6.0%)                | .001 |
| No                             | 187 (100.0%)             | 79 (94.0%)              |     |
| Distant metastases             |                          |                          |
| Yes                            | 8 (4.3%)                 | 11 (13.1%)              | .01 |
| No                             | 179 (95.7%)              | 73 (86.9%)              |     |
| Cancer-related death           |                          |                          |
| Yes                            | 3 (1.6%)                 | 5 (6.0%)                | .11 |
| No                             | 184 (98.4%)              | 79 (94.0%)              |     |

lAB = low axillary burden, hAB = high axillary burden.

### Table 3

| Multivariate analysis for preoperative predictive factors of high axillary burden. |
|---------------------------------|--------------------------|------------------|------------------|
|                                 | Prediction of high axillary burden | OR | 95% CI | P value |
| Age at diagnosis                |                          | 1.00 | 0.97-1.02 | .90 |
| Lesion size on imaging          |                          | 1.04 | 1.00-1.08 | .05 |
| Mammographic findings           |                          |     |        |      |
| BI-RADS 3 vs 1                  |                          | 1.56 | 0.37-6.68 | .55 |
| BI-RADS 4 vs 1                  |                          | 0.98 | 0.39-2.49 | .97 |
| BI-RADS 5 vs 1                  |                          | 0.50 | 0.12-2.01 | .33 |
| Ultrasound findings             |                          |     |        |      |
| U-RADS 3 vs 1                   |                          | 0.26 | 0.04-1.74 | .17 |
| U-RADS 4 vs 1                   |                          | 0.63 | 0.21-1.82 | .39 |
| U-RADS 5 vs 1                   |                          | 1.35 | 0.37-4.92 | .65 |
| Multifocal disease              |                          |     |        |      |
| Yes vs no                       |                          | 2.90 | 1.44-5.84 | .003 |
| Histological type               |                          |     |        |      |
| Invasive lobular vs ductal      |                          | 1.35 | 0.56-3.26 | .51 |
| Grading                         |                          |     |        |      |
| 2 vs 1                          |                          | 1.45 | 0.37-5.74 | .60 |
| 3 vs 1                          |                          | 2.34 | 0.51-10.74 | .27 |
| Biological portrait             |                          |     |        |      |
| Luminal A vs TNBC               |                          | 1.25 | 0.31-5.09 | .76 |
| Luminal B vs TNBC               |                          | 1.05 | 0.29-3.76 | .94 |
| HER2-positive vs TNBC           |                          | 1.01 | 0.06-18.40 | .99 |
| Lympho-vascular invasion        |                          |     |        |      |
| Present vs absent               |                          | 1.49 | 0.78-2.86 | .23 |
| Extramedal extension            |                          | 5.51 | 2.27-13.41 | .002 |
| Positive SLNs/Total SLNs ratio  |                          | 10.95 | 2.50-47.93 | .001 |

CI = confidence intervals, OR = odds ratio, SLN = sentinel lymph node.
relevance, since no LRR was observed in the former group vs. 6.0% in the latter group \( (P = .001) \), and distant metastases were 3-fold more frequent in hAB patients \( (P = .01) \), highlighting 2 distinct cohorts of patients from a prognostic point of view. Considering that cancer-related baseline variables were substantially balanced between the 2 groups, particularly biological subtype \( (P = .98) \), histological type \( (P = .11) \) and grading \( (P = .12) \), the extent of axillary nodal involvement confirmed to be a key prognostic determinant, as well established in literature.\(^{[19]}\)

A proper distinction of patients with low or hAB is therefore mandatory to properly escalate or de-escalate adjuvant treatments, following what has been insistently recommended even in a recent St. Gallen consensus conference.\(^{[20]}\) A personalized treatment of breast cancer should not simply translate into less ALNDs, but rather should address the most appropriate axillary surgery for each patient. Notably, chemotherapy was confidently avoided in 66.8% of lAB patients despite 1 or 2 macro-metastatic axillary nodes, and these patients experienced significantly less events compared to hAB (Log-rank \( P = .001 \) for LRR and \( P = .01 \) for DM). Oppositely, up to 58% of patients accrued in the Z0011 trial were treated by upfront chemotherapy despite low-risk features (T1-T2 Luminal-type cancers) and despite a micro-metastatic SLN in 44.6% of cases, in the absence of precise information about their axillary status.\(^{[21]}\) Is a less accurate staging of the axilla really a benefit for node-positive patients, if chemotherapy is then routinely used? Nodal involvement is still a fundamental predictive factor. As recently demonstrated by the MINDACT trial and recommended by the American Society of Clinical Oncology, the use of genomic biomarkers assays to guide decisions on adjuvant chemotherapy in these patients may be adopted, but the correct knowledge of axillary status is indispensable.\(^{[21]}\) Indeed, patients with more than 3 positive nodes are considered at higher risk and could take advantage from chemotherapy, while some patients with 1-3 positive nodes may safely avoid chemotherapy if classified as low-risk based on cancer biology.\(^{[22]}\)

Guidelines indicate the irradiation of supraclavicular and internal mammary nodes when 4 or more metastatic axillary nodes are encountered.\(^{[23]}\) Accordingly, loco-regional radiotherapy was administered in 10.7% of lAB patients only vs. 53.6% of hAB cases \( (P < .0001) \), but no LRR was observed in the formers. Therefore, distinguishing N2 from N1 patients is still relevant to properly tailor the adequate radiotherapy for each patient, because the majority of N1 patients undergoing breast-conserving surgery could safely receive only whole-breast irradiation.\(^{[21]}-^{[23]}\) Remarkably, the majority of Z0011 patients received whole-breast irradiation with high tangential field to cover at least axillary level 1.\(^{[22]}\) The AMAROS trial showed that axillary irradiation is not free from complications, despite fewer than ALND, and up to 15% of patients experienced lymphedema one year after treatment.\(^{[9]}\) Thus, again the question is: always better to ignore the exact axillary nodal burden and propose routine axillary radiotherapy, also in patients with 1-2 positive nodes?

According to what emerged from the logistic regression in the present study, the strongest predictor is the ratio between the number of positive SLNs and the total of harvested SLNs (OR 10.95, \( P = .001 \)). In other words, also the number of negative

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Figure 2. Nomogram to predict more than 2 positive axillary nodes in patients fulfilling the Z0011 inclusion criteria.

Figure 3. Performance of the proposed nomogram in predicting more than 2 positive axillary nodes evaluated by receiver operating curve.
SLNs is necessary to predict residual nodal disease, and a higher mean of negative SLNs per patient was associated to IAB ($P=.01$). A patient with 1 retrieved SLN which resulted to be metastatic has a higher probability of residual nodal disease compared to another patient with 1 positive and 1 negative SLN. Another fundamental parameter to estimate the risk of hAB is the presence of ENE, as previously reported in other models. Indeed, ENE is strongly predictive of >2 positive nodes, and better refines the risk prediction independently from the number of retrieved SLNs. Also multifocal disease was a relevant predictor for hAB, but its usefulness is much less clear considering that it is observed in a low proportion of patients.

Among the tested nomograms to predict nonsentinel nodal disease, the Mayo and MSKCC models showed the best ROC curves, since these nomograms greatly rely on the number of negative SLNs, and a higher total score is assigned if zero negative SLNs are retrieved. An overall weak performance was observed with the other nomograms, with lack of specificity and classification of most patients as high-risk. The inaccuracy was due to the generally low number of negative SLNs and the fact that these nomograms were developed to globally predict non-sentinel nodal disease, and not to specifically discriminate IAB from hAB patients. Therefore, the use of currently validated nomograms may lead to over-estimation of axillary burden and subsequent increase in unnecessary ALND or use of adjuvant chemotherapy or loco-regional irradiation, thus losing the opportunity offered by the Z0011 findings if 1-2 SLNs only are retrieved.

The present study has 2 major limitations. First, findings derived from a relatively small retrospective series of patients, thus selection bias could have occurred especially in the analysis of outcomes. Distribution of some baseline characteristics was unbalanced between IAB and hAB patients, and ROC curves could be affected by unbalanced data, posing a risk of biased conclusions. Secondly, the developed nomogram has been internally validated by bootstrap technique, but only external validation could really confirm its clinical value. Therefore, the observed higher AUC of the present nomogram, compared to performance of the other published nomograms in our series, should be considered potentially overestimated. Further comparative studies on larger external series are needed to validate these findings.

In conclusion, the present study proposes a novel nomogram specifically developed to predict the presence of >2 positive nodes in patients treated by breast-conserving surgery who fulfill the Z0011 inclusion criteria, in whom 1-2 SLNs only are retrieved. This nomogram, if externally validated, might safely select those patients in whom ALND still could be necessary for a proper staging to guide subsequent adjuvant treatments.

Author contributions

FC and LS conceived and designed the analyses; SA performed the analyses; DB, CM and LV collected data and contributed to data analyses; MT, LS and FC wrote the manuscript.

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