LEADING ARTICLE

Evaluation of a breast cancer nomogram for predicting the likelihood of additional nodal metastases in patients with a positive sentinel node biopsy

Ann. Ital. Chir., 2012 83: 461-468
pii: S0003469X12017630

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AIM: *Completion axillary lymph node dissection (CALND) performed as a standard procedure after a positive sentinel node biopsy (SLNB) in breast cancer patients results, in almost 40-70% of cases, in no additional positive nodes. A nomogram has been developed at Memorial Sloan Kettering Cancer Center (MSKCC) to predict the likelihood of non-sentinel node metastases (NSLNM) after a positive SLNB. Aim of study was to assess the accuracy of MSKCC nomogram in our community breast cancer population.*
MATERIAL OF STUDY: *From a retrospective database of 276 breast cancer patients we evaluated 62 consecutive cases who underwent CALND after a positive SLNB. Patient and tumor characteristics were collected and the nomogram was used to calculate the probability of NSLNM. The accuracy of MSKCC nomogram was tested by the Receiver Operating Characteristic (ROC) curve. The Area Under the Curve (AUC), sensitivity and specificity were calculated for a 10% cut-off value.*
RESULTS: *Presence of macrometastases (p=0.03) and its extranodal extension (p=0.013) in sentinel node were associated with NSLNM, while other tumor and patient characteristics were not. The accuracy of MSKCC nomogram as measured by AUC was 0.67. The nomogram showed 95% sensitivity and 14% specificity. We revised the nomogram by incorporating the presence of extranodal extension and we obtained a new test with improved specificity (84%).*
DISCUSSION: *The modified predictive model is a useful tool in predicting the likelihood of NSLNM in our cohort of patients and may help decision regarding the need of completion axillary lymph node dissection.*

KEY WORDS: Breast cancer, Nomogram, Sentinel node.

Introduction

Axillary staging is still the single most important prognostic factor in breast cancer patients. Sentinel lymph node biopsy (SLNB) can accurately stage axilla in early breast cancer clinically node negative patients. Completion axillary lymph node dissection (CALND) is recommended by international guidelines as the gold standard for patients with proven metastases in the sentinel lymph node (SLN), in order to improve accurate staging and achieve local control of disease[1,2].
However, in almost 40-70% of positive SLNB, no additional NSLN metastases is detected. In these patients, it has been demonstrated that CALND offers no prognostic nor therapeutic benefits and adds significant risk of mor-

Pervenuto in Redazione Marzo 2011. Accettato per la pubblicazione Giugno 2011.
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bidity in terms of lymphedema, paresthesias and numbness[3-6].
Furthermore, even for patients with positive SLNB, the impact of immediate CALND on survival remains controversial since the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial[7], the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial[8], the Dutch MIRROR trial[9] and other studies[7,10-14] have not demonstrated a survival advantage in performing axillary dissection.
In order to avoid unnecessary CALND in patients with positive SLNB, several studies have investigated many clinicopathologic factors that may predict the risk of NSLN metastases[15-25]. None of these characteristics alone can identify a subset of patients with low risk for further axillary metastases, therefore, some authors have combined these factors and have developed mathematical models or scoring systems to predict the likelihood of additional nodal metastasis in patients with positive SLNB[26-30].
The first nomogram, which combines 8 variables, was published in 2003 by Van Zee and colleagues from the Memorial Sloan Kettering Cancer Center (MSKCC)[31]. The predictability of MSKCC nomogram has been validated with several studies[30,32-38], so it has been internationally accepted. However, other trials showed its limitations and loss of accuracy in certain series of patients[28,29,39-41].
The aim of the study was to assess the accuracy of the MSKCC nomogram in predicting NSLN metastases in a consecutive series of early breast cancer patients observed at our Surgical Department in order to test its generalizability.

Material and methods

Patients selection

We retrospectively reviewed 276 consecutive breast cancer patients who underwent SLNB at the Department of General Surgery of Trieste University between January 2003 and May 2009.
Our study population is the result of a selection of 62 breast cancer patients with positive SLNB who had CALND.
Data and clinical information were recorded from patient charts, radiology and pathology reports.
The study group was collected according to the following criteria:
– pathological diagnosis of primary breast carcinoma demonstrated by fine needle aspiration (FNA) or core biopsy (CB) or VAB-Mammotome®;
– American Joint Committee on Cancer (AJCC)[42] clinical T1-T2 disease at presentation;
– clinical and/or pathological negative axilla (ultrasound-guided FNA);
– SLNB performed at the Department of General Surgery of Trieste University;
– definitive surgical treatment (breast conserving surgery or mastectomy and delayed CALND) performed at the Department of General Surgery of Trieste University;
– pathological analysis of surgical samples performed at the Department of Pathology of Trieste University.
We excluded from the study patients who had primary chemotherapy.

Technique of SLNB

The SLN was identified by preoperative lymphoscintigraphy associated, in a few cases, to peritumoral intraoperative injection of Blue Patent V.
According to our protocol, the day before surgery the patient received ^{99}Tc-labeled sulfur colloid injected subdermal surrounding the tumor. For non-palpable lesions the injection was guided by a charcoal-marker previously placed under ultrasound (US) or stereotactical guidance. On the day of surgery a handheld gamma detection probe (Ecam-Siemens®) was used to scan the axilla transcutaneously in order to identify the most radioactive area and perform SLNB.
For patients who underwent lymphatic mapping with combination of radiotracer and blue dye, 5-7 mL of Blue Patent V was injected into the breast peritumorally and the breast was compressed intermittently for 5-7 minutes.
Any lymph node with blue dye uptake, radiotracer uptake or both was identified as SLN and excised. The dissection was conducted till background axillary radioactivity decreased at values inferior to tenfold maximum activity and after all blue-stained nodes were excised.
At the same time the patient underwent breast surgical procedure in terms of conservative surgery or mastectomy followed by immediate reconstruction.

Pathological evaluation of SLN

The SLN was analysed according to our institutional protocol. In the present series no intraoperative examination of frozen sections nor imprint cytology were performed and definitive analysis provided standard hematoxylin and eosin (H&E) and immunohistochemical staining (IHC).
From 2003 to 2008, SLNs were serially sectioned at 50 μm, after 2008 at 100 μm and alternate levels were evaluated by routine H&E staining and analyzed for cytokeratin by IHC.
The pathologist evaluated the following features:
– number of negative SLNs;
– number of positive SLNs;
– ratio between positive SLNs and total amount of SLNs excised;

– metastases size: we considered SLN as macrometastatic if the largest metastases diameter exceeded 2 mm, as micrometastatic if the largest metastatic diameter was smaller than 2 mm. Patients with isolated tumor cells (ITC) in the SLN, defined as metastases size inferior to 0.2 mm, were excluded from the study group, because they didn't undergo CALND.
Method of detection of SLN metastases: routine H&E, serial H&E, IHC.
presence of extranodal extension in the SLN.

Data analysis

Variables routinely documented included patient age, primary tumor pathological size, presence of lymphovascular invasion, multifocality, hystological type (ductal or lobular) and grade, estrogen receptor status and the SLN characteristics previously reported.
Univariate analysis (Chi-square test, F-Fisher test and Mann-Whitney test) was made in order to find out any correlation between NSLN metastases and certain pathological characteristics.
The online "frozen-no" version on MSKCC nomogram was downloaded from the site http://mskcc.org/mskcc/htlm/5794.cfm and was used to calculate the risk of axillary NSLN positivity in each case.
The likelihood of additional nodal metastases measured by the test was matched with NSLN status obtained thanks to CALND. To measure the discrimination of the nomogram, a receiver operating characteristic (ROC) curve was constructed and the area under the curve (AUC) was calculated. It is generally accepted that the AUC values 0.7-0.8 represent considerable capacity of a test to discriminate a diseased from a non-diseased subject across all possible levels of positivity. However, assuming the test to be positive for a cut-off predictive percentage risk of 10% or more, both sensitivity and specificity were calculated.
Statistical analysis was conducted with software R (R Project for Statistical Computing).

Results

We evaluated the records of 276 consecutive patients who underwent SLNB for breast cancer between January 2003 and May 2009. Sixty-two of these (22.5%) had at least one positive SLN and subsequently underwent CALND.
Information about the characteristics of our study group are listed in Table I.
The median patient age was 60.9 years (range, 33-84). The median tumor size was 17 mm (range, 7-50 mm) and multifocality was present in 18 patients (29%). The predominant primary tumor histological type was invasive ductal carcinoma (50 patients, 80.7%); 12 patients had invasive lobular carcinoma (19.3%). Most tumors were histological grade 2 (36 patients, 58.1%). In 87.1% of cases the primary tumor showed estrogen receptor positivity and lymphovascular invasion was documented in 24 patients (38.7%).
SLNB allowed the dissection of a median number of 2.7 SLNs (range 1-9). SLN characteristics are listed in Table II. With CALND we were able to excise a median of 13.9 NSLNs (range, 10-30). After CALND, 43 patients out of 62 (69.3%) had NSLN free of tumor while other 19 patients presented further axillary NSLN metastases (30.7%).
Table III shows the results of the statistical analysis to determine the relationship between clinicopathologic factors and NSLN positivity. The presence of macrometastases of more than 2 mm in size (p=0.032) and extranodal extension in SLN (p=0.013) were significantly associated with NSLN positivity. Age, primary tumor size, multifocality, estrogen receptor status, histological type and grade, lymphovascular invasion, number of SLNs totally dissected, number of positive SLNs, ratio and method of detection of metastases in SLN were not statistically associated with NSLN involvement.
The overall predictive accuracy of the nomogram, as measured by the AUC was 0.67 (Fig. 1). Sensitivity and specificity of the nomogram in identifying patients with NSLN metastases at threshold-predicted probability of 10% were respectively 95% and 14%.

Table I - *Descriptive characteristics of the patients population.*

Age	**N° cases (n= 62)**
≤50	14 (22.6%)
>50	48 (77.4%)
Tumor size (cm)	
≤0.5	0 (0%)
0.6-1.0	12 (19.4%)
1.1-2.0	31 (50%)
2.1-3.0	16 (25.8%)
3.1-5.0	3 (4.8%)
≥5.1	0 (0%)
Tumor type and nuclear grade	
Ductal I	6 (9.7%)
Ductal II	36 (58.0%)
Ductal III	8 (12.9%)
Lobular	12 (19.4%)
Multifocality	
Yes	18 (29%)
No	44 (71%)
Lymphovascular invasion	
Yes	24 (38.7%)
No	38 (61.3%)
Estrogen receptor status	
Positive	54 (87%)
Negative	8 (13%)

Table II - *Descriptive characteristics of the SLN.*

Age	N° cases (n= 62)
Method of metastases detection	
Immunohistochemistry	7 (11.3%)
Serial H&E	11 (17.7%)
Routine H&E	44 (71%)
Frozen section	0 (0%)
Number of positive SLNs	
1	47 (75.8%)
2	12 (19.4%)
3	2 (3.2%)
4	0 (0%)
5	0 (0%)
6	1 (1.6%)
7	0 (0%)
≥8	0 (0%)
Number of negative SLNs	
0	19 (30.6%)
1	17 (27.4%)
2	14 (22.6%)
3	4 (6.4%)
4	0 (0%)
5	4 (6.4%)
6	1 (1.6%)
7	1 (1.6%)
≥8	2 (3.2%)
Metastases size (mm)	
≥ 2	39 (63%)
< 2	23 (37%)

Table III - *Results of statistical analysis of relationship between NSLN metastases and patients clinicopathological features.*

Predictive Factor	p-value
Metastasis size ≥ 2 mm	0.03
Extranodal invasion	0.01
Histological type	0.08
Histological grade	0.17
Lymphovascular invasion	0.16
Number of SLNs totally dissected	0.16
Number of positive SLNs	0.16
Estrogen-receptor positivity	0.24
Primary tumor size	0.77
Multifocality	0.77
Ratio positive SLN/SLN totally dissected	1
Method of metastastases detection	1

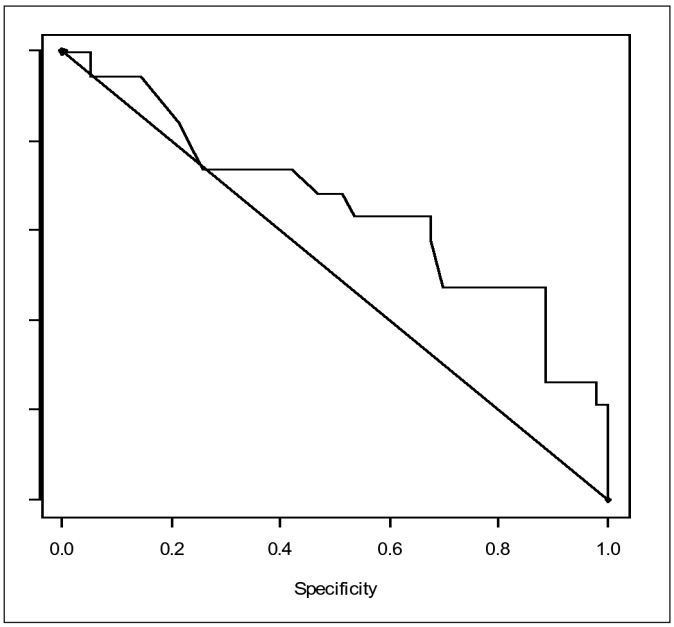

Fig. 1: Receiver operating characteristics curve for the MSKCC nomogram.

Table IV - *Results of MSKCC nomogram with cut off value of 10% in predicting the status of NSLN (sensitivity .95, specificity .14).*

	MSKCC nomogram neg (≤10%	MSKCC nomogram pos (>10%)	Tot.
NSLN metastases			
no	6	37	43
yes	1	18	19
Tot	7	55	62

Table V - *Results of the new test (MSKCC nomogram with cut off value of 10% and presence of extranodal invasion as predictive factor) in predicting the status of NSLN (sensitivity .95, specificity .84).*

	MSKCC nomogram neg (≤10%) extranodal invasion	MSKCC nomogram pos (> 10%) extranodal invasion	Tot.
NSLN metastases			
no	36	7	43
yes	1	18	19
Tot	37	25	62

The probability of NSLN metastases as calculated by the nomogram with a selected cut-off at 10% was cross matched with the presence or absence of extranodal extension, which is a predictive factor of NSLN positivity typical of our population and not considered by MSKCC investigators (Table IV and V).
The modified test showed sensitivity and specificity of respectively 95% and 84%.

Discussion and commentary

The aim of axillary dissection in clinically node negative breast cancer patients is to stage the disease and to guide therapeutic decision making by determine the need of adjuvant therapy [1,2].
SLNB is well demonstrated to be a less invasive alternative to the routine CALND historically performed.

SLNB is an accurate technique which provides precise staging as well as prognostic information with lower risk of morbidity if compared to CALND, as demonstrated by many studies [5,43,44].

Therefore, SLNB has become the gold standard of treatment for clinically node negative early breast cancer patients. CALND is still recommended for patients with metastatic SLN, in order to achieve regional disease control and provide further prognostic information [2].

However, there is a growing evidence to suggest that, in clinically node negative patients with positive SLNB, CALND may not be always necessary. From the prognostic perspective, the axillary status can be successfully and precisely determined by SLNB alone[2,5]. From the therapeutic point of view, adjuvant systemic therapy is usually given to the great majority of patients with positive SLNB and tangential field irradiation commonly used in association of breast conserving surgery treats much of axilla.

Furthermore, two large prospective clinical trials[7,10] and a number of smaller studies of varying designs from the past 5 years[4,9,11-14] failed to demonstrate a survival advantage in performing immediate CALND in clinically node negative patients. In addition, at American Society of Clinical Oncology (ASCO) 2010 Annual Meeting, AE Giuliano and colleagues presented the results of the ACOSOG Z0011 trial[8]. In the study, clinical T1-2 N0 M0 breast cancer patients with at least 1 or 2 positive SLN were randomised to either no further treatment or CALND. No significant differences in overall survival at 8 years and disease-free survival between patients treated with CALND and those treated only by SLNB were found. The trial has been closed prematurely due to slow accrual and failed to reach the target of 1900 patients. Despite this, it remains the largest perspective randomised phase III study which compares CALND versus observation in breast cancer SLNB positive patients. Moreover, 40-70% of patients with positive SLNB present no further axillary metastases at CALND[3,5,6]: it seems that a large group of patients will not receive any benefit from CALND and will potentially suffer from its morbidity.

So, since the prognostic and therapeutic value of CALND is placed under discussion and constitutes centre of much debate, it could be useful to identify a subset of positive SLNB patients in which CALND can be avoided.

In our series, in 69.3% of cases the SLN was the only metastatic lymph node, so those patients underwent unnecessary CALND.

Several clinicopathologic characteristics of both the primary tumor and the SLN influence the risk of NSLN metastases[15-25]. The size of primary tumor and the size of SLN metastases have been shown in many studies to be independent predictive factors for NSLN metastases[15]. Other features have been reported as predictive of further axillary involvement: number of positive SLNs, ratio between positive SLNs and SLNs globally dissected, lymphovascular invasion, estrogen-receptor status. However, because of the variability in study designs and in cohorts of patients analyzed, none of these factors alone could precisely estimate the risk of NSLN metastases.

According to several studies[15-20], in our cohort of patients the presence of a SLN metastases greater than 2 mm was strongly related to NSLN positivity. On the other hand, primary tumor size was not statistically associated with high risk for NSLN metastases probably because the average tumor size in our series is smaller than that reported by others. In the study population of Van Zee et al.[31], that has constituted the basis for the creation of the MSKCC nomogram, 88% of patients presented primary tumor size smaller than 30 mm, having the other patients lesions greater than 30 mm. Our study population consists of 96% of patients with lesions smaller than 30 mm with an average tumor size of around 17 mm. Similar data were presented by Cserni et al.[45]: they showed that in a series of cases selected for small size of primary tumor the relationship between tumor size and risk for NSLN metastases is feeble.

Furthermore, in our experience, the presence of extracapsular extension by the SLN metastases was strongly associated to higher risk of NSLN positivity. This finding, which represents an important predictive factor in our experience, is not used by Van Zee and colleagues in the nomogram: this could probably imply a loss of discrimination power of the MSKCC nomogram when applied to the patients of our database. As a matter of fact, the overall predictive accuracy of the nomogram in our study group as measured by the AUC was 0.67.

This nomogram has been previously validated at several institutions and it has been extensively demonstrated as a useful tool for calculating the estimate risk of NSLN involvement[30,32-38].

But other institutions have concluded that the nomogram has limitations. According to Alran et al[37], who presented a study which validated the MSKCC nomogram, practitioners must be cautious when using the MSKCC nomogram in patients with micrometastases: in the study 35% of 588 patients had micrometastases and the nomogram could not be able to predict the NSLN status in this subgroup of patients. Similar results were reported by Gur and colleagues[36] and are coherent with our experience of a study population with 37% of patients with micrometastatic SLN. Conversely, Kohrt et al.[30] validated the nomogram with an AUC value of 0.77 in a study cohort with 93% of micrometastasis rate. Such heterogeneous findings could be explicated by considering that the MSKCC nomogram does not include the size of SLN metastases as a predictive parameter and uses the method of SLN detection as a surrogate of metastases size, with frozen section detecting the largest metastases and IHC alone detecting the smallest.

Moreover, differences in the pathologic assessment of the SLN could be the likely cause of the different results

obtained by various studies. As proposed by Kocsis et al[39], thinner sections and more detailed tissue sampling could reduce the number of metastases detected by IHC alone and potentially contribute to alter the accuracy of the nomogram. At our institution we do not perform frozen sections nor imprint citology of the SLN and we usually provide serially sectioning at 100 µm with possible impairment of the accuracy of the nomogram.
Another important difference among studies is the variability in surgical dissection technique of SLNB. Several institutions, including MSKCC investigators and our own, advocate removing all nodes with blue dye tracer uptake or radioactive tracer uptake or both, while other investigators usually stop dissection after a certain number of SLNs removed[46]. As a consequence, the number of SLN dissected and excised may alter the nomogram accuracy, since an increased number of involved NSLN may correspond to fewer SLNs removed at mapping.
The accuracy of MSKCC nomogram in our patients population was not optimal and its quite limited reproducibility is due to two possible reasons.
First, our cohort of patients differs from MSKCC: we reported a strong correlation between metastases size and presence of NSLN involvement, but the nomogram considers the factor only in an indirect way, by using the diagnostic method for metastases as a surrogate for its size. Secondly, the nomogram does not consider the presence of extranodal invasion of SLN, which was the most powerful predictive characteristic in our series.
For a cut-off value of 10% we calculated a sensitivity of 95%, but a specificity of 14% which is absolutely inadequate because it relies on a high percentage of false-positive cases. As a consequence, the low specificity may be the cause for a high number of unnecessary CALND in patients thought to be metastatic but being not involved.
In order to improve the specificity of the test and to adapt it at our own population with its typical characteristics, we re-evaluated each case and introduced the presence or absence of extranodal invasion as a corrective factor. We obtained a new test derived from the combination of the risk estimated by the MSKCC nomogram and the presence or absence of our most powerful prognostic factor with the same sensitivity but an improved specificity (84%).

Conclusions

The MSKCC nomogram showed a fairly accurate prediction of NSLN involvement in our cohort of breast cancer patients. However it should be used with caution when counseling patients about the risk of additional nodal disease, because of its low specificity. It seems that consideration of extranodal extension of disease may be useful in our own population to improve the specificity of the test and helps accuracy of prediction that may guide decision making regarding the need of completion axillary lymph node dissection in high risk patients.

Authors' disclosures of potential conflicts of interest
The authors indicated no potential conflicts of interest.

Riassunto

OBIETTIVO: Le attuali linee guida prevedono l'esecuzione della dissezione ascellare completa (DA) in tutte le pazienti portatrici di carcinoma mammario e linfonodo sentinella (LS) metastatico. Tale procedura, nel 40-70% dei casi, non evidenzia ulteriori metastasi linfonodali ascellari. Allo scopo di evitare l'esecuzione di linfadenectomie ascellari potenzialmente inutili, al Memorial Sloan Kettering Cancer Center (MSKCC) è stato sviluppato e validato un nomogramma in grado di esprimere la probabilità metastasi ai linfonodi ascellari non sentinella. Scopo del lavoro è la valutazione dell'applicabilità di tale algoritmo alla presente popolazione di pazienti con carcinoma mammario e biopsia del linfonodo sentinella positiva (BLS).
MATERIALI E METODI: A partire da un database di 276 pazienti sottoposte a BLS presso il Nostro Istituto è stata eseguita un'analisi retrospettiva delle pazienti portatrici di LS metastatico e sottoposte a DA. In particolare è stato applicato il nomogramma elaborato al MSKCC per calcolare la probabilità di metastasi ai linfonodi non sentinella propria di ciascuna paziente. L'accuratezza di tale nomogramma è stata, quindi, testata mediante la costruzione di una curva ROC ed il calcolo dell'area al di sotto della curva (AUC), della sensibilità e della specificità del test per un valore di cut-off pari al 10%.
RISULTATI: Nella casistica in esame, la presenza di macrometastasi al LS (p=0.03) ed il superamento capsulare da parte della stessa (p=0.013) sono risultate due caratteristiche correlate in maniera statisticamente significativa alla presenza di coinvolgimento neoplastico dei linfonodi non sentinella. L'applicazione del nomogramma del MSKCC alla nostra popolazione di pazienti ne ha dimostrato la buona accuratezza (AUC pari a 0.67) ed un'ottimale sensibilità (95%) a fronte di una specificità non adeguata (14%). L'introduzione del superamento capsulare quale fattore correttivo di calcolo ha portato all'elaborazione di un nuovo algoritmo caratterizzato da una migliore specificità (84%) che ne consente l'applicabilità alla popolazione in esame.

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