

Clinicopathologic factors predicting involvement of nonsentinel axillary lymph nodes in breast cancer patients: Is axillary dissection always indicated?



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Clinicopathologic factors predicting involvement of non sentinel axillary lymph nodes in breast cancer patients: is axillary dissection always indicated?

AIM: *The aim of this study was to determine factors that predict non-sentinel axillary lymph nodes (NSLNs) metastases in breast cancer patients with positive sentinel node biopsy (SLNB).*

MATERIAL OF STUDY: *We reviewed the records of a consecutive series of 176 breast cancer patients who underwent SLNB at our institution. From the database we analysed those cases with one or more positive sentinel lymph nodes (SLNs) in order to determine factors predicting NSLN metastases.*

RESULTS: *From a series of 176 consecutive patients, we evaluated 41 cases (23.3%) with positive SLNB. Subsequent completion axillary lymph node dissection (CALND) revealed NSLN metastases in 15 cases (36.6%). The significant variables predictive of NSLN involvement were the presence of macrometastases with extranodal extension ($p=0.048$), the presence of more than one positive SLN ($p=0.08$) and a ratio between positive SLN and SLNs globally dissected higher than 0.5 ($p=0.05$).*

DISCUSSION: *CALND is the gold standard for patients with positive SLNB, but results, in almost 40-70% of cases, in no additional positive nodes and its therapeutic benefit remains controversial. Clinicopathologic factors predictive of NSLN metastases may be useful in identifying a subset of patients with lower risk of further axillary involvement.*

CONCLUSIONS: *In patients with early breast carcinoma and a positive SLNB, the size of SLN metastases, the presence of extranodal extension, more than one positive SLN and a nodal ratio higher than 0.5 are the factors that significantly increase the frequency of additional axillary positive lymph nodes.*

KEYWORDS: Axillary metastases, Breast cancer, Prediction.

Introduction

In the last decades the management of breast cancer has changed dramatically. From the Halsted concept of a disease localized in the breast tissue with an orderly pat-

tern of metastases moving from the primary tumor to regional lymph nodes and then to the systemic circulation, we moved to another hypothesis, which identifies breast cancer as a systemic disease since its own birth. Lymph node involvement and distant metastases are reflective of a complexity of factors, most of them related to primary tumor biological and morphological features.

Therefore, gradually the extent of breast operations has evolved from radical mastectomy to modified radical mastectomy to breast conserving surgery (quadrantectomy or lumpectomy followed by radiation therapy)^{1,2}.

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Regarding to clinically lymph node early breast cancer patients, axillary dissection has become a staging procedure, performed in order to gain prognostic information and to help decision making especially for adjuvant systemic therapy since axillary status is still the single most important prognostic factor in breast cancer patients^{3,4}. Over the past decade, sentinel lymph node biopsy (SLNB) has emerged as an important tool for determining the involvement of the axillary lymph nodes in clinically node negative early breast cancer patients. Several studies and many prospective trials have demonstrated that SLNB can accurately stage axilla because the status of sentinel lymph node (SLN) precisely reflects the status of the entire nodal basin⁵⁻⁷. Therefore SLNB has become a less invasive alternative to axillary dissection. Completion axillary lymph node dissection (CALND) is still indicated for those patients with clinically positive axillary lymph nodes in order to achieve local control of disease and in early breast cancer patients with positive SLNB in order to improve accurate staging. CALND may also offer an advantage in terms of reduced regional recurrence in patients who harbor residual axillary lymph node metastases, but in almost 40-70% of positive SLNB, no additional NSLN metastases is detected⁸⁻¹⁰. In those patients, CALND offers no prognostic nor therapeutic benefits, since the removal of negative lymph nodes does not provide any benefit and adds significant risk of morbidity in terms of lymphedema, paresthesias and numbness⁸⁻¹¹. Furthermore, even for patients with positive SLNB, CALND has been questioned, because its survival benefit remains uncertain^{12,13}. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial¹⁴, the American College of Surgeons Oncology Group (ACOSOG) Z-0011 trial¹⁵, the Dutch MIRROR trial¹⁶ and other studies¹⁴⁻²¹ failed of demonstrating a survival advantage in performing axillary dissection. In order to identify a subset of patients with positive SLNB and low risk or NSLN metastases, several studies have investigated many clinicopathologic factors that may predict the risk of NSLN metastases²²⁻³². Patients

with a predicted small chance of residual axillary lymph node metastases after a positive SLNB might be able to safely avoid CALND and its morbidity. Conversely, prediction of the high likelihood of residual axillary lymph node metastases may identify patients for whom CALND is probably still necessary.

In this study we analysed various clinicopathologic features of early breast cancer patients with positive SLNB in order to determine factors that might help estimate the risk of NSLNs involvement.

Materials and methods

PATIENTS SELECTION

We retrospectively reviewed the records of 176 consecutive breast cancer patients who underwent breast cancer surgery and SLNB at the Department of General Surgery of Trieste University in the last four years. Our study population is the result of a selection of 41 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)³³ clinical stage T1 or T2 disease at presentation, with an estimated maximum size of lesion of 30 mm;
 - clinically and pathologically negative axilla;
 - SLNB performed at the Department of General Surgery of Trieste University;
 - definitive surgical treatment 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.

TABLE I - Results of statistical analysis of relationship between NSLN metastases and patients clinicopathological features.

Predictive factor	p-value
Metastasis size \geq 2 mm and extranodal extension	0.048
Multiple metastatic SLNs	0.008
Ratio positive SLN/SLN totally dissected	0.05
Histological type	0.08
Patient Age	0.84
Estrogen-receptor positivity	0.16
Histological grade	0.17
Lymphovascular invasion	0.19
HER2 presence	0.61
Primary tumor size (T)	0.72
Ki67 \geq 25%	0.72

SURGICAL TREATMENT

All patients underwent surgical procedure for breast cancer, either mastectomy or breast conserving surgery. The choice of performing a mastectomy instead of a quadrantectomy followed by radiation therapy in early breast cancer patients was based on the primary tumor size and localization as well as on the presence of multifocality, of a non-favourable proportion between the size of the tumor and the average of breast tissue, and, last but not least, on the patients requests. Mastectomy was performed according to skin sparing technique and was followed, whenever possible, by immediate reconstruction, either autologous either prothetic.

Breast conserving surgery was performed according to Veronesi technique of quadrantectomy, as it is presented in FONCaM guidelines³⁴. For non-palpable lesions, surgical excision was guided by a charcoal marker placed under ultrasound or stereotactical guidance preoperatively. All patients were submitted to postoperative radiation therapy, according to international recommendation. We performed no intraoperative radiotherapy.

At the same time of breast surgery, patients underwent SLNB. The sentinel node (SLN) was identified by preoperative lymphoscintigraphy associated, in several cases, to peritumoral intraoperative injection of Blue Patent V. According to our protocol, the day before surgery the patient received ⁹⁹Tc-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) 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, 5-7mL of Blue Patent V was injected into the breast peritumorally and the breast was compressed intermittently for 5 to 7 minutes.

A small axillary incision was made on the most radioactive area, and dissection with electrocautery was performed in order to carefully isolate each lymph node from the surrounding fatty tissue leaving intact the nodal capsule.

Any lymph node with blue dye uptake, radiotracer uptake or both was considered 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.

The nodes were immediately formalin fixed and sent to definitive pathological assessment.

All patients with positive SLNB underwent CALND according to Berg's 3 levels performed as a second, delayed surgical procedure. NSLNs were evaluated at definitive pathologic examination only with hematoxylin and eosin (H&E) and their total number as well as the number of positive ones were recorded.

PATHOLOGICAL EVALUATION OF SLN

The SLN was analysed according to our institutional protocol. No intraoperative examination of frozen sections nor imprint cytology were performed and definitive analysis provided standard H&E and immunohistochemical staining (IHC).

SLNs were bisected and after serially sectioned at 100 µm. One section of each pair was routinely stained with H&E whereas the other section was stained for cytokeratins by IHC.

The original histologic slides of all positive SLNs were reviewed and the actual size of the metastases was assessed and described. The recorded largest size of the metastases corresponded to its maximum diameter in the plane of the section or to the thickness of the metastatic foci calculated according to the number of involved contiguous sections and to the sectioning interval between them. According to the size of the SLN metastases, 5 categories were identified as proposed by the current AJCC-TNM classification:

- pN0(sn)(i-) No regional lymph node metastases histologically, negative IHC;
- pN0(sn)(i+) Malignant cells in regional lymph node(s) 0.2 mm (detected by H&E or IHC including isolated tumor cells-ITC);
- pN1mi(sn) Micrometastases (>0.2 mm and/or >200 cells but none >2.0 mm);
- pN1a(sn) Metastases in 1–3 axillary lymph nodes, at least one metastasis >2.0 mm;
- pN2(sn) Metastases in 4–9 axillary lymph nodes.

No molecular staining with RT-PCR were performed, so pathologic classification was not comprehensive of pN0(sn)(mol-) and pN0(sn)(mol+) categories.

Patients with positive SLNB with pathologic stage pN1(sn)(i+) was excluded from the analysis since they did not undergo CALND.

The pathologic analysis evaluated also the following features:

- number of negative SLNs;
- number of positive SLNs;
- ratio between positive SLNs and total amount of SLNs dissected;
- presence of extranodal extension in the SLN.

DATA ANALYSIS

In order to find out any correlation between NSLN metastases and certain clinicopathologic features, multiple variables were analysed in each of three categories: patient, tumor and SLN characteristics. Variables routinely documented included age, primary tumor pathological size, presence of lymphovascular invasion, histological type (ductal, lobular or other) and grade, estrogen receptor status, ki67 positivity defined as ki67 ≥ 25%, HER2 positivity eventually confirmed by FISH and the SLN characteristics previously reported.

Univariate analysis was carried out using the Chi-square test, F-Fisher test and Mann-Whitney test for categori-

cal variables and the T-Test of Student for continuous variables.

Statistical analysis was conducted with software R (R Project for Statistical Computing).

Results

Out of 176 consecutive breast cancer patients who underwent SLNB, 41 of them (23.3%) had at least one positive SLN and subsequently underwent CALND. The median patient age was 60.4 years (range, 38-84). The most frequent location of the tumor within the breast was the superior external quadrant (51.2%, n=21) and in 10 cases (24.4%) there was multifocality. Thirty-six patients (87.8%) underwent breast conservative surgery and had a quadrantectomy followed by post-operative radiation therapy, while in 5 cases (12.2%) we performed a skin sparing mastectomy with immediate reconstruction. The median tumor size was 17,2 mm (range, 6-50 mm). Thirty cases (73.2%) were recorded as T1 according to current ALCC-TNM classification: 7 T1b and 23 T1c. Ten patients (24.4%) had T2 lesions smaller than 30 mm while one patient was discovered to have a greater lesion. The predominant primary tumor histological type was invasive ductal carcinoma (32 patients, 78%); 5 patients had invasive lobular carcinoma (12.2%) and 4 patients had an apocrine lesion (9.7%). Most tumors were histological grade 2 (34 patients, 82.9%). In 85.4% of cases the primary tumor showed estrogen receptor positivity and HER2 presence was documented in 3 cases (7.3%). Lymphovascular invasion was recognizable in 16 patients (39%).

SLNB allowed the excision of a median number of 2.9 SLNs (range 1-11). Out of 41 patients, in 30 cases (73.2%) we found only one metastatic SLN, while in the rest of patients (n=11, 26.8%) there were multiple positive SLNs. Pathologic assessment revealed 16 (39%) micrometastases and 25 (61%) metastasis foci greater than 2mm.

Fifteen patients (36.6%) had additional metastases upon CALND and 26 patients (63.4%) had NSLN free of tumor. With CALND we were able to excise a median of 13.7 NSLNs (range, 10-30).

Table 1 shows the results of the statistical analysis to determine the relationship between all the variables and NSLN positivity. The presence of SLN macrometastases associated with extranodal extension ($p=0.048$), the presence of more than one positive SLN ($p=0.08$) and a ratio between positive SLN and SLNs globally dissected higher than 0.5 ($p=0.05$) were significantly associated with NSLN positivity. Conversely, age, primary tumor size, histological type and grade, lymphovascular invasion, estrogen receptor status, ki67 positivity, HER2 presence and number of SLNs totally dissected were not statistically associated with NSLN involvement.

Discussion and Commentary

The main role of axillary dissection in clinically node negative breast cancer patients is to stage the disease and to help therapeutic decision making by determine the need of adjuvant therapy^{3,4}.

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^{5,6,11}.

Therefore SLNB has become the standard of treatment for clinically node negative breast cancer patients. CALND is still recommended for patients with metastatic SLN, in order to achieve regional disease control and provide further prognostic information⁴.

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^{4,5}. 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^{14,17} and a number of smaller studies of varying designs from the past 5 years^{9,16,18-21} 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, A. Giuliano and colleagues presented the results of the ACOSOG Z0011 trial¹⁵. 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 prospective randomised study which compares CALND versus observation in breast cancer SLNB positive patients. In the majority of cases, patients with positive SLNB present no further axillary metastases at CALND^{5,8,10}, therefore it seems that a large group of those patients will not benefit from CALND and will potentially suffer from its morbidity. Moreover, since the prognostic and therapeutic value of CALND is placed under discussion and constitutes centre of much debate, it is useful to identify a subset of positive SLNB patients in which CALND can be avoided.

In our series, 63.4% of patients with a positive SLNB who underwent CALND were found to have no residual disease in the axilla. The rate is similar to that published by other investigators²²⁻²⁵.

Many studies²³⁻³² have identified factors that seem to be associated with the presence of NSLN involvement. Degnim et al.²² conducted a meta-analysis comparing 11 different articles and found general concordance among studies regarding the association between certain pathologic characteristics and NSLN metastases. Despite methodologic differences, five individual characteristics were associated with the likelihood of NSLN involvement: size of the primary tumor greater than 20 mm, lymphovascular invasion in the primary tumor, size of the metastases in SLN greater than 2 mm, extranodal extension in the SLN and presence of more than one positive SLN.

In our series we found similar results: the presence of a macrometastases of more than 2 mm associated with extranodal extension, a nodal ratio ≥ 0.5 and the presence of more than one positive SLNs were strongly associated to further axillary metastases.

Several studies advocated tumor size as one of the strongest predictors of axillary recurrence after positive SLNB in breast cancer patients. Hwang et al.³² reported no NSLN metastases in patients with T1a lesions whereas patients with T2, T3 and T4 tumors were associated with positive NSLNs in 54%, 77% and 80% of cases, respectively. Similar data were presented by Kamath²⁵, Joseph²⁷ and Chu¹² who published a NSLN metastases rate of 13% for T1b lesions, 38% for T2 and 71% for T3 tumors. Conversely in our experience primary tumor size was not related to an increased risk of NSLN involvement. This finding is probably explained if we analyse the descriptive characteristics of our series of patients: our study population consists of 97.6% patients with lesions smaller than 30 mm and more than 73% of patients had T1 lesions with an average tumor size of around 17 mm. Similar data were presented by Cserni et al.³⁵: 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.

Another significant predictor of NSLN metastases found in several studies is the presence of lymphovascular invasion in the primary tumor. In our work the feature was not significantly correlated to an augmented risk of NSLN involvement ($p=0.19$). Similarly, other characteristics related to the patient (age) or the primary tumor (estrogen receptor status, ki67 $\geq 25\%$, HER2 presence, histological type and grade) were not predictive of NSLN status in our series and are considered as predictors of NSLN involvement only in a few studies^{36,37}. Conversely, characteristics of the SLN are more often considered as predictors of axillary involvement, as demonstrated by several authors^{25,30,32,35-37}. In our series the presence of more than one positive SLN as well as a nodal ratio of more than 0.5 were strongly associated to higher risk of NSLN positivity ($p=0.008$). This finding is coherent with studies performed by Rahusen³⁰, Wong³⁸ and Turner³⁶ and with the Degnim meta-analysis²². Moreover, a metastases size of more than 2 mm

is a significant predictor of NSLN metastases in most studies^{25,30-32,35-37}. In our own series the feature showed a relationship with NSLN positivity when associated to the presence of extranodal extension, which is another important prognostic factor recognized in several studies^{31,35,36}.

Conclusions

Among patients with early breast cancer and positive SLNB it is possible to identify different subset of cases with significantly different risk for further axillary involvement according to the presence of macrometastases associated to extranodal extension, the presence of more than one positive SLN and a nodal ratio ≥ 0.5 . However, until the role of CALND would be clarified by large prospective randomized clinical trials, axillary dissection must be considered as the first option. In patients with a predicted small chance of residual axillary disease, the choice to perform or not a CALND could be discussed by a multidisciplinary board and proposed to the patient.

Riassunto

OBBIETTIVO: Scopo del lavoro è la determinazione di fattori predittivi di coinvolgimento metastatico dei linfonodi non sentinella (LNS) in pazienti con carcinoma mammario e biopsia del linfonodo sentinella (BLS) positiva.

MATERIALI E METODI: È stata eseguita un'analisi retrospettiva delle pazienti sottoposte a BLS presso il Nostro Istituto negli ultimi 4 anni. Sono state valutate le pazienti portatrici di metastasi al linfonodo sentinella sottoposte a dissezione ascellare, allo scopo di individuare fattori clinico-patologici predittivi di ulteriori metastasi ai LNS.

RISULTATI: Da una casistica di 176 casi, è stata estrapolata una serie di 41 pazienti (23.3%) portatrici di linfonodo sentinella metastatico. La dissezione ascellare ha permesso l'identificazione di ulteriori metastasi in 15 casi (36.6%). La presenza di macrometastasi al linfonodo sentinella associata al superamento capsulare ($p=0.048$), la presenza di più di un linfonodo sentinella metastatico ($p=0.08$) ed una ratio tra il numero di linfonodi sentinella positivi ed il numero di linfonodi sentinella globalmente asportati maggiore di 0.5 ($p=0.05$) sono risultati fattori predittivi di ulteriori metastasi ai LNS.

DISCUSSIONE: La dissezione ascellare costituisce ancora oggi il trattamento di scelta nelle pazienti portatrici di carcinoma mammario e BLS positiva. Nel 40-70% dei casi, la linfoadenectomia non evidenzia ulteriori focolai metastatici ascellari e risulta, quindi, di dubbio valore prognostico e terapeutico. L'identificazione di fattori clinico-patologici predittivi di coinvolgimento metastatico

dei LNS è finalizzata all'individuazione di un sottogruppo di pazienti a basso rischio di metastasi linfonodali nelle quali, in futuro, proporre l'astensione dall'esecuzione della dissezione ascellare.

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