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ORIGINAL ARTICLE

Prognostic role of micrometastases in sentinel lymph node in patients with invasive breast cancer

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ABSTRACT

Background and Purpose of the study: Axillary lymph node status at the time of diagnosis remains one of the most important prognostic factors in women with breast cancer. Sentinel lymph node biopsy (SLNB) proved to be a reliable method for the evaluation of axillary nodal status in early-stage invasive breast cancer. The prognostic value and potential therapeutic consequences of SLN micrometastases remains a matter of great debate.

Patients and Methods: From January 1998 to March 2011, 1,976 consecutive patients with non-metastatic invasive breast cancer underwent surgical treatment; 1,080 of them (54.6%) underwent SLNB. We collected data regarding demography, preoperative lymphoscintigraphy, type of surgery, histopathologic and immunohistochemical features and adjuvant treatment.

Main findings: A mean number of 2.1±1.4 (range 1–13) SLN per patient were collected, a total of 2,294 nodes. SLNs were macrometastatic in 16.7% of patients and micrometastatic in 3.3%. Among the patients with positive SLN 93.6% underwent complete ALND. The overall survival (OS) and disease-free survival (DFS) of 72 patients with micrometastases in SLN at 60 months was 100%, similar to patients with negative SLN (98.7%), quite different from the DFS of N1–N3 patients (85.8%). Statistically significant differences in OS and DFS were observed between patients with N1mi and the group with N1–N3 sentinel node ($p < 0.001$ and $p = 0.04$) and also between patients with negative SLN and those with macrometastatic SLN ($p < 0.001$ for both).

Conclusion: SLN micrometastases could represents an epiphenomenon of peritumoral lymphovascular invasion which impacts independently on the survival of patients with invasive breast cancer.

1. Introduction

Axillary lymph node status at the time of diagnosis remains one of the most important prognostic indicators for women with breast cancer. [1] The presence of lymphogenic metastases and number of lymph nodes involved significantly contribute to adjuvant systemic treatment decision; in fact they are associated with an increased probability of recurrence and mortality. [2,3]

The goal of axillary lymph node dissection is to provide accurate staging information and local control of disease. However, the procedure has many potential complications, including lymphedema, persistent seroma, shoulder disfunction and paresthesias. [4]

Nowadays, sentinel lymph node biopsy (SLNB) provides information on the axillary node status with lower morbidity than complete axillary lymph node dissection (ALND). Therefore, according to the results of several international randomized trials SLNB is considered the standard of care for patients with early breast cancer and negative axillary nodes. [5,6]

The complexity of breast tumor biology has changed cancer treatments, consequently the choice of administering systemic therapy is influenced by a variety of clinical and pathology-related factors, with lymph node tumor status influencing but not necessarily dictating the use of chemotherapy. [7] These evolving concepts have called into question the need for ALND, especially for limited sentinel lymph node involvement.

Published data suggest that the absence of metastatic tumor cells in the sentinel lymph node accurately predicts the absence of metastases in the remaining axillary nodes in 95–100% of cases. [8–10] Actually, SLNB may be more sensitive to detect metastases than axillary node dissection. [4] Compared with analysis with hematoxylin and eosin (H&E) only in axillary lymph node dissection specimens, the use of step sectioning and immunohistochemistry in the sentinel lymph node results in a more accurate histopathologic examination

and is associated with a higher detection rate of small metastases (micrometastases and isolated tumor cells). [11,12] In the 7th edition of the AJCC staging system the concept of "micrometastases" (N1mi) has been introduced in the official staging criteria: micrometastase is defined as a metastases measuring from 0.2 mm to not more than 2.0 mm. [13]

However, the prognostic significance of micrometastases in the sentinel node is currently unclear and creates a new dilemma in the clinical management of patients with breast cancer. [14] In this study we examine the overall survival and disease free survival of a large cohort of patients in order to assess the prognostic meaning of sentinel node micrometastases.

2. Patients and methods

From January 1998 to March 2011, 1,991 consecutive patients with invasive breast cancer underwent surgical treatment at the Division of General Surgery of Ospedale di Circolo, University of Insubria Varese.

For the present study, 15 patients with distant metastases at the time of diagnosis were excluded, hence the sample consisted of 1,976 patients, whose mean age at diagnosis was 61.1±12.4 years; 1,080 of them (54.6%) underwent sentinel lymph node biopsy. The other patients did not undergo sentinel node biopsy either because they were treated before the introduction of the sentinel lymph node biopsy technique into routine clinical practice (2001) or due to evidence of metastatic axillary nodes.

We retrospectively collected data regarding demography, pre-operative lymphoscintigraphy, type of surgery, histopathologic and immunohistochemical features and adjuvant treatment.

Pathologic assessment included evaluation of the size, grade, histological type, peritumoral vascular invasion of the primary tumor and lymph node status.

Data regarding tumor expression of estrogen and progesterone receptors, Ki-67 antigen, HER-2 and p53 over-expression were also collected.

The nodal status was determined according to the 7th edition of the AJCC cancer staging manual. [13] If no regional lymph node metastasis was detected, the tumor was classified as pN0.

In case of micrometastases (larger than 0.2 mm but none larger than 2 mm in greatest dimension) the tumor was classified as pN1mi. If nodal metastases larger than 2 mm were diagnosed, the tumor was classified as pN1. [13]

2.1. Lymphatic mapping and operative technique

Sentinel node mapping was performed using a radiolabelled colloid. The day before surgery ^{99m}Tc- labelled nanocolloid (Nanocoll) was injected intradermally above the tumor site. Lymphoscintigraphy was performed preoperatively to identify lymphatic flow to axillary lymph nodes, hot spots were marked on the skin.

SLN was intraoperatively identified by use of a gamma probe (Neoprobe); all hot lymph nodes were excised and labelled separately as SLN, until all hot lymph nodes had been removed, and the background count of the axilla was < 10% of the hottest lymph node. [14] If no SLNs were found, a complete ALND was performed.

2.2. Surgical treatment

All patients received adequate local treatment (breast-conserving surgery or total mastectomy) plus SLNB or ALND.

2.3. Pathological examination of sentinel nodes

Intraoperative frozen section analysis of the axillary SLN was routinely conducted in order to perform axillary dissection during the same operative procedure in case of lymphatic metastases.

Lymph nodes > 5 mm in diameter were bisected, nodes ⩽5mm were not bisected but totally submitted for frozen section analysis; the sections were cut at 50–200 μm intervals and they were examined with H&E. In addition, the sentinel nodes were fixed in formaline and embedded in paraffin for definitive histopathologic analysis. During the definitive histopathologic analysis the sections were stained with both H&E and immunohistochemically with antibodies against keratin. [14,15]

2.4. Adjuvant therapy

When breast-conservative surgery was performed, patients received adjuvant radiotherapy with 50 Gy over 5 weeks with a boost of 10 Gy to the tumor site, marked with clips during surgery in patients without contraindications for radiotherapy.

Moreover, adjuvant therapy consisted of hormone treatment (tamoxifen or aromatase inhibitors), and/or chemotherapy according to established prognostic factors (age, comorbidities, axillary lymph node status and features of primary tumor). [16,17]

On the basis of the St. Gallen Consensus recommendations, [17,18] patients with SN micrometastases were considered SN negative and adjuvant therapy was administered only according to the characteristics of the primary tumor.

2.5. Follow up

After surgery, patients were observed every 4 months in the first 3 years, every 6 months in the next 2 years, and once a year thereafter; mammography and breast ultrasound were performed annually.

Registry offices were actively contacted for additional information, especially for the cause of death, when patients were lost to follow up.

Follow up started at the time of the operation. As per December 2011, 63 patients (3.2%) were lost to follow up; in the survival analyses these were "censored" at the time of last contact.

For all patients, the median follow-up was 53.4 months (range 1–160 months) and for the survivors the median follow-up was 55.3 months (range 1–160 months).

2.6. Statistical analysis

The primary end-points were overall and disease-free survival of our group of patients in order to calculate the survival impact of SN micrometastases.

Disease-free survival (DFS) was defined as the lenght of time from the date of surgery to any relapse; overall survival (OS) was defined as the time from surgery until the date of cancer-related death.

Survival rates for DFS and OS were estimated by the Kaplan–Meier method. The survival comparisons between the different groups were carried out by the Log-rank test.

The secondary aim of this study was to identify predictors for micrometastases in SLN. We subdivided patient and tumor-related factors. Continuous variables were expressed as mean and standard deviation (SD) or as median and range. The association between micrometastases and patients and tumor-related factors were analyzed by non-parametric test as appropriate.

Multivariate analysis was performed by stepwise backward logistic regression, including only variables with $p < 0.1$ at univariate tests.