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Completion axillary lymph node dissection can be avoid in patients with invasive breast cancer and sentinel lymph node micrometastases.

BACKGROUND: *The prognostic value of sentinel lymph node (SLN) micrometastases in invasive breast cancer patients is still widely debated. Even if, in the absence of unequivocal guidelines, the axillary lymphadenectomy is not still performed in the routine clinical care of these patients.*

MATERIALS AND METHOD: *We have retrospectively analyzed 897 patients with operable invasive breast cancer and clinically negative axillary lymph nodes underwent conservative surgery or total mastectomy with SLN biopsy. Two groups of patients with SLN micrometastases and isolated tumor cells (ITC) were considered, the first one treated with completion axillary dissection, the second one not followed by further surgical axillary procedure. The incidence of axillary recurrences has BEEN evaluated in both groups and only in the first group of patients the involvement of the remaining lymph nodes was analyzed.*

RESULTS: *Micrometastases were found in 67 (7.4%) patients and ITC in 8 (0.9%) patients. 14 (20.9%) patients with micrometastases and 1 (12.5%) patient with ITC underwent completion axillary dissection. 53 (79.1%) patients with micrometastases and 7 (87.5%) with ITC didn't receive further surgical axillary procedure. No axillary recurrences were found during a median follow up of 65.7±8.69 months in both groups of patients.*

CONCLUSIONS: *Based on the results and according to some recent randomized trials we can say that completion axillary dissection can be safely avoided when micrometastases are found in sentinel lymph nodes. It should be performed anyway, depending on the analysis of the biomedical profile of the tumor.*

KEY WORDS: Breast Carcinoma, Micrometastases Axillary Lymphnode Dissection, Sentinel Lymphnode

Introduction

Axillary nodal status has traditionally been the most important prognostic factor in staging breast cancer and determines, among other parameters, the need for subsequent adjuvant treatment. Because of its high sensitivity and accuracy in predicting axillary lymph node status, sentinel lymph node biopsy (SLNB) for breast cancer

is accepted as a standard procedure, which makes it possible to avoid unnecessary axillary lymph node dissection (ALND) ¹. Depending on its size, axillary lymph node metastases are classified as macrometastases (diameter >2 mm), micrometastases (diameter in between 0.2 and 2 mm) and isolated tumor cells (ITC) (diameter ≤ 0.2 mm). Currently ALND is the standard procedure in patients with SLN macrometastases, but it isn't suggested on patients with ITC in the SLN, the more that the TNM classify those patients as N0(i+). Instead the indications to completion ALND in case of patients with SLN micrometastasis is still debated. It is estimated that only 18% of the patients with micrometastases and/or ITC in the SLN present metastatic involvement of the others axillar lymph nodes ², so that guidelines are gradually shifting away from clearing the axilla if micrometa-

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stasis are found during SLNB^{1,3}. Furthermore, recently data from the National Cancer Data Base from the United States examined for 2203 patients with micrometastases treated between 1998 and 2000 showed no significant difference in axillary recurrence or survival for patients treated by SLNB alone compared with patients treated by SLNB and completion ALND⁴. In this retrospective cohort study, patients with SLN micrometastases or ITC treated with ALND have been checked and the involvement of the remaining LNs analyzed. Patients with micrometastases or ITC in the SLN not followed by ALND have been checked as well, and the incidence of axillary node recurrences has been evaluated in both groups.

Materials and Methods

A retrospective study has been conducted on 897 patients with operable invasive breast carcinoma with clinically negative axillary lymph nodes that underwent conservative surgery or total mastectomy with SLNB at our Institution from January 2006 to December 2013. In all patients the diagnosis of infiltrating breast carcinoma was made by fine-needle aspiration cytology or by percutaneous core biopsy under stereotactic or ultrasound control. Evaluation of the axillary lymph nodes was done by clinical and ultrasound examinations of the axilla and fine needle aspiration cytology of the suspicious lymph node. The histological results of the needle biopsy was confirmed in all cases by the histological results of the operative specimen, proving an high diagnostic accuracy by this procedure in the preoperative diagnosis of breast cancer as well as demonstrated in our own experience⁵.

LYMPH NODE MAPPING AND OPERATIVE TECHNIQUE FOR SLNB

The day before surgery, all patients underwent lymphoscintigraphy by injection of ⁹⁹Tc-labeled human albumin colloid (10-12 MBq of Tc-99m in 0.2 ml of albumin colloid). The periareolar subdermal injection of the radiotracer was preferred because of the high level of accuracy⁶. The SLN was identified by acquiring a double projection of the scintigraphic images 15, 30, and 180 minutes after the injection of the radiotracer. A cobalt pen was used to locate the cutaneous projection of the SLN. For the intraoperative identification of the SLN, we used a radio-guided surgical probe (neo2000 Gamma Detection Systems®) about 10 min before the beginning of surgery detection. In a few cases, when the radio-guided surgical probe recorded a weak radiotracer signal, a subareolar injection of 0.5-0.8 ml of vital stain (1% lymphazurin) was performed about 10 min before the beginning of surgery as well. The hot and/or blue lymph nodes were removed, their radioactivity was ver-

ified out of the operating field by the same probe, and then they were immediately submitted to frozen section (FS).

PATHOLOGICAL EXAMINATION

SLNs with a diameter of less than 5 mm were frozen intact, whereas nodes with a diameter greater than 5 mm were bisected longitudinally and frozen. Two 4 µm frozen sections were taken from the optimal cross-sectional surface of one half of the lymph node and stained with hematoxylin and eosin (H&E) for intraoperative examination. For definitive histopathological examination, all the remaining tissue was formalin-fixed and paraffin-embedded. Two serial sections, 4 µm thick, were obtained for each block at a cutting interval of 50 µm throughout the whole lymph node. For each step, the first section obtained was stained with H&E. When neoplastic cells were not observed or when the result was ambiguous on H&E sections at each step, the remaining sections were stained with the use of the monoclonal antibody for pancytokeratins AE1/AE3 (Dako). Immunohistochemical analysis was performed using the avidin biotin peroxidase complex method. Brief counterstaining in Mayer's hematoxylin followed immunostaining. If more than one SLN was obtained from a patient, all the nodes designated as SLN were examined in this way.

Metastases were classified as micrometastases (diameter ≤2 mm) or macrometastases (diameter ≥2 mm); single tumor cells or small clusters of cells (diameter <0.2 mm) were defined as isolated tumor cells (ITC).

SURGICAL PROCEDURE

All the patients underwent synchronous excision of the breast cancer either by conservative surgery or total mastectomy and SLN biopsy. In cases of non palpable breast lesions, a guided wire was placed in the tumor site under either stereotaxic or ultrasonographic guidance. All patients with SLN macrometastases in FS underwent immediate completion ALND. If the SLN was negative at FS but was found to contain macrometastases in the final histopathology, patients underwent delayed completion of total ALND.

In case of SLN micrometastases at FS confirmed at final histopathology the patients underwent immediate or delayed completion ALND until 2008, then since the early months of 2009 completion ALND was not performed and these patients, as well as those with negative SLN, received clinical and ultrasonographic examination of the axilla every six months to detect possible axillary lymph node recurrences.

Then, in the group of patients with SLN micrometastases that underwent ALND, we analyzed the incidence

of non sentinel axillary lymph node metastases at final histological examination. In the group of patients with SLN micrometastases that didn't undergo ALND, we analyzed the incidence of axillary lymph node recurrences.

Results

The mean age of the 897 patients was 57.16 ± 10.31 years (range 29-87 years). The mean tumor diameter (histopathological measurement) was 17.73 ± 9.07 mm (range 4-56 mm). The characteristics of the tumours are summarized in Table I.

861 (95.9%) patients underwent conservative surgery, and 36 (4.1%) underwent total mastectomy. In 889 cases (99.1%) the SLN was accurately detected intraoperatively, the mean number of them was 1.96 ± 0.31 (range 1-8). Only in 3 (0.9%) cases, although identified by the preoperative lymphoscintigraphy, they weren't detected intraoperatively. In these cases immediate ALND was performed and only 2 of them had metastatic axillary lymph nodes at the histopathological examination.

TABLE I - Tumor features

	Number	%
Histologic type		
Ductal Infiltrating	748	83,4%
Lobular Infiltrating	69	7,7%
Ductal + Lobular Infiltrating	16	1,8%
Other	64	7,1%
Tumor size		
pT1a (0 - 0,5 cm)	56	6,2%
pT1b (0,5 - 1,0 cm)	206	22,9%
pT1c (1,0 - 2 cm)	322	35,9%
p T2 (> 2 cm e ≤ 5 cm)	302	33,7%
p T3 (> 5 cm)	11	1,2%
Grading		
G1	141	15,7%
G2	557	62,1%
G3	199	22,1%
Estrogen Receptors		
positive	801	89,54%
negative	78	10,46%
Progesterone Receptors		
positive	618	89,2%
negative	713	79,5%
HER-2/neu overexpression		
Yes	521	58,1%
No	376	41,9%
Multifocality	89	9,9%

At FS histopathological examination SLNs were negative in 683 (76.4%) patients, macrometastases were found in 195 (21.8%) patients, and micrometastases in 16 (1.8%) cases. Only in 3 cases (0.3%) the pathologist postponed the diagnosis at the definitive examination of the SLN. In 1 case the SLN was negative; in 2 cases micrometastases were found. Although it has high diagnostic accuracy, FS of SLN is burdened by a low rate of false negative diagnosis⁷. Indeed in 78 (11.3 %) patients with negative SLN at FS the final histopathological examination found macrometastases in 21 cases, micrometastases in 49 cases and ITC in 8 cases. The 22 patients with macrometastases underwent completion ALND whereas the patients with micrometastases and ITC didn't.

In total 67 (7.4%) patients with micrometastases and 8 (0.9%) with ITC were both found at FS and at final histopathological examination. The characteristics of these patients are summarized in Table II. 14 (20.9%) patients with micrometastases and 1 (12.5%) patient with ITC received completion ALND, while 53 (79.1%) patients with micrometastases and 7 (87.5%) patients with ITC didn't receive any additional surgery in the axilla. Furthermore, in 12 of these patients, in addition to SLNB, a sampling of palpable non-sentinel lymph node was performed⁸ but in no case were found metastases at final histopathological examination of them.

TABLE II - Tumor features in cases with micrometastases and ITC in SLN.

	Micrometastases	ITC
Tumor size (mm)	21,7 (range 4-55)	19,1 (range 9-32)
Histologic type		
Ductal Infiltrating	56 (83.6%)	7 (87.5%)
Lobular Infiltrating	6 (6.9%)	1 (12.5%)
Ductale+Lobular Infiltrating	4 (3.4%)	0
Other	1 (1.7%)	0
Grading		
G1	8 (11.9%)	2 (25.0%)
G2	40 (59.7%)	5 (62.5%)
G3	19 (28.3%)	1 (12.5%)
Estrogen Receptors		
positive	61 (91.1%)	7 (87.5%)
negative	6 (8.9%)	1 (12.5%)
Progestinic Receptors		
positive	60 (89.5%)	6 (75.0%)
negative	7 (10.4%)	2 (25.0%)
HER-2/neu overexpression		
Yes	30 (44.8%)	3 (37.50%)
No	37 (55.2%)	5 (62.50%)
Multifocality	9 (13,4%)	1 (12.50%)

Regarding the 15 patients that underwent completion ALND, only 2 (13.3%) cases had metastatic involvement of the other axillary lymph nodes. In both cases the primary breast carcinoma had unfavorable features as a high grade differentiation (G3), a high cellular proliferation index, multifocality and high score of HER-2/neu receptors.

Finally, at a median follow-up of 65.7 ± 8.69 months (range 42-84 months) neither the group of patients treated with completion ALND nor those that didn't received further treatment of the axilla, developed axillary recurrences and/or distant metastases.

Discussion

The staging of the axilla obtained through the study of SNL is considered a highly effective and accurate method, burdened with a very low incidence of false negatives. The current guidelines recommend performing ALND exclusively in patients with positive SLN, although it is estimated that only in 40% of cases with positive SLN metastases occur in other axillar nodes⁹. No additional surgery is now unanimously indicated for ITC in the SLN, considered absolutely irrelevant in terms of adverse prognosis¹⁰. However, the indication to perform the ALND in the presence of micrometastases in the SLN is still widely debated. Unlike macrometastases, they have an uncertain prognostic significance and the guidelines aren't unanimous on the behavior the surgeon must keep in their presence.

Over the last few years several clinical trials have been conducted in order to clarify what the optimal choice of therapy in case of micrometastases in the SLN was. The results obtained in the first studies on the subject recommend to perform a complete ALND in these patients, as sentinel lymph node micrometastases were associated with high rates of additional lymph node metastases and recurrences¹⁰. Subsequently the prospective randomized trial AATRM has instead shown how the removal of only the sentinel lymph node represents, together with a valid adjuvant therapy, an effective means of locoregional control of the disease avoiding ALND¹¹. Similar results were also obtained from the trial IBCSG 23-01¹², which showed that there is absolute uniformity in terms of overall survival and disease-free survival at 5 years among patients with micrometastases in SLN subject to completion ALND and those in which there has been no additional surgical treatment of the axilla. The fact that the surgical excision of the primary tumor is always followed by adjuvant therapy (radiotherapy, hormonal therapy or systemic therapy) when deemed appropriate for the type of surgical treatment carried out and the cancer's biological and histopathological characteristics.

These conclusions correspond to our experience. The incidence of metastases in other axillary nodes in cases of micrometastases in the sentinel node was 13.3%, only

two cases in which the primary tumor biological characteristics were also particularly unfavorable.

Currently, the theory that the main factors predisposing to axillary recurrence are genetic characteristics and histopathological of the primary tumors such as size, histological grade and¹³ the pattern of gene expression of the tumor seems to prevail¹⁴. Only in such cases the ALND may be indicated even with minimal metastatic involvement of SLN.

In our experience, the indication for ALND in the presence of micrometastases and / or ITC in the SLN has been modified over the years. Completion ALND was performed in patients with micrometastases and/or ITC in SLN until 2008. Since 2009, on the basis of the preliminary results of the mentioned randomized trials in which more precisely defined the prognostic significance of micrometastases in SLN, the complete ALND is no longer performed. In addition, more recently, we evaluated the choice to execute the ALND relying also on biomorphologic characteristics of the primary tumor, considering as important risk factors for axillary recurrence some parameters such as multifocality, the absence of hormone receptors, the high histological degree and the over expression of HER2/neu. It seems, in fact, that the multifocal or multicentric cancers are associated with the presence of metastasis to axillary lymph nodes more frequently than monofocal tumors¹⁵. Similarly, the gene expression pattern of the primary tumor is related to the probability of axillar metastases, as well as to locoregional recurrences¹⁶. It was shown that the molecular subtypes "triple negative" and HER2/neu-positive are those at greatest risk of positive axillar lymph nodes, as well as a worse prognosis¹⁷⁻¹⁹. Although, to date, guidelines on surgical treatment of the axilla aren't unanimous, based on the results of various studies it must be considered absolutely the choice of not performing the ALND in the presence of micrometastases in SLN. In these patients, however, postoperative adjuvant therapies are absolutely valid instruments of control for both the locoregional metastasis that for the distant metastases. In our experience, in the group of patients with SLN micrometastases and ITC followed by no additional ALND there were no recurrences to axillary lymph nodes nor to distant metastases. Considering furthermore that the risk of cancer recurrence is greater in the first two years after surgery²⁰, and that the patients we studied have received a minimum of 42 months follow-up, we can conclude that, in our experience, prognosis of patients with SLN micrometastases and ITC followed by no additional ALND is comparable to that of patients with negative SLN.

Conclusions

Notwithstanding the importance of postoperative adjuvant therapy, particularly chemotherapy²¹, it can be con-

cluded that in patients with SLN micrometastases ALND does not improve the prognosis and that the ALND does not have any absolute indication. While waiting for more precise and shared guidelines we believe that ALND must be carefully assessed case by case, particularly taking into account the high bio-morphological characteristics of the primary tumor.

Riassunto

Il significato prognostico delle micrometastasi nel linfonodo sentinella nelle pazienti affette da carcinoma della mammella è ancora ampiamente dibattuto. Anche se, in assenza di univoche linee guida, nella pratica clinica la linfadenectomia ascellare in queste pazienti non viene più eseguita di routine.

Abbiamo condotto uno studio retrospettivo su 897 pazienti affette da carcinoma invasivo della mammella con linfonodi ascellari negativi, sottoposte a chirurgia conservativa o a mastectomia totale con biopsia del linfonodo sentinella. Le pazienti in cui è stata diagnosticata la presenza di micrometastasi del linfonodo sentinella sono state considerate in due diversi gruppi. In un primo gruppo, trattato con linfadenectomia ascellare totale è stata valutata l'incidenza di metastasi a carico dei rimanenti linfonodi ascellari. Un secondo gruppo non ha ricevuto alcun trattamento aggiuntivo dell'ascella e le pazienti sono state seguite con controlli periodici clinico strumentali. In entrambi i gruppi è stata valutata l'incidenza di eventuali recidive ascellari.

All'esame istologico estemporaneo ed al successivo esame istologico definitivo del linfonodo sentinella, in 51 pazienti (6,83%) sono state evidenziate micrometastasi, in 8 pazienti (1,07%) erano presenti cellule tumorali isolate. Quindici di queste pazienti sono state sottoposte a linfadenectomia ascellare totale. Solo in 2 casi (13,33%) sono state ritrovate metastasi a carico dei rimanenti linfonodi ascellari. Quarantaquattro pazienti non hanno ricevuto alcun trattamento aggiuntivo dell'ascella. In queste pazienti nessuna recidiva ascellare è stata registrata durante un follow-up medio di 125,7±9,65 mesi (range 42-102 mesi).

Sulla base dei risultati ottenuti in questo studio ed in linea con alcuni recenti trials randomizzati si ci sentiamo di concludere che la linfadenectomia ascellare può essere evitata nei casi con micrometastasi nel linfonodo sentinella. Una sua eventuale indicazione può essere valutata caso per caso considerando come fattori di rischio per la recidiva ascellare alcune caratteristiche biomorfologiche del tumore primitivo.

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