

Sentinel lymph node biopsy in patients with pure and high-risk ductal carcinoma *in situ* of the breast

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ABSTRACT

Aims and background. The role of sentinel lymph node biopsy in patients initially diagnosed with ductal carcinoma *in situ* resides in determining the predictors of invasive disease. The aim of the present study was to examine the incidence of sentinel lymph node metastases in a selected group of patients, with characteristics of high-risk ductal carcinoma *in situ*, in order to determine the clinical usefulness of sentinel lymph node biopsy.

Methods. A total of 90 patients with a biopsy diagnosis of ductal carcinoma *in situ* were treated. Fifty-two patients with high-risk ductal carcinoma *in situ* had sentinel lymph node biopsy. The following characteristics of the primary tumor were considered as indicative of a risk of invasive disease: presence of palpable mass, mammographic mass, multicentric disease that required mastectomy, and histologically high nuclear grade or non-high nuclear grade with necrosis. Subdermal injections of ^{99m}Tc-labeled human albumin and subareolar injection of blue dye were used for sentinel lymph node identification. All sentinel nodes were sectioned serially and stained with hematoxylin and eosin. Immunohistochemical analysis was performed using a cytokeratin monoclonal antibody.

Results. A positive sentinel lymph node was found in only one patient (1.9%). The patient had a double lesion, and core-needle biopsy showed an atypical ductal hyperplasia and an intermediate degree of ductal carcinoma *in situ*. At pathologic review of the specimen, no invasive aspect was detected.

Conclusions. The results of our study indicate that sentinel lymph node metastasis in pure ductal carcinoma *in situ* is extremely uncommon. We therefore suggest that sentinel lymph node biopsy might be indicated for patients with ductal carcinoma *in situ* detected as a palpable mass or as large extensive microcalcifications, as well as for patients who are undergoing mastectomy, especially with immediate reconstruction.

Introduction

Ductal carcinoma *in situ* (DCIS) is characterized by proliferation of neoplastic ductal epithelial cells confined to the basement membrane of mammary ducts. The disease currently accounts for approximately 20% of all screening-detected breast cancers¹. Since invasion of the basement membrane by definition does not occur, the disease is localized to the breast with no spread to regional lymph nodes or distant sites. However, the breast cancer-specific mortality rate for patients with DCIS is 1-2%², and about 1% of patients with a diagnosis of pure DCIS have been found to have metastases on axillary lymph node dissection (ALND)^{3,4}. Obviously, this apparent discrepancy indicates that there must be occult invasion in some patients with DCIS diagnosis. However, the rate of nodal metastasis has been considered low enough to abandon ALND as a routine procedure in DCIS because of the significant morbidity associated with the procedure⁴.

Key words: breast cancer, ductal carcinoma *in situ*, mastectomy, sentinel lymph node biopsy.

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The introduction of sentinel lymph node (SLN) biopsy has signaled a paradigm shift in surgery of the axilla for breast cancer management⁵ and has led to the investigation of its possible role in DCIS. Among the early and largest studies of SLN biopsy for DCIS published, Cox *et al.*⁶ reported a 13% rate of lymph node metastasis using immunohistochemistry for analysis of SLN. The authors interpreted their findings to mean that it is not possible to predict which patients with DCIS will have lymph node metastases and therefore concluded that all patients with DCIS should undergo SLN biopsy. All this has given rise to much controversy, because the clinical significance of immunohistochemistry-positive lymph nodes is uncertain.

The increasing use of stereotactic and ultrasonographic-guided core needle biopsy for the diagnosis of breast lesions (owing to the limited sampling inherent in these techniques) has led to the histologic underestimation of invasive disease, which is well acknowledged and reported to occur in 16-35% of patients^{7,8}. The use of a vacuum-assisted biopsy reduces this upgraded rate to 0-19%⁷⁻¹⁰.

Therefore, the dilemma about SLN biopsy in patients initially diagnosed with DCIS resides in determining the predictors of invasive disease.

The following characteristics of the primary tumor were considered as indicative of risk of invasive disease: presence of a palpable mass, a mammographic mass, multicentric disease that required mastectomy, and histologically high nuclear grade or non-high nuclear grade with necrosis^{8,11,12}. Until predictors of invasive cancer are clearly identified, the role of SLN biopsy in this group will remain undefined.

The aim of the present study was to examine the incidence of SNL metastases in a selected group of patients, treated in a single institution, with characteristics of high-risk DCIS and a diagnosis of pure DCIS, in order to determine the clinical usefulness of SLN biopsy in these patients and to identify those with occult invasion.

Methods

Patients

From January 2000 to September 2008, a total of 880 patients with breast cancer were treated at the Institute of General Surgery, University of Bari. Ninety patients had a biopsy diagnosis of pure DCIS. The patients with microinvasion at final pathology were excluded. Fifty-two (57.7%) patients with high-risk DCIS had SLN biopsy. Patients with DCIS were considered to be at high risk and were selected for SLN biopsy if there was sufficient concern that an invasive component would be identified in the specimen obtained during the definitive surgery – in particular, with a preoperative diagnosis of >2 cm DCIS, a high nuclear grade, or in those in whom a

mastectomy was indicated (i.e., multifocal disease or large-volume disease in a small breast).

Preoperative tissue diagnosis was performed by using stereotactic (mammography based) or ultrasonographic-guided core needle biopsy.

Patient clinical characteristics, pathologic data, treatment methods and mammographic data were prospectively recorded in a computer data base, and a retrospective review was then performed. All the patients were operated on by the same surgeon (GD).

Technique

Axillary lymphatic mapping and SLN biopsy were performed as described elsewhere^{13,14}. Briefly, in patients with a palpable tumor, lymphoscintigraphy together with injection of vital dye to identify the SLN was performed. Patients with non-palpable lesions underwent injection by ultrasound guidance. The day before surgery, 8 to 12 MBq of ^{99m}Tc-labeled human albumin colloid particles (80-200 nm) in 0.4 ml of saline were administered in four subdermal injections in the skin immediately over the breast lesion. Planar scans of the involved breast and axillary area, in anterior and lateral projections, were acquired 15-30 min and 3 h after tracer injection. After scanning, the skin over the first node to take up tracer (defined as the SLN) was marked.

A hand-held gamma probe equipped with a collimator (Neoprobe, Dublin, OH, USA) was applied to the skin above the SLN to confirm the hot spot. Signals picked up by the probe were translated into digital readout and acoustic signals. The intensity and frequency of the acoustic signals were directly proportional to the level of radioactivity detected. Approximately 10-20 min before axillary incision, a single subareolar injection (4 ml of methylene blue dye) was given into the upper-outer edge of the areola according to the technique described by Kern¹⁵. Regardless of the tumor location or the site of previous biopsies, the injection of blue dye is given into the upper-outer edge of the areola (right breast, 10 o'clock; left breast, 2 o'clock) and directed medially toward the nipple.

A small skin incision was made, a blunt dissection was performed to identify a blue-impregnated lymphatic channel, and the lymphatic chain was followed until the first node (SLN) was identified. The gamma probe guided the dissection to a blue-stained afferent lymphatic channel or blue-stained node emitting the highest activity, which was excised and tagged as the SLN. Sometimes two or more nodes were picked up by the probe. All axillary nodes with counts $\geq 10\%$ of the *ex vivo* counts of the most radioactive lymph node were removed and designated as SLN. After the specimen was rechecked, the wound was re-examined after SLN removal to ensure that all radiolabeled lymph nodes were removed.

Finally, the axilla was explored by digital examination to detect any grossly enlarged or hard lymph nodes, in order to decrease the risk of suspicious or obvious dis-

ease in the axilla. Evidently, it becomes an issue of the limitations of the SLN biopsy.

Pathologic evaluation

For all the patients, the SLN were processed whole or sectioned along the long axis into two sections and then submitted for routine processing. Each paraffin-embedded tissue block was sectioned serially according to the scheme proposed by the European Institute of Oncology¹⁶ and stained with hematoxylin and eosin. When metastatic carcinoma was not apparent on the hematoxylin and eosin-stained slides, immunohistochemical analysis was performed using a cytokeratin monoclonal antibody CAM 5.2 Becton-Dickinson (1:20) only when suspicious cells were identified.

To identify myoepithelial cells in DCIS, we used monoclonal antibody for calponin (Dako 1:150) and for p-63 (Dako 1:20). Immunohistochemical analysis was performed using the avidin biotin peroxidase complex method. Brief counterstaining in Mayer's hematoxylin followed immunostaining.

Statistical evaluation

The data were analyzed with SPSS for Windows (release 12; SPSS Inc., Chicago, IL, USA). The analysis of clinical, histological and surgical characteristics was descriptive (percentage for qualitative variables, mean, and range for age) without comparison.

Results

The 52 patients with pure DCIS had an average age of 56 years (range, 27-86). The characteristics of the patients are reported in Table 1. Of the 52 patients, 15 (28.8%) had a palpable tumor and 37 (71.2%) a nonpalpable mass. Mammographic presentation was microcalcifications only in 37 patients (71.2%), radiologic mass with microcalcifications in 11 patients (21.1%), and radiologic mass in 4 patients (7.7%).

Twenty-nine patients (56%) were treated with conservative surgery (quadrantectomy) and 23 (44%) with mastectomy, largely skin-sparing mastectomy with immediate reconstruction.

A total of 84 SLN were biopsied. At least one SLN was found in all of them; an average of 1.6 SLN were identified per patient (range, 1-5). A single SLN was found in 29 (55.8%) patients, 2 SLN in 15 (28.8%), and 3 or more in 8 (15.4%).

A positive SLN was found in only 1 patient (1.9%). She was a 50-year-old patient whose mammography showed a double lesion in the right breast. The first lesion was located in the upper-outer quadrant and it was composed of microcalcifications within a 1.2 cm area, and the second lesion was located in the lower-inner quadrant and showed a solid lesion of 3 cm in diameter

Table 1 - Characteristics of 52 patients with pure DCIS who underwent SLN biopsy

Characteristic	No.	%
Laterality		
Left	31	(59.6)
Right	21	(40.4)
Tumor location		
Upper-outer quadrant	19	(36.5)
Other	33	(63.5)
Clinical presentation		
Palpable mass	15	(28.8)
Non-palpable mass	37	(71.2)
Radiologic presentation		
Microcalcifications	37	(71.2)
Radiologic mass & microcalcifications	11	(21.1)
Radiologic mass	4	(7.7)
Mean Ø of DCIS lesion on mammogram (cm) (range)	2.5	(0.4-7)
Two or more quadrants involved on mammogram	23	(44)
Tumor grade		
1	8	(15.4)
2	16	(30.8)
3	28	(53.8)
Type of surgery		
Conservative	29	(56)
Mastectomy	23	(44)

with microcalcifications. Both lesions underwent a vacuum-assisted core needle biopsy. The former turned out to be atypical ductal hyperplasia and the latter, an intermediate degree DCIS with solid and cribriform aspects.

The patient was suggested to undergo first an SLN biopsy and then a skin-sparing mastectomy with immediate reconstruction. Two SLN were identified and one of them, at the histopathologic examination with hematoxylin and eosin, showed a micrometastasis of <1 mm in diameter. The patient underwent a skin-sparing mastectomy and an ALND.

The 15 non-SLN examined showed no metastases. The histological examination of the breast showed a 3 cm area in the lower-internal quadrant, first diagnosed as infiltrating ductal carcinoma mildly differentiated, having wide *in situ* solid and cribriform ductal aspects with focal peritumoral vascular invasion. The overlying left gland had multiple foci of microglandular sclerosing adenosis, microcalcifications and stromal fibrosis.

Immunohistochemistry for p63 and calponine resulted positive both in the *in situ* carcinoma foci and in the initially considered invasive areas. No positive stain was observed in SLN metastasis for myoepithelial markers. Despite the large number of samples and of histological sections observed, in the end no invasive aspect was detected. The only pattern of an invasive nature of the lesion was denoted by a small embolic vascular invasion (Figure 1).

The immune phenotype pattern showed estrogen and progesterone receptors were positive respectively in 60% and 40% of neoplastic cells. The fraction of proliferating

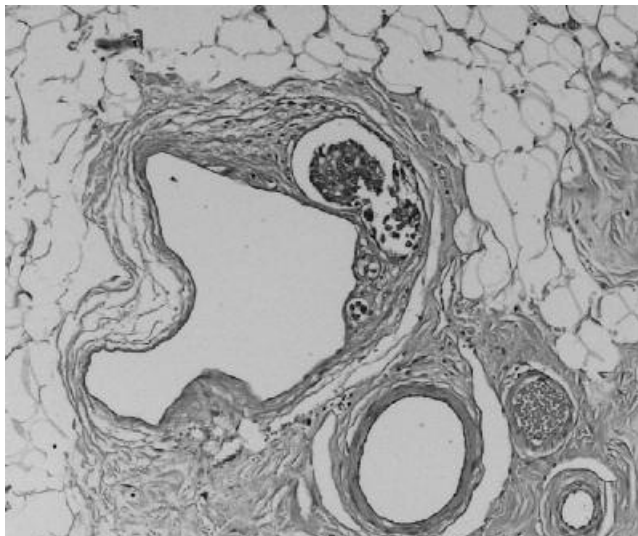


Figure 1 - Small peritumoral embolic vascular invasion (Hem-& eos, $\times 100$).

erating neoplastic cells (Ki 67) corresponded to 6%, and there was no membrane immunoreactions for Her 2/neu.

Discussion

Controversy exists with regard to the optimal management of DCIS patients. However, when routine axillary dissection is performed, the rate of lymph node metastasis is extremely low ($<1\%$)^{3,4}. The increasing rate of SLN-positive testing has led some authors to strongly recommend SLN biopsy in all patients suffering from DCIS⁶. Further studies confirmed, to a lesser extent, a higher rate of SLN-positive testing when examined by using immunohistochemical techniques, detecting only micrometastases (<2 mm) in a high rate (70-100%) of positive SLN^{12,17-19}. Moore *et al.*²⁰ reported 84% isolated tumor cells and 9% micrometastases in SLN.

The need to select subgroups of patients with DCIS in order to make a selective approach to SLN biopsy has led some authors to detect risk factors that predict foci of an occult invasive tumor. Historically, risk factors reportedly associated with invasive disease have included large tumors, high-grade tumors, tumors with comedo-type necrosis, and the presence of a palpable mass or a mass that is appreciated by imaging studies^{11,21,22}.

In our study, we performed SLN biopsy only in 52 patients with the necessary requisites to identify a high-risk DCIS. Only in one patient with two lesions (and one of them was 2.5 cm in diameter) did we detect, by performing an SLN biopsy, a micrometastasis (<1 mm), both by hematoxylin-eosin and by immunohistochemistry, in one of two SLN. ALND on the remaining 15 lymph nodes did not reveal any further metastases. His-

tological examination of breast, although accurate and precise, did not identify the invasive cancer that caused the micrometastasis in the SLN, even though a focus of embolic vessel invasion was present just nearby positive p63 and calponine neoplastic foci.

This result is not infrequent. Moore *et al.*²⁰, in a retrospective multi-institutional study, performed SLN biopsy on 470 high-risk patients with DCIS and reported SLN metastases in 43 (9%) patients. All available pathological slides of the primary tumor and sentinel nodes for patients with a positive SLN and DCIS were re-reviewed. The pathological re-review of the primary DCIS revealed 2 cases with previously unrecognized microinvasion and 7 cases with micro- or macrometastases in the SLN, but no invasive carcinoma was detected in the breast tissue of 6 of these 7 women. Tamhane *et al.*²³ evaluated the axillary lymph nodes in 26 patients with DCIS diagnosed by core or open biopsy who underwent mastectomy and found cytokeratine-positive cells in axillary lymph nodes in 6 (23%). Final pathology review revealed no invasive cancer in patients with lymph node metastases.

This illustrates the difficulty of screening a large amount of breast tissue for microinvasion. Nevertheless, before performing a mastectomy it is necessary to accurately and extensively examine the breast lesion histologically, even considering the great difficulty in identifying a microinvasive cancer present in about 50% of cases, particularly when the lesion is large or multicentric. Our study supports this theory; actually, the only patient with a positive SLN had undergone mastectomy, due to the multicentricity and dimensions of lesions. No other patient who underwent mastectomy or conservative surgery for smaller lesions showed any metastasis in the SLN, even though she was at high risk for the presence of a high-grade tumor, comedo-type or necrosis.

The results of our study lead us to make two comments: what meaning do we give to a metastatic SLN in a patient with DCIS where the infiltrating cancer has not been identified? Moreover, is it possible to restrict the high-risk DCIS attribute only to patients in need of a mastectomy, i.e., for large tumors clinically and/or mammographically detected, or in case of multicentric lesions?

In answer to the first question, Carter *et al.*²⁴ and Diaz *et al.*²⁵ reported the migration of benign and malignant cells to axillary lymph nodes after a simple procedure such as a breast needle biopsies. In the aforementioned reported study, Tamhane *et al.*²³ in 6 of 26 patients with DCIS found cytokeratine-positive cells in axillary lymph nodes. At a mean follow-up of 5 years, no patient had developed a local recurrence or distant disease. Given these findings, the authors concluded that the immunohistochemistry-detected positive cells in the axillary lymph nodes were likely a result of passive transport of cells displaced into lymphatics during

a previous biopsy and were not clinically significant. There is no general consensus for these attractive theories, and for this reason we chose the most cautious therapeutic strategy for our patients. According to Intra *et al.*²⁶, our patient with DCIS and a positive SLN was considered and treated for invasive carcinoma, in which the invasive foci were not identifiable because it was removed or occult.

As for the second consideration, at present there is no consensus on the risk factors associated with invasive disease. In many studies on prognostic factors, high-grade tumor and tumor with comedo-type necrosis in univariate analysis were predictors of invasive cancer. However, multivariate analysis revealed that predictors of a positive SLN biopsy were only a clinical and/or a mammographic mass^{18,26,27}. Moran *et al.*²⁸ reported that SLN biopsy was performed in patients with DCIS >2.5 cm in diameter or when mastectomy was required. Sakr *et al.*²⁹ found larger DCIS to be a predictor of upstaged disease and believe that SLN biopsy could help to avoid undertreatment of patients with DCIS programmed for mastectomy. Zavagno *et al.*³⁰, in a retrospective evaluation on 102 patients with pure DCIS and who underwent SLN biopsy, found only one patient (0.98%) with a positive SLN. The authors concluded that only patients in need of a mastectomy should have SLN biopsy performed at the time of breast surgery.

The results of our study are in accord with those obtained by the aforementioned authors. We therefore propose to consider at risk of occult invasive cancer those patients who, due to dimension or multicentricity of lesions, must undergo a mastectomy, especially with immediate reconstruction, because at the detection of an infiltrating cancer the SLN biopsy cannot be carried out. Moreover, an eventual ALND after application of a tissue expander might affect the planning of breast reconstruction. We believe that performing SLN biopsy before mastectomy and immediate reconstruction simplifies surgical planning.

Conclusions

Our results confirm that a metastatic SLN occurs infrequently in pure DCIS, and when it is proved with certainty, the infiltrating cancer may not be detected in the surgical specimen. We agree with the authors that do not recommend routine SLN biopsy in patients with DCIS. Moreover, the prognostic significance of these immunohistochemistry-detected metastases remains unclear and does not seem to affect survival in these patients³¹.

Since the finding of SLN metastases in pure DCIS is extremely uncommon, as the results of our study show, you may wonder whether this diagnostic obstinacy as well as the efforts to prove SLN metastasis in a small

number of cases by using expensive and sophisticated techniques, might discount a more remarkable clinical aspect, that is how this diagnostic obstinacy can affect an already excellent prognosis.

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