

## Sentinel Lymph Node Biopsy in Intraductal Carcinoma of the Breast with Microinvasion

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**Abstract:** Ductal carcinoma *in situ* with microinvasion (DCISM) is a separate clinical and pathological entity, distinct from pure ductal carcinoma *in situ* (DCIS), with a low but well-known metastatic potential. Due to the low rate of axillary metastases in DCISM, there is controversy regarding the indication for complete axillary dissection (CAD) to stage the axilla. Sentinel lymph node biopsy (SNLB) could be routinely proposed to accurately stage the axilla avoiding the morbidity of a CAD. From March 1996 to December 2002, out of 4602 SLNBs performed for invasive carcinoma of the breast, 41 patients with DCISM in the definitive diagnosis were selected. Metastasis in the SLN were detected in 4 of 41 (9.7%) patients. Two of the 4 patients had only micrometastasis in the SLN. In three of these patients, the SLN was the only positive node after CAD. SLN biopsy should be considered as a standard procedure in DCISM patients. Complete AD may not be mandatory if only the SLN contains micrometastatic disease.

**Key words:** Breast cancer, ductal carcinoma *in situ*, microinvasion, sentinel lymph node, metastasis

### INTRODUCTION

Ductal carcinoma *in situ* with microinvasion (DCISM) represents less than 1% of all breast cancers<sup>[1]</sup>. Although microinvasion is a property of infiltrating disease, the potential for lymphatic metastatic spread is not obvious and the subsequent optimal surgical approach to the axilla is controversial<sup>[2-4]</sup>.

The aim of this study was to determine the prevalence of SLN metastasis in a series of patients with DCISM of the breast, to determine the clinical usefulness of the SLNB in these patients and, finally, to identify if patients at higher risk of dissemination to the axillary lymph node exist.

### MATERIALS AND METHODS

Between March 1996 and December 2002, 4602 patients with clinically node-negative breast carcinoma underwent SLNB at the European Institute of Oncology in Milan, Italy and were prospectively included into a database. To be offered SLNB, the patients had to have cytologically or histologically verified breast carcinoma 3 cm or less in size (measured clinically and/or by imaging techniques) and clinically uninvolved axillary lymph nodes.

Among these patients, 41 patients (aged between 29 and 67 years, average 35.6) affected by DCISM, were included in the current investigation.

**Lymphoscintigraphy:** Lymphatic mapping was performed using a radiocolloid technique as previously described<sup>[5]</sup>. Briefly, 5-10 MBq of <sup>99m</sup>Tc-labeled colloidal particles of human albumin size range 20-80 nm, (Nanocol; Nycomed Amersham-Sorin, Saluggia-VC, Italy) in 0.2 ml of isotonic sodium chloride solution were injected close to the tumor subdermally or peritumorally, the day before surgery or the same day. Lymphoscintigraphy was then carried out 5-30 min post injection and repeated after 3 h if no SLNs were evident in early images. The skin projection of the lymph node was then marked and used as a landmark when beginning the operation. If the primary tumor was non-palpable we performed a new technique that we called ROLL (Radioguided Occult Lesion Localization) to localize the tumor using Tc-99m macroaggregates. For SLN identification the same procedure described above was performed on the skin projection of the occult lesions<sup>[6]</sup>. In case of diffuse microcalcifications in which total mastectomy was indicated, the lymphoscintigraphy was performed using a single subdermal periareolar injection of the radiotracer (Nanocol, Nycomed Amersham-Sorin, Saluggia-VC, Italy)<sup>[7]</sup>.

**Surgery:** SLN biopsy took place 4-20 h after injection of radiolabeled albumin. A gamma ray-detecting probe (Neoprobe 2000, Ethicon, Inc, Somerville, NY) was employed to locate the radioactive lymph node and facilitate its removal. All the nodes uptaking the

radiotracer were classified as sentinel nodes and were removed for histopathologic examination.

**Histopathologic examination:** The surgically removed breast lesions were thoroughly sampled for histopathologic examination. In case of microcalcifications, the specimens were sliced and subjected to x-ray examination to ensure complete sampling of all the microcalcification-containing tissue. Specimens without calcifications were extensively sampled taking at least one block/cm of the lesion. Samples from the surrounding tissue were also examined and in case of mastectomy, the areola-nipple complex was also evaluated histologically<sup>[8-11]</sup>.

The SLNs were bisected fresh along the major axis if larger than 5 mm and fixed in 10% formalin for 6-8 h, before being embedded in paraffin. Lymph nodes less than 5 mm were embedded uncut. Fifteen pairs of paraffin-embedded sections, 4 µm thick, were cut at 50 µm intervals. If residual tissue was left, additional pairs of sections were cut at 100 µm intervals until the lymph node was entirely sectioned. One section of each pair was stained with hematoxylin and eosin (H and E).

**RESULTS AND DISCUSSION**

In 20 patients the clinical presentation was a palpable breast mass, 3 patients had diffuse microcalcifications, 14 patients had a single cluster of microcalcifications and 3 patients had non palpable mammographic or ultrasonographic abnormalities (Table 1). One patient's presentation was unknown. Out of 41 patients, 31 (75.6%) were treated with wide resection and 10 (24.4%) with mastectomy. Fifty-one SLNs were identified and examined: 25 patients had one SLN, 10 had two SLNs and 2 had three SLNs.

**Pathologic findings:** SLN metastasis were detected in 4 of the 41 patients (9.7%). Two of the 4 patients with a positive SLN had only micrometastasis (<2 mm). The SLNs were the only affected nodes in 3 patients who underwent subsequent CAD. In the other macrometastatic SLN patient, 4 metastatic I Berg level lymph nodes were found. No immunohistology was needed for the detection of metastasis (Table 1).

DCIS with microinvasion (DCISM) is a separate clinico-pathologic entity, distinct from pure DCIS without microinvasion<sup>[12-16]</sup>.

In our series, using the TNM classification and following the criteria of Rosen and Obermann<sup>[8]</sup> for the definition of the primary tumor, we found 41 DCISM (0.9%) of 4602 consecutive breast cancer submitted to breast surgery and SLNB, with a 9.7% incidence of metastatic lymph nodes.

Table 1: Main characteristics of 41 DCISM patients evaluated

	SLN positive N=4(9.7%)	SLN negative N=37(90.3%)
<b>Clinical presentation*</b>		
Diffuse microcalcifications	0 (0%)	3 (8.3%)
Palpable mass	3 (75%)	17 (47.3%)
Non-palpable opacity	0 (0%)	3 (8.3%)
Cluster of microcalcifications	1 (25%)	13 (36.1%)
<b>Histology</b>		
Ductal	3 (75%)	34 (91.2%)
Lobular	1 (25%)	2 (5.4%)
Other	0 (0%)	1 (2.6%)
<b>Tumor grade°</b>		
G1	2 (50%)	5 (13.9)
G2	2 (50%)	12 (33.3%)
G3	0 (0%)	19 (52.8%)
<b>Hormonal receptor status°</b>		
Oestrogen receptor +	2 (50%)	13 (36.1%)
Oestrogen receptor -	2 (50%)	23 (63.9%)
Progesterone receptor +	2 (50%)	21 (58.3%)
Progesterone receptor -	2 (50%)	15 (41.7%)
<b>Proliferative rate (Ki67)°</b>		
≤ 20%	2 (50%)	19 (52.8%)
> 20%	2 (50%)	17 (47.2%)
<b>Perivascular invasion</b>		
Present	0 (0%)	0 (0%)
<b>Multifocal</b>		
No	3 (75%)	33 (89.2%)
Yes	1 (25%)	4 (10.8%)
<b>Comedo-DCIS associated</b>		
	0 (0%)	10 (27.2%)

\*In 1 patient the clinical presentation was unknown. ° In 1 patients Tumor grade, Hormonal receptor status and proliferative rate were undetectable. DCISM: Ductal carcinoma *in situ* with microinvasion. SLN: Sentinel Lymph Node

Table 2: Axillary involvement in DCISM patients treated by axillary dissection

References	Years	N° patients	Axillary metastasis
Wong <sup>[5]</sup>	1990	41	0 (0%)
Rosner <sup>[13]</sup>	1991	36	1 (2.7%)
Silver and Tavassoli <sup>[6]</sup>	1998	38	0 (0%)
Jimenez <sup>[19]</sup>	1998	69	5 (7.2%)
Le Bouëdec <sup>[20]</sup>	1999	60	3 (5%)
Padmore <sup>[21]</sup>	2000	11	0 (0%)
Wasserberg <sup>[15]</sup>	2002	57	3 (5.3%)

DCISM: Ductal carcinoma *in situ* with microinvasion

The current prevailing view is that microinvasive carcinoma carries a very low risk of associated axillary nodal metastatic disease, which is similar to extensive high grade DCIS in several series and has a comparable favorable prognosis with a low risk of subsequent development of metastatic disease and death<sup>[15]</sup>. For this reason, some authors<sup>[13,16-19]</sup> have advocated no CAD for DCISM (Table 2). The very low rate of axillary involvement in all reported cases could be due to the fact that all these patients were treated with the standard CAD in which only three to six H and E stained sections per lymph node are cut at 100-500 µm intervals and examined. This standard technique is not able to detect all axillary micrometastasis as SLNB does and could underestimate the axillary involvement rate of DCISM<sup>[20-24]</sup>. Immunocytochemical staining for cytokeratins or other epithelial markers may be helpful for reducing the risk of missing micrometastatic foci but did not increase the rate

of axillary metastasis when they were compared to H and E stained serial multi sections technique. In only 4% of the positive cases the H and E findings were questionable and cytokeratin immunostaining on the adjacent section was useful for confirming the presence of malignancy.

The techniques of lymphatic mapping and SLN biopsy have also been applied to cases of pure DCIS and DCISM in some series. Previous study demonstrated that, due to the low prevalence of metastatic involvement, in pure DCIS completely excised by radical surgery, SLN biopsy can be avoided. It may only be considered in cases of DCIS with a higher risk of harboring an invasive component at definitive histology (large solid tumors or diffuse or pluricentric microcalcifications), especially undergoing mastectomy, in which a successive SLN biopsy can no longer be performed<sup>[25]</sup>. Present results confirm previous results: four patients (9.7%) of 41 affected by DCISM had metastatic sentinel nodes<sup>[26-27]</sup>. In two cases, there were micrometastasis. In three cases, no further positive lymph nodes were found after CAD. In one patient with macrometastatic SLN, four further positive axillary lymph nodes were found.

Due to the low number of positive SLN patients and the subsequent imbalance of the two groups, it is impossible to perform any kind of comparison between the SLN positive and negative DCISM patients (Table 1). Anyway, with the only exception of the clinical presentation, we did not observe any difference between the biological characteristics of the two groups. Only the clinical presentation of the neoplasm seems to be important to predict the risk of SLN metastasis. In three of 4 patients with metastatic SLN a large breast mass was palpable while in non-metastatic SLNs group only 47% of patients had palpable mass. Anyway, any kind of conclusion in this direction is impossible.

In conclusion, due to the significant rate of axillary metastasis in DCISM breast cancer, SLN biopsy should be considered a standard procedure in all these patients. SLNB can detect lymph node micrometastasis and accurately stage the axilla avoiding morbidity of a CAD. Complete AD may not be mandatory if only the SLN has micrometastatic disease. Informed consent and a careful discussion with the patients are very important in this decision.

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