

## SHORT COMMUNICATION

# Dermal invasion matters in breast cancer sentinel lymph node biopsy results

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## Abstract

The aim of this study was to evaluate whether cancer invasion of the dermis could hamper drainage of the radiotracer in breast cancer patients who were undergoing a Sentinel Lymph Node Biopsy (SLNB) procedure. Ten patients who presented with T1-T2 breast cancer with dermal invasion alone as confirmed by a punch biopsy of skin were evaluated. For the SLNB procedure, a lymphoscintigraphy was performed 2 hours after intratumoral administration of 2 mCi (74 MBq) of <sup>99m</sup>Tc nanocolloid. The sentinel lymph nodes (SLN) were evaluated for the presence of tumor cells by hematoxylin-eosin staining and, when negative, by immunocytochemistry using anti-cytokeratin antibody (CAM 5.2). No migration of radiotracer was found in three patients, and one patient had a false negative SLN, so altogether the technique failed in four patients (40%). Axillary nodes proved to be positive in seven patients (70%). The high rate of failure in the lymphatic mapping and the high proportion of axillary positivity suggest a causal relationship with the invasion of the dermis, with possible implications for the validity of the SLNB procedure.

## Keywords

Sentinel node; Breast; Dermal invasion

## 1. Introduction

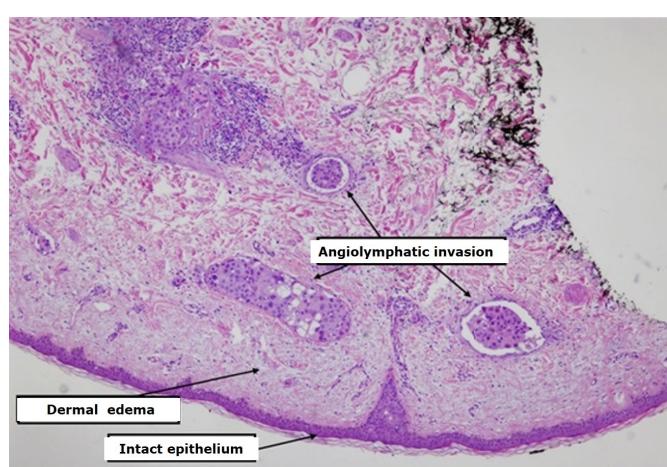
The classification of cancer according to the TNM (Tumor Node Metastasis) staging system is constantly evolving to take into account changes in oncological criteria, along with new treatments and prognostic factors. The technique known as Sentinel Lymph Node Biopsy (SLNB) offers a very high diagnostic accuracy. However, if a new indication for SLNB is included or modified, some uncertainty is created which can only be resolved by carrying out clinical studies that validate the changes in criteria.

According to the edition (7th, 2010) of the TNM staging manual [1], the invasion of dermis alone is insufficient justification to classify a tumor as T4. This change affects cases involving infiltration of the skin, which have been reclassified as Stage I/II, making patients meeting these conditions eligible for a SLNB procedure.

Prevalence of this situation can be estimated using data from the study by Gurth [2], in which 21% of 166 patients classified as T4 were reclassified as Stage I/II. Cancers in these patients mostly corresponded to small tumors next to the skin that had invaded the dermis and angiolymphatic structures (Fig. 1). In this scenario, lymphatic drainage can be altered, thus hampering implementation of the SLNB technique.

The aim of present study is to assess whether neoplastic invasion of the dermis but not the epidermis can hamper the drainage of an injected radiotracer from the tumor site to

sentinel lymph nodes, thereby leading to a false negative result in a SLNB procedure.



**FIGURE 1.** Skin punch biopsy showing dermal but not epidermal carcinoma invasion. (H&E,  $\times 20$ )

## 2. Methodology

This was a retrospective and descriptive study jointly undertaken by the Hospital Universitari Germans Trias i Pujol and Corporació de Salut del Maresme i la Selva in Catalonia,

Spain. The study sample consisted of ten patients who had been treated between January 2014 and December 2017, all of them consecutive T1-T2 breast cancer patients eligible for SLNB procedure, with dermal but not epidermal invasion, as proven by skin punch biopsy. Recurrent breast cancer patients were excluded.

Lymphoscintigraphy was performed 2 hours after intratumoral administration of 2 mCi (74 MBq) of  $^{99m}\text{Tc}$  nanocolloid (Nanocoll®). Tracer administration was guided by sonography or mammography; hence, the radio-guided occult lesion localization technique was also available. Sentinel node (SN) detection was performed by physicians from the same nuclear medicine department in all cases.

After intraoperative SN detection and biopsy, specimens were evaluated for the presence of tumor cells both intraoperatively with a fast variation of the May Grünwald-Giemsa staining technique, and definitively using hematoxylin-eosin staining on serial sections. Whenever hematoxylin-eosin stains were negative, immunocytochemistry using an anti-cytokeratin antibody (CAM 5.2) was performed. In the event of a positive result, standard axillary lymph node dissection (ALND) was performed. Also, ALND was mandatory in cases where SNs could not be identified.

Study data was collected from a multicenter digital database. The study variables were the patient's clinical and diagnostic characteristics, the results of the skin punch biopsy, details of breast and axillary surgery, the results of the SLNB procedure, and details about axillary involvement if ALND was indicated.

A false negative result was defined by taking histologic analysis obtained through ALND as the 'gold standard'.

Due to the small sample size, only descriptive analysis was performed.

Approval was obtained from the Ethics Committee at each institution, and written consent for biopsy was obtained from every participating patient.

### 3. Results

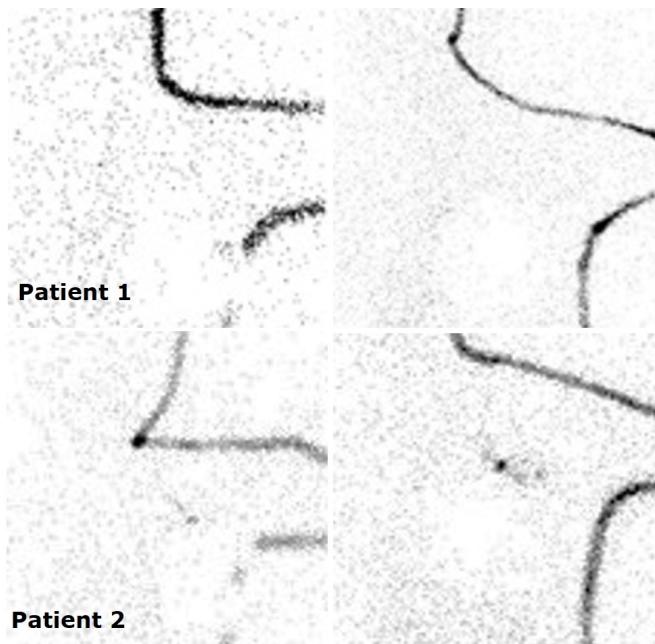
Table 1 summarizes the clinical and diagnostic characteristics of each patient included, the results of the skin punch biopsy, and breast and axillary surgery details.

All ten patients had a diagnostic punch biopsy, eight of them on the nipple areola complex (NAC) and two on the scar from previous surgery due to benign disease. Five of the tumors were classified as T1 and the other five were classified as T2.

One (elderly) patient had received neoadjuvant endocrine therapy, and was operated on one year after treatment.

The SLNB procedure failed in patients (40%), in three cases because of a lack of lymphatic drainage and in the fourth because the procedure yielded a false negative result (Fig. 2).

Positive nodes were found in a total of seven patients (70%). They were one patient with micrometastasis; two patients with macrometastasis; the patient with a false negative SLN; and three patients with no migration. ALND in the three patients with no SN identification showed 2 positive nodes out of 19, 11/12, and 4/15, respectively.



**FIGURE 2. Lymphoscintigraphy.** Top row. Patient 1 (\* in Table 1): No tracer migration. One positive enlarged non-sentinel node harvested. After ALND 11 out 12 nodes were positive, 6 of them showing extracapsular extension. Bottom row. Patient 2 (\*\* in Table 1): Tracer drainage to II level. One positive non-sentinel node was harvested showing extracapsular extension.

### 4. Discussion

The 2010 edition of the TNM staging manual states that small tumors with infiltration of the dermis are eligible for SLNB procedure if non-affected epidermis is proved. In the absence of that condition, these patients are excluded from SN detection.

In the course of 4 years we consecutively collected patient data to assess the consequences of this specific change in the SLNB eligibility criteria. In this period, only ten patients fulfilled the study inclusion criteria. Despite the fact that is quite a small sample of patients, two interesting observations stand out.

Firstly, seven of the ten participating patients (70%) showed axillary node involvement, a relatively high proportion. These results are surprising, considering the small tumor size and their mostly 'less aggressive' biological profile (eight of the patients would be described as having a Luminal A profile).

Secondly, the high rate of failure in the lymphatic mapping is surprising, given that published studies have described detection rates of 94%–98.6% [3]. We found no migration of radiotracer in 3 three patients, and a false negative node in another. For the purposes of this study, a false negative result was defined by taking histologic analysis obtained through standard axillary lymph node dissection as the 'gold standard' in accordance with a previous validation study [4]. On the other hand, as the study's aim was to assess whether neoplastic invasion of the dermis could hamper the drainage of radio-tracer, results of palpation or dye were not considered.

TABLE 1. Patient characteristics.

Age	Physical exam	Diagnosis	Punch biopsy	Lymphoscintig	Breast surgery	SN Detection	Breast pathology	Node pathology
50 (1)	Lump on scar	Core biopsy	Dermal invasion	Aberrant drainage	Lumpectomy	SN Contralateral SN	IDC 13 mm + DCis <25% Perineural invasion HR+ HER2- Ki 67 18%	SN-
81	NAC induration	Core biopsy	Dermal invasion	Normal drainage	Lumpectomy	SN	IDC 40 mm + DCis <25% Perineural invasion HR+ HER2-	SN-
45	Periareolar eczema + microcalcifications	Core biopsy	Paget disease	Normal drainage	Mastectomy	SN	IDC 3mm + DCis 27 mm No perineural invasion HR- HER2+ Ki 67 30%	SN-
50	Lump in areola	Punch biopsy	Dermal invasion	Normal drainage	Lumpectomy	SN	IDC 23 mm + DCis 5% Invasion of epidermis No perineural invasion HR+ HER2- Ki 67 5%	SN micrometastasis
45	NAC retraction	Punch biopsy	Dermal invasion Perineural invasion	Normal drainage	Central lumpectomy	SN	IDC 17mm + DCis 25% Perineural and angiolympathic invasion HR+ HER2- Ki 67 20%	SN macrometastasis ALND 1/12
67	Periareolar lump	Core biopsy	Isolated tumoral cells in dermis	Normal drainage	Mastectomy	SN	IDC 13 mm HR+ HER2- Ki 67 20%	SN macrometastasis ALND 1/10
83 (2)	Erythema and periareolar lump	Core biopsy	Dermal invasion	No migration	Lumpectomy	failed	IDC 13 mm + DCis 10% Angiolympathic invasion HR+ HER2-	ALND 2/19

TABLE 1. Continued.

Age	Physical exam	Diagnosis	Punch biopsy	Lymphoscintig	Breast surgery	SN Detection	Breast pathology	Node pathology
72 *(3)	Lump on scar	Core biopsy	Dermal invasion	No migration	Lumpectomy	failed	IDC 30 mm Perineural invasion HR+ HER2- Ki 67 22%	ALND 11/12 (extracapsular extension in 6 nodes)
72 **	Periareolar tenderness	Core biopsy	Dermal invasion	Level II drainage	Mastectomy	SN and suspicious node	IDC 15 mm + DCis 25% Angiolymphatic invasion Dermal and epidermal invasion HR+ HER2- Ki 67 55%	Positive enlarged node SN- (False negative) ALND 1/15
65	NAC retraction	Core biopsy	Dermal invasion	No migration	Mastectomy	failed	IDC 33 mm + DCis <25% Angiolymphatic invasion Dermal and epidermal invasion ER+ PR- HER2+ Ki 67 <20%	ALND 4/15

NAC: Nipple areola complex; IDC: Invasive ductal carcinoma; DCis: Ductal carcinoma in situ; HR: Hormonal receptors; ER: Estrogen receptors; PR: Progesterone receptors; HER2: Human epidermal growth factor receptor 2; Ki 67: proliferation marker Ki-67; SN: Sentinel node; ALND (number of positive nodes/total).

(1): Reduction mammoplasty; (2): Endocrine neoadjuvant therapy; (3): Previous benign surgery.

\*, \*\* corresponds to patients described in Fig. 2.

Other factors may be involved in hampering radiotracer drainage. However, at least with regard to type of radiotracer, injection site and image acquisition, our protocols have been validated and are currently operational.

It is also true that prior previous surgery may alter lymphatic drainage, although it is not regarded as a contraindication for SLNB. In our study group, one patient presented with previous benign surgery and another had undergone endocrine neoadjuvant therapy, and neither showed no migration of radiotracer (and then were shown to be positive by ALND). So we cannot rule out the possibility that this lymphatic blockage was due to histological changes because of these previous interventions.

Nonetheless, our results suggest that infiltration of the angiolympathic structures of the dermis and subcutaneous tissue, can block the passage of the radiotracer, notwithstanding a small tumor size. This possibility should be considered, even in cases where the cutaneous punch does not show any angiolympathic invasion.

A larger study might be able to demonstrate a causal relationship between the invasion of the dermis and the failure of the SLNB technique in patients of these characteristics. However, even our limited results point to the need for greater awareness of not only the high likelihood of axillary infiltration in breast cancer patients but also, more importantly, the high failure rate of the SNLB procedure in detecting such infiltration.

## AUTHOR CONTRIBUTIONS

MS, MR and JFJ designed the research study. MS, MR, EC, AU and LH performed the research. MS and MR analyzed the data. MS, MR and GM wrote the manuscript. All authors read and approved the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This work was approved by the Clinical Research Ethics Committee of the Hospital Universitari Germans Trias i Pujol (Ap-

roval number: CI-19-001).

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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