

# Importance of Sentinel Lymph Node Biopsy in Surgical Therapy of *in situ* Breast Cancer

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**Abstract** The aim of this retrospective study was to determine the rate of sentinel lymph node (SLN) positivity in patients with a final diagnosis of ductal *in situ* cancer (DCIS) of the breast. Between October 2002 and January 2007, 57 patients with DCIS underwent wide excision after radio-guided lesion localization; 53 of them (53/57, 93%) had participated in simultaneous SLN mapping. SLNs were analysed by 250-micron step-sectioning with haematoxylin and eosin staining and immunohistochemical evaluation. The histologic investigation verified pure breast DCIS in 44 cases (44/57, 77.2%), DCIS with microinvasion in eight cases (8/57, 14%) and lobular *in situ* breast cancer in five cases (5/57, 8.8%). SLNs were identified in 49 cases (49/

53, 92.5%) and removed in 48 cases (48/53, 90.6%), i.e. an average of 1.6 SLNs per patient. In four patients (4/53, 7.6%), the SLN biopsy was unsuccessful because of the failure of the radiocolloid substance to migrate. In these cases, axillary sampling was performed. In one case (1/53, 1.9%), only a parasternal SLN was detected; this was not removed. Histologic analysis of the SLNs and the axillary lymph nodes with haematoxylin and eosin or cytokeratin immunohistochemistry did not prove the presence of metastases. The international data and our present results suggest that routine SLN biopsy is not to be recommended in pure DCIS cases. If the final histology verifies an invasive or microinvasive tumour, or if mastectomy is to be performed, SLN mapping is suggested.

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## Introduction

The extensive use of mammography for screening has resulted in the recognition of increasing numbers of malignant breast tumours in an early stage. From this respect, there has been a considerable rise in the rate of ductal carcinoma *in situ* (DCIS) of the breast. Before the widespread introduction of mammographic screening, only 1–2% of the recognized breast cancers comprised DCIS, but at present the rate of detection by mammographic screening of non-palpable breast cancers is approximately 20% [1–5]. In line with the extensive use of mammographic screening, the surgical treatment too has undergone change: conservative breast surgery has replaced the earlier radical breast surgery, and axillary lymph node dissection (ALND)

has likewise been replaced by sentinel lymph node (SLN) biopsy, which is currently the established method with which to assign the axillary lymph node status in early breast cancers [6, 7]. If the histologic diagnosis is *in situ* breast cancer, however, the indication of SLN biopsy is controversial. The histologic types of *in situ* breast cancers are DCIS and lobular *in situ* cancer (LCIS), the more important of these in clinical practice being DCIS. A special histologic type is DCIS with microinvasion (DCIS mic); in this group there is a possibility of metastases to the lymph nodes, but this is less frequent than in cases of invasive breast cancer [8]. DCIS is a preinvasive stage. In 30–50% of the cases untreated patients with DCIS will develop invasive cancer during 10–20 years [9]. DCIS is defined as a non-invasive breast cancer, and is widely considered not to give metastases to the lymph nodes, so that ALND would comprise overtreatment [4, 5, 9–13]. Nonetheless, a number of studies have reported the detection of metastases in SLNs in patients with DCIS, though with a very low incidence.

We found it of interest to investigate the indication of SLN biopsy when the final histologic diagnosis was DCIS.

## Materials and Methods

The preoperative examinations undergone by our patients comprised at least mammography, ultrasound breast investigation and fine-needle aspiration cytology (FNAC) or core-needle biopsy (CNB). The radioguided occult lesion localization (ROLL) technique and double-marking SLN biopsy were used simultaneously [6]. One day preoperatively, under X-ray or ultrasound guidance, 0.4 ml radiocolloid ( $^{99m}\text{Tc}$ )-labelled human colloid albumin was injected into the tumour. Lymphoscintigraphic examination followed 4 h later and the projection of the SLNs on the skin was marked from two sides. On the next day, 10 min before the operation, a second marking substance, Patent Blue dye in a volume of 2 ml, was injected in the subareolar region of the breast. During the operation, we determined the peak of the radiocolloid activity with a gamma probe and removed the tumour, taking into account the preoperative findings. The excision was performed to the pectoral fascia. The excised specimen was marked with orientation stitches and specimen mammographic tests were performed.

**SLN Histological Examination** SLNs were examined in serial sections at intervals of 250  $\mu\text{m}$  by means of haematoxylin-eosin (H&E) and cytokeratin immunohistochemical (IHC) staining. During the examination of the SLNs, one lymph node was on average divided into three blocks, depending on its size. one block contained two

sections, and one block was pored twice; on average therefore, 15 sections were prepared from each SLN. This latter method facilitated the recognition of the micro-metastases and isolated tumour cells (ITCs) in the SLNs [10, 14, 15].

## Results

Between October 2002 and January 2007, 57 patients in whom the final histologic diagnosis was *in situ* breast cancer underwent wide excision via a ROLL technique. The median age of the patients was 55.8 years (range 40–77 years). 52 patients (52/57, 91%) participated in FNAC, and three (3/57, 5.3%) in CNB (Table 1). Preoperative histologic results were not available on two patients.

The final histological examination verified LCIS in five of the 57 patients (5/57, 8.8%), pure DCIS in 44 (44/57, 77.2%) and DCIS mic in eight (8/57, 14%) two patients had palpable tumours: one was a high-grade DCIS mic, and the other was a high-grade DCIS. Both were extensive tumours.

DCISs have a number of histologic subtypes (solid, cribriform, papillary, micropapillary or comedo) [9]. The most important factors are the presence of comedo necrosis and the grade of the tumour cells [16] (Table 2).

Simultaneous SLN biopsy was planned in 53 of the 57 patients (53/57, 93%), while three (3/57, 5.3%) underwent only wide excision and one (1/57, 1.7%) axillary sampling without planned SLN biopsy. In four of the 53 patients (4/53, 7.5%), SLNs were not identified because of the failure of the radiocolloid substance to migrate; axillary sampling was performed to remove the axillary lymph nodes at level I. In two patients, only a parasternal SLN was detected; this was removed in only one patient. In 48 patients (48/53, 90.6%), successful SLN biopsy was performed.

Seventy six SLNs were removed (average 1.6, range 1–4). No metastases were detected in the SLNs. The histologic

**Table 1** Results of preoperative FNACs and CNBs

Methods	Code	No. of patients	Rate (%)
<b>FNAC</b>		52	100
No cells detected	C1	24	46.2
Benign disease	C2	3	5.8
Atypical disease	C3	2	3.8
Suspected malignancy	C4	8	15.4
Malignant cells	C5	15	28.8
<b>CNB</b>		3	
Benign disease	B2	1	
Malignant disease	B5	2	

FNAC fine-needle aspiration cytology, CNB core-needle biopsy

**Table 2** Classification of the tumours on the basis of the histologic parameters

Histologic grading	No. of patients
<b>Pure DCIS</b>	
Grade I	32
Grade II	3
Grade III	9
Presence of comedo necrosis	
Yes	36
No	8
<b>DCIS mic</b>	
Grade II	1
Grade III	7
Presence of comedo necrosis	
Yes	6
No	2

examinations did not reveal metastases in the axillary lymph nodes in the patients in whom axillary sampling was carried out.

Eleven of the 57 patients (11/57, 19.3%) required a second, complementary operation: mastectomy in six cases, and reexcision in 5. Residual tumour was verified in all patients treated with mastectomy, and in two patients treated with reexcision.

## Discussion

An increasing number of cases of non-palpable breast tumours have been recognized since the introduction of mammographic screening. The same holds for the incidence of DCIS among early-detected breast cancers [5]. DCIS is defined as non-invasive breast cancer, and is therefore not expected to give metastases [4, 5, 9, 11, 12]. The Consensus Conference on the Treatment of In Situ Ductal Carcinoma of the Breast in 1999 accepted the

**Table 3** Literature results on SLN positivity rate in patients with a final diagnosis of pure DCIS

Reference	Year	No. of patients	SLN+ patients	Rate (%)
Kelly et al. [11]	2003	134	3	2.2
Farkas et al. [25]	2004	44	0	0
Veronesi et al. [12]	2005	508	9	1.8
Wilkie et al. [24]	2005	559	27	4.8
Zavagno et al. [5]	2005	102	1	1
Leidenius et al. [21]	2006	74	5	6.8
Mabry et al. [22]	2006	171	10	5.8
Katz et al. [23]	2006	110	8	7.3
Török et al. [13]	2006	40	2	5

suggestion that it was unnecessary to perform ALND if the diagnosis was pure DCIS [17]. However, some authors consider that SLN biopsy in pure DCIS is controversial, even though it might appear unnecessary.

A number of studies have been published on this issue (Table 3). In 2003, the European Institute of Oncology Team reported metastases in the SLNs in seven of 223 patients with pure DCIS (7/223, 3%). six of the seven patients underwent axillary block dissection, but other metastases were not detected [18]. Two years later, the same institute published new results, in which the SLN positivity rate was decreased (9/508, 1.8%) [12]. Similar findings were published by the Cleveland Clinic Breast Center (3/134, 2%), the Clinica Chirurgica at the University of Padova (1/102, 1%), the Breast Surgery Unit at the Helsinki University Central Hospital (5/74, 6.8%), the John Wayne Cancer Institute in Santa Monica (10/171, 5.8%), the Department of Radiation Oncology in Massachusetts (8/110, 7.3%), the H. Lee Moffitt Cancer Center (in 2005; 27/559, 4.8%), and the Hungarian Cancer Institute (2/40, 5%) [5, 11, 13, 19–22]. The New Orleans Ochsner Clinic Foundation investigated 44 patients with pure DCIS and found no metastasis in the SLNs (Table 3) [23].

Other studies have investigated the presence of SLN metastasis when the final diagnosis was DCIS mic. These results can be seen in Table 4 [8, 22, 24, 25]. Thus, the rate of SLN positivity in these literature reports ranged from 0% to 13% in patients with pure DCIS, and from 10% to 30% in those with DCIS mic.

How can a tumour be defined as non-invasive if it gives metastasis to the lymph nodes? One explanation may be an inappropriate histologic diagnosis. A microinvasive or invasive focus that can give metastasis can not be detected in the specimen besides the DCIS. An accurate preoperative histologic diagnosis is therefore important if the patient is suspected of having DCIS of the breast.

The main preoperative method utilized to take samples of tumours in our institute is FNAC, but this is not appropriate for the identification of DCIS preoperatively. FNAC was not informative (C1) in 49% of our patients in whom *in situ* breast cancer was detected, and malignant cells (C5) were observed in only 24.5%, but the presence of

**Table 4** Literature results on SLN positivity rate in patients with a final diagnosis of DCIS mic

Reference	Year	No. of patients	SLN+ patients	Rate (%)
Intra et al. [8]	2003	41	4	9.7
Camp et al. [26]	2005	17	5	29.4
Wilkie et al. [24]	2005	51	7	13.7
Zavagno et al. [27]	2006	43	4	9.3

DCIS could not be diagnosed. CNB is a more effective method than FNAC, but FNAC is the primary preoperative method in Hungary because of its cheapness [26].

However, the literature indicates that CNB is not a reliable method either. A group from Tampa investigated 613 patients: 290 (290/613, 47%) underwent preoperative CNB, 301 (301/613, 49%) excisional biopsy and nine (9/613, 2%) FNAC. DCIS mic was detected in 62 patients. Twenty of the 62 (20/62, 32%) underwent CNB, 40 (40/62, 65%) excisional biopsy and two (2/62, 3%) FNAC. The final histologic examination indicated that 15 of the 301 patients (15/301, 5%) with excisional biopsy had a proven invasive component besides the DCIS. The rate in CNB was higher (38/290, 13%). The rate in preoperative DCIS mic patients was also higher: four of the 40 (4/40, 10%) with a preoperative excisional biopsy and six of the 20 patients (6/20, 30%) with a preoperative CNB had a proven invasive component in the sample [22].

These results demonstrate that CNB is not a perfect method with which to detect pure DCIS, because there can be an invasive component in the specimen besides the DCIS.

Another important circumstance is the pathological examination of the SLNs. SLNs were examined by H&E serial sectioning at 250  $\mu\text{m}$  and by IHC [14, 15], an effective method with which to verify micrometastasis (<2 mm) and ITC metastasis (<0.2 mm) in the SLNs. The more detailed the preparation of the SLN, the greater the chance that metastasis will be found in it, and this too can cause different results concerning SLN positivity.

A group from the Bethesda National Cancer Institute reported that the rate of SLN positivity detected by IHC lay in the range 2–13% when the diagnosis was high-grade DCIS, and in the range 8–20% when it was DCIS mic [27]; this was in contrast with the earlier ALND method, which revealed an average of 2% positivity in the lymph nodes. The studies from New York Columbia University and the Netherlands Cancer Institute furnished similar results. These studies investigated patients with a long-term follow-up (102–127 months) and found that, as compared with SLN-negative patients, the survival time was not influenced by the presence of micrometastasis or ITC metastasis in the SLNs if this was detected only by IHC. Accordingly, these patients did not require other surgical treatment [10, 15].

It is important that patients with SLN positivity underwent ALND, and other metastases were not detected in the removed lymph nodes. In the majority of the SLN-positive patients, only micrometastasis was detected. These results suggest that axillary block dissection is unnecessary.

It is clearly important to establish the possibility of lymph node metastasis on the basis of the preoperative diagnosis. A number of authors have searched for factors

that could help identify patients with DCIS at an increased risk of the presence of an invasive component besides the DCIS. They found an increased frequency of invasive tumour in DCIS patients when there was microinvasion in the specimen, when the DCIS was of high-grade, when the tumour was palpable, when the mass was detected by mammography, and when the preoperative diagnosis was made by CNB [22]. SLN biopsy was suggested to be justified only in these selected cases.

The literature and our own experience lead us not to recommend SLN biopsy in all patients with DCIS. SLN biopsy can be necessary in certain circumstances: if the preoperative histologic diagnosis indicates a microinvasive focus in the sample, then SLN is necessary simultaneously, and if the final histologic examination indicates an invasive or microinvasive focus, SLN biopsy should be recommended as a second step.

It is further suggested that, if the indication is an extensive DCIS tumour, and the patients must be treated with mastectomy, then simultaneous SLN biopsy is recommended, because an invasive or microinvasive focus can not be detected in the tumour and SLN biopsy is impossible after mastectomy. If the histologic examination detects micrometastasis or ITC metastasis in the SLNs, no other operation is necessary.

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