

## Original Article

# Selective sentinel node biopsy after intratumour administration of radiotracer in breast cancer patients treated with neoadjuvant chemotherapy in relation to the level of tumor response<sup>☆</sup>



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## ABSTRACT

**Purpose:** Our objective was to analyze the accuracy of the sentinel node biopsy, taking into consideration the scintigraphy detection rate after the intratumoural administration of the radiopharmaceutical in patients with breast cancer who received neoadjuvant chemotherapy.

**Materials and methods:** The study included 60 patients with a diagnosis of invasive breast carcinoma, stage T1–T3, who received treatment with neoadjuvant chemotherapy, and were subsequently subjected to breast surgery and sentinel node biopsy after intra-tumor administration of the radiopharmaceutical.

**Results:** Scintigraphic detection of some sentinel node was achieved in 55/60 patients (91.6%). When those cases that received a second injection of the radiopharmaceutical, performed peri-areolarly due to a lack of tracer migration, were excluded, the detection rate dropped to 70% (42/60). When the detection of sentinel node, or its absence, was compared in those 42 patients, no differences were found with age, laterality-location of the lesion, size pre- and post-neoadjuvant chemotherapy, histological grade, or immunohistochemical profile. There were significant differences when comparing the groups according to the degree of pathological tumor response, both with the Miller–Payne system (non-detection 44.4%–detection 16.7%,  $p = 0.003$ ) as well as the residual cancer burden (72.2–28.6%,  $p < 0.01$ ).

**Conclusions:** The scintigraphic detection of the sentinel node after intratumoural administration of the radiopharmaceutical in patients with breast cancer who received neoadjuvant chemotherapy was below the optimal value, and sometimes a further, peri-areolar, injection was necessary, probably in relation to an alteration in the lymphatic drainage pathways. There was a significant inverse relationship between the detection of the sentinel node and level of pathological tumor response.

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## Detección selectiva del ganglio centinela tras administración intratumoral del radiotrazador, en pacientes con cáncer de mama tratadas con quimioterapia neoadyuvante en relación con el grado de respuesta tumoral

## RESUMEN

**Objetivo:** Nuestro objetivo fue analizar el rendimiento de la biopsia selectiva del ganglio centinela valorando la detección gammagráfica tras la administración intratumoral del radiofármaco en pacientes con cáncer de mama que recibieron quimioterapia neoadyuvante.

**Material y métodos:** Sesenta pacientes con diagnóstico de carcinoma infiltrante de mama, estadios T1–T3, que recibieron tratamiento con quimioterapia neoadyuvante fueron sometidas posteriormente a cirugía mamaria y biopsia del ganglio centinela mediante administración intratumoral del radiofármaco.

**Resultados:** Se consiguió la detección gammagráfica de algún ganglio centinela en 55/60 pacientes (91,6%). Cuando se excluyeron los casos con reinyección periareolar del radiofármaco por falta de migración, la detección fue del 70% (42/60). Cuando se comparó la detección o no del ganglio centinela en estas 42

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pacientes, no se encontraron diferencias en función de la edad, lateralidad-localización de la lesión, tamaño pre y posquimioterapia, grado histológico del tumor o perfil inmunohistoquímico. Si existieron diferencias significativas al comparar los grupos según el grado de respuesta patológica del tumor, valorado tanto con el sistema de Miller-Payne (no detección 44,4%-detección 16,7%,  $p = 0,003$ ) como con el sistema *residual cancer burden* (72,2%-28,6%,  $p < 0,01$ ).

**Conclusiones:** La detección gammagráfica del ganglio centinela tras administración intratumoral del radiofármaco en pacientes con cáncer de mama que recibieron quimioterapia neoadyuvante estuvo por debajo del valor óptimo, siendo necesaria en ocasiones la reinyección periareolar, lo que podría estar en relación con una alteración de las vías de drenaje linfático. Existió una significativa relación inversa entre detección del ganglio centinela y el grado de respuesta patológica tumoral.

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## Introduction

Selective sentinel node biopsy (SLNB) is currently the technique of choice for initial axillary staging in patients with breast cancer (BC) who present a clinically and sonographically negative axilla. On the other hand, neoadjuvant chemotherapy (NAC) as primary systemic therapy, has not only allowed a greater number of conservative surgeries, but also to develop in vivo monitoring of treatment response and prognostic evaluation of these patients.<sup>1</sup>

The latest Spanish consensus on SLNB in BC establishes that in patients with an initially clinical/sonographically negative axilla (cN0), SLNB may be performed both before and after primary systemic therapy. Similarly, in initially cN1/N2 patients with a clinical and sonographic negativization of the axilla after neoadjuvant treatment (cyN0) may have SLNB performed after the primary systemic treatment, avoiding axillary lymphadenectomy when the SLN is negative.<sup>2,3</sup>

However, there remains a widespread controversy about performing SLNB in patients with BC post NAC, because high rates of false negatives.<sup>4,5</sup>

As for the technique, there is also some variability, as there are 2 ways for percutaneous administration of the radiopharmaceutical: Superficial administration (subdermal, intradermal and periareolar) and deep administration (peritumoral or intratumoral). The latter is recommended by the guides<sup>3</sup> because it is supposed that it reflects the connection between the tumor and lymph drainage territories. Furthermore, it highlights better further drainage areas complementary to the axillaries.

In order to definitively assess the response to NAC, it is necessary to proceed with a pathological examination of the resected tumor. There are numerous publications that demonstrate improved survival for those patients with a pathological complete response [pCR] after NAC with respect to the patients without this response.<sup>6</sup>

It is reported that chemotherapy treatment affects not only tumor cells, but also the stroma or tumor bed on which they grow, as well as the surrounding lymph drainage territories. As a result of this alteration, the NAC can affect the detection technique of the SLN.<sup>5</sup> Our objective was to analyze the profitability of the SLNB in the scintigraphic detection using intratumoral administration of the radiopharmaceutical in patients with BC who received NAC. Thus, the degree of detection is analyzed exclusively with intratumoral injection of the radiopharmaceutical, to thereby, determine the effect of NAC on deep drainage pathways. For this, detection rate in these patients was correlated with the degree of tumor response.

## Material and methods

### Patients and method

A retrospective study was conducted between November 2010 and September 2014 of patients with invasive breast carcinoma,

ductal histological type (no special type), stages T1–T3, with a negative axilla in the clinical-sonographic examination and who were treated with NAC. Out of a total of 340 women with BC seen in this period of 4 years, 60 women who met the inclusion criteria described were selected.

SLNB was performed after completion of neoadjuvant treatment, the same day of surgery, with intratumoral administration of 74 MBq (2 mCi) of <sup>99m</sup>Tc-nanocolloid albumin (Nanocoll®). The radiopharmaceutical was obtained in unit dosage form through an external radiopharmacy, wherein at least 95% of the colloidal particles had a diameter of  $\leq 80$  nm. In palpable tumors, the radiopharmaceutical was administered by intratumoral injection in the Nuclear Medicine Department, while in non-palpable tumors the injection was performed with either ultrasound or stereotactic guidance in the Radiology Department (Aloka Prosound sonograph, Hitachi Medical Systems Europe Holding AG, Switzerland; Mammomat Inspiration digital mammograph and prone table for performing digital stereotactic, Siemens, Germany). In cases where there was no migration of the radiopharmaceutical, we proceeded to a new periareolar injection of 37 MBq (1 mCi). This dose was prepared with a new nanocolloid vial and the new imaging was performed after 60 min.

Imaging was performed with a Philips Brightview gamma camera with 2 detectors (Brightview Philips, Best, The Netherlands) with a LEHR collimator, with planar projections, arm and breast traction toward the midline when necessary. Systematic SPECT was not performed except in cases where it was considered appropriate due to difficulty in locating the SLN. A limitation of our study was not having SPECT/CT equipment. When necessary, the injection site was covered with leaded material, in which case, images were both performed with and without leaded materials, paying particular attention so as not to miss possibly masked SLN in proximity. Images were systematically made at the 30 and 120 min marks, and after the detection of the SLN, we proceeded to mark on the skin in indelible ink and the patient was referred to surgery. The location in the operating room was performed with a gamma detecting probe (Navigator®, Dilon Technologies, USA). The average time between the first nanocolloidal injection and the surgery ranged from 3 to 4 h, depending on whether it was necessary to perform a periareolar reinjection.

Anatomopathological SLN analysis was performed intraoperatively. After dissection of the lymph node, cross sections of 1–2 mm thickness were conducted, taking imprints of each slice for cytology. In nodes with macroscopic areas suspected of metastatic infiltration, sections were analyzed by freezing one of the slices, staining with hematoxylin-eosin (H & E) quickly. In lymph nodes with no suspicious areas, and those negative in the frozen section, nodal tissue were processed for molecular analysis using the system *one step nucleic acid amplification*, Sysmex® (OSNA, Japan), by homogenization, ultracentrifugation and subsequent detection RT-PCR of mRNA of CK19. Full lymphadenectomy was performed in cases where macrometastases was detected in the SLN (defined by

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