

## A Novel Dual Technique Combining Radiotracer and Magnetism for Restaging Axilla after Neoadjuvant Therapy in Axillary Node-positive Breast Cancer Patients

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### Abstract

Surgical treatment of the axilla in patients with breast cancer has changed with the arrival of the neoadjuvant systemic therapies (NST); the role of axillary lymph node dissection with the use of radiotracers, fluorescent particles, surgical clips and radioactive seeds appears to play a significant role following these systemic therapies. We present a novel dual technique (<sup>99m</sup>Tc-Nanocoll® or <sup>99m</sup>Tc-Lymphoseek®) for sentinel lymph node biopsy (SLNB) and the use of magnetic seed (Magseed®) for the achievement of more accurate and less invasive method to restaging the axilla after NST.

**Keywords:** Breast; Chemotherapy; Neoadjuvant; Neoplasms; Sentinel lymph node biopsy

**Abbreviations:** BMI: Body Mass Index; HER: Human Epidermal Growth Factor Receptor; BCS: Breast Conserving Surgery; CEN: Central Portion; UQ: Upper Quadrants; UOQ: Upper Outer Quadrant; OQ: Outer Quadrants; pCR Pathological Complete Response

### Introduction

In the last years, the surgical treatment of the axilla in patients with locally advanced breast cancer has undergone profound changes with the arrival of the neoadjuvant systemic therapies (NSTs). The major clinical benefit of these treatments is the downstaging of the disease, reporting a complete axillary pathological response in 22%-74% of patients, depending on tumor subtype [1-3].

Nowadays, the most important goal is to design individualized treatment strategies for those patients who have responded to NST, to avoid an overtreatment and the side effects associated with the axillary lymph node dissection (ALND) [4,5].

The tools that are currently available to localize the lymph nodes which have responded to NST, go through the sentinel lymph node biopsy (SLNB) with the use of radiotracers, colorants, fluorescent particles, and the combinative placement of surgical clips or/and radioactive seeds in the previous involved lymph node, among others.

Many studies have been published on the diagnostic performance of SLNB after NST in clinically node positive breast cancer patients, reporting conflicting outcomes concerning the identification rate of a

sentinel lymph node and the false-negative rate (FNR) of the technique [6,7].

Here, we report five cases of a novel dual technique for evaluation of axillary response to NST using a radiotracer (<sup>99m</sup>Tc-Nanocoll® or <sup>99m</sup>Tc-Lymphoseek®) for SLNB and marking with magnetic seeds (Magseed®) the pathologically proven positive clipped node under ultrasound guidance, two or three days before surgery.

### Case Reports

Five patients with diagnosis of T2 N1 M0, (stage IIb) breast cancer and axillary involvement evidenced by ultrasound and MRI, underwent neoadjuvant chemotherapy treatment.

At the first medical examination, four patients had palpable axillary nodes and three patients had a palpable primary tumor; the immunohistochemistry analysis showed two patients with triple negative profile (Ki67 60%-70%) and three with Luminal B HER2 negative-like profile (Ki67 7-30%) (Table 1).

	N
No. of patients	5
Median age (years)	57 (53-78)
BMI (median)	25.6 (21.63-37.53)
<b>Tumor histology</b>	
Lobulillar	1
Ductal	4

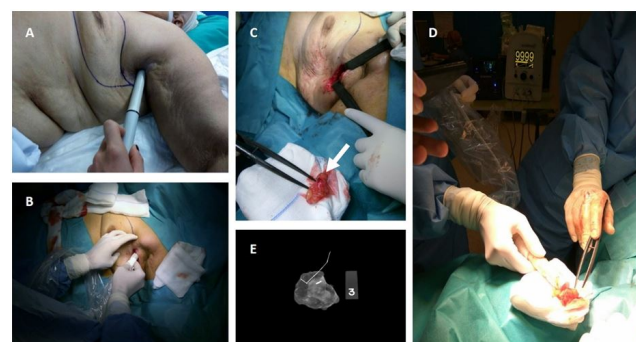
Subtypes	
Luminal B-HER2 neg-like	3
Triple negative	2
Extent of disease	
Multifocal	2
Multicentric	1
Unique	2
Clinical TNM stage	
T2 N1 M0	5
Tumor Stage	
IIB	5
Primary Breast Tumor Site	
CEN	1
UQ	1
UOQ	1
OQ	2
No. of abnormal nodes on ultrasound at diagnosis	
2	1
3	1
4	1
≥ 5	2
Breast pCR	
Complete	2
Partial	2
No response	1
Axillary Pcr	
Complete	3
Partial	2
Type of breast surgery	
Mastectomy	2
BCS	3

**Table 1:** Patient and tumor characteristics.

Pathologically positive axillary node was marked under ultrasound guidance by a surgical clip before the start of NST; in cases with more than one pathological node was observed, the larger one or the one located below the lower edge of the pectoralis minor muscle (Berg level I) was clipped. After NST, two patients had complete axillary response and the other three had partial one, all of them assessed by image (ultrasound and MRI).

After neoadjuvant treatment, one Magseed® was inserted into the center of the clipped node under ultrasound guidance, few days before intervention (1-4 days). The day before surgery, we performed an intratumoral injection of 111 MBq (3mCi) in 0.4 ml of <sup>99m</sup>Tc-albumin nanocolloid (Nanocoll®) or 74 MBq (2 mCi) of <sup>99m</sup>Tc-Tilmanocept (Lymphoseek®) with similar volume; then a lymphoscintigraphy was started (30 and 120 minutes after injection), showing axillary migration of the radiotracer. After lymphoscintigraphic images, the situation of SLN was marked on skin with an indelible pen and, afterwards, an axillary scan was performed with a hand-held gamma detector probe, in order to better depict the SLN situation.

In the operating room, SLNB was performed by gamma probe guidance, following our conventional approach. However, we used a magnetic detector as well for ascertaining the signal coming from Magseed® placed inside the pre-NST pathologic node (Figure 1).

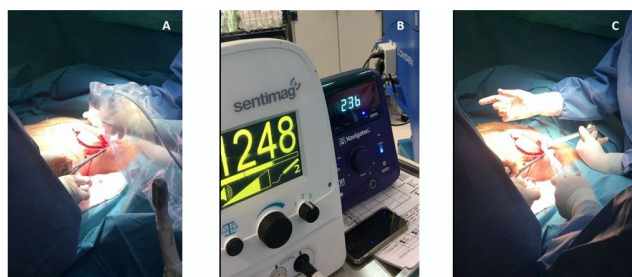


**Figure 1:** Magseed® detection. (A-B) Axillary tracing with magnetism detector probe, (C) paramagnetic seed in the clipped node (arrowhead), (D) *ex vivo* confirmation, (E) clip + seed radiology confirmation.

SLN were found and excised in all patients with an average of 3 SLN per patient (range 1-4). There was a concordance between one of the sentinel lymph nodes and the location of the paramagnetic seed (Figure 2). After sentinel node retrieval an ALND was done.

In the pathological study of the resected nodes, macrometastases were reported in 3 patients and no tumoral remaining cells were described in the remaining two.

Interestingly, two of these patients showed a good concordance between Magseed® and sentinel node; however, there was a discordant case (Magseed® placed in a node that was not retrieved as sentinel node during SLNB). In two of these three patients, ALND showed lymph node involvement in other lymph nodes.



**Figure 2:** Concordance between (A-B) magnetic and (B-C) gamma detector probes.

## Discussion

Currently, with the increased use of NST, there is a need for achieve a less-invasive axillary staging after that treatment. However, there is no accurate enough non- invasive method for restaging the axilla after NST [8].

ALND is the standard practice in those patients with metastatic involvement before NST. It is associated with morbidities in 40% of patients, such as lymphedema and functional limitations [4]. Those patients, converting to node negative status after NST could benefit from omitting an axillary lymph node dissection. The key-point is to find and implement a reproducible diagnostic test that can select the patients with axillary pathological complete response (pCR) [9].

In the search for less-invasive axillary staging after NST, the first studies published used an arbitrary cut-off value of 10% for false-negative rate (FNR), based on earlier results in clinical node negative patients undergoing primary surgery. The SN FNAC [10], SENTINA [11] and ACOSOG [12] studies showed remarkably results near this FNR edge (range 8%-15%) [13].

In order to reduce this FNR, studies like MARI [14], marked the positive proven nodes with radioactive iodine seeds or the ACOSOG Z1071, where a resection of the clipped node at the same time of SLNB, were performed, reporting FNRs near of the 7%. These previous findings led to the implementation of hybrid techniques like in TAD or RISAS studies. The first one marked the clipped node (positive pre-NST) with a radioactive iodine seed after NST completion with a FNR of 2%, and the second one, with pending results, marked the positive proven node with radioactive iodine seed before the beginning of the NST.

We present a novel dual technique using a radiotracer ( $^{99m}\text{Tc}$ -Nanocoll® or  $^{99m}\text{Tc}$ -Lymphoseek®) for SLNB and marking the proven positive clipped node with a magnetic seed (Magseed®) under ultrasound guidance, before surgery, due to the clinical practice difficulties to detect the clip in the lymph nodes previously marked by ultrasound in the operating room.

Magseed® is a paramagnetic steel and iron oxide seed, that is easily seen despite its size (5 x 1 mm) on mammography and ultrasound. Its helical shape optimizes tissue in-growth and ensures it stays in place. This seed is detectable using the Sentimag® probe, which generates an alternating magnetic field to magnetize the iron oxide particles within the Magseed® [15].

The magnetic seed offers the benefits of radio-seeds (used in MARI approach), but without the regulatory issues associated to radiation. These seeds were launched on 2016 and it is usually used for localize non-palpable breast cancer.

## Conclusion

Based on our preliminary findings, we propose its potential use, in combination with traditional radio-guided SLN approach, for the achievement of more accurate and less invasive method to restaging the axilla after NST.

## Conflicts of Interest

The authors declare that there is no conflict of interest.

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