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 (99mTc-Nanocoll® or 99mTc-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; Chemotheraphy; 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 (99mTc-Nanocoll® or 99mTc-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).

| No. of patients | 5 |
|-----------------|---|
| Median age (years) | 57 (53-78) |
| BMI (median) | 25.6 (21.63-37.53) |

**Tumor histology**

- Lobulillar: 1
- Ductal: 4
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 $^{99m}$Tc-albumin nanocolloid (Nanocoll®) or 74 MBq (2 mCi) of $^{99m}$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.](image)

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.

| Table 1: Patient and tumor characteristics. |
|------------------------------------------|
| **Subtipes**                               |
| 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 |
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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