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Superparamagnetic iron oxide as a tracer for sentinel node biopsy in breast cancer: A comparative non-inferiority study

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Abstract

Aims: The gold standard for detection of Sentinel Lymph Nodes (SLN) is a combined radioisotope and blue dye breast injection, using a gamma probe (GP). A new, non-radioactive method was developed, using a tracer (Sienna+®) of superparamagnetic iron oxide (SPIO) nanoparticles and a manual magnetometer (SentiMag®) (SM). The IMAGINE study was designed to show the non-inferiority of SM compared to GP, for the detection of SLN in breast cancer patients with SLN biopsy indication.
Methods: From November 2013 to June 2014, 181 patients were recruited, and 321 nodes were excised and assessed ex-vivo. Readings from both SM and GP devices were recorded during transcutaneous, intraoperative, and ex-vivo detection attempts.
Results: At the patient level, ex-vivo detection rates (primary variable) with SM and GP were 97.8% and 98.3% (concordance rate 99.4%). Transcutaneous and intraoperative detection rates were 95.5% vs 97.2%, and 97.2% vs 97.8% for SM and GP respectively (concordance rates $>$ 97%). At the node level, intraoperative and ex-vivo detection rates were 92.5% vs 89.3% and 91.0% vs 86.3% for SM and GP respectively. In all cases the non-inferiority of SM compared to SM was shown by ruling out a predefined non-inferiority margin of 5%.
Conclusions: Our study showed the non-inferiority of SM as compared to GP. Moreover, the ex-vivo and intraoperative detection rates at the node level were slightly higher with SM.

Keywords: Invasive breast cancer; Sentinel lymph node biopsy; Superparamagnetic iron oxide (SPIO); SentiMag®; Sienna+®

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Introduction

In Europe, breast cancer is the most common cancer in women, with an incidence of 429 900 new cases per year, and represents 28.9% of overall cancers.[1] Breast cancer propagates mainly through the lymphatic system and, classically, lymph node involvement is the most important prognostic factor for breast cancer management.[2] Sentinel lymph nodes (SLN) are the first nodes receiving lymphatic drainage from the tumour, and therefore those with the highest probability of affectation.[3] Currently, the SLN biopsy is a standard technique used in breast cancer patients with clinically and radiologically negative axilla for the purposes of staging and prognosis.[4] The SLNB was introduced in the 90s, and significantly reduces the morbidity associated with axillary lymphadenectomy.[5,6]

The gold standard for the detection of the SLN is a combined technique, in which both a radioisotope and blue dye are injected in the breast, and after some time to allow migration through the lymphatic chain, a gamma probe is used to detect SLNs. Lymphatic nodes that are blue or radioactive are considered SLNs and are excised. The main disadvantages of this technique are the exposure of both patients and physicians to radiation and radioisotope short half-life, availability, handling and disposal.[7,8]

A new, non-radioactive method has been developed for the identification of SLNs. This method uses a tracer (Sienna+®) composed of superparamagnetic iron oxide (SPIO) nanoparticles and a manual magnetometer (SentiMag®). When injected intravenously, SPIOs have been used as contrast agents for magnetic resonance imaging (MRI), and their characteristics are well known.[9,10] When injected subcutaneously, SPIO moves and accumulates into sentinel nodes within minutes, and iron deposition is seen predominantly within SLN sinuses and macrophages. In the event of metastatic involvement of the node, SPIOs are seen to deposit within uninvolved areas of the node only.[11] The nodes can be visualized by MRI imaging and during surgery, since the marked SLN are often coloured brown or black.[12] Sienna+® is a blackish-brown sterile aqueous suspension of SPIO carboxydextran-coated particles that is intended for use with the SentiMag device. The carboxydextran coating prevents agglomeration while maintaining biocompatibility. The particle diameter, including the organic coating, is 60 nm, ideally suited for SLNB. This diameter enables the SLNs to selectively filter out the particles and is similar to the particle size of standard radioisotope tracers.

In order to evaluate the performance of the SentiMag®/Sienna+® (SM) as compared to the gamma-probe (GP) technique (the standard practice in the Spanish healthcare system), we designed the "Isotopic vs. Magnetic Intraoperative Node Evaluation" (IMAGINE) multicentre study, to be conducted in 9 Spanish hospitals with extensive experience in SLNB. The study was designed to show the non-inferiority of SM as compared to the GP technique, for the detection of SLN in breast cancer patients in whom a SLN biopsy is indicated.

Materials and methods

Study subjects

In 9 Spanish hospitals, breast cancer patients were recruited for the study if they were 18 years of age or older, had a SLN biopsy programmed, and were preoperatively node negative, clinically and radiologically. Patients were excluded if they had received neoadjuvant therapy, were intolerant to iron or dextran compounds (present in Sienna+), the administration of a radioisotope was contraindicated, had disorders implying high iron concentration, or had a pacemaker or other metallic device implanted in the thorax wall. The study was approved by the Institutional Review Board (IRB) of the participant centres and all patients had to provide their informed consent to participate in the study.

Preoperative procedures and SLN detection methods

For the identification of the SLN, patients received an injection of radioisotope tracer, and optionally, an injection of methylene blue, according to the standard protocol of each centre. The day of the surgery, two ml of Sienna+® were diluted in saline, obtaining a final volume of 5 ml that was injected subcutaneously in the subareolar area (after anaesthesia but previous to the methylene blue injection if vital dye was used as a tracer), and followed by a 5 min massage of the injection site. Intradermal injection of the tracer must be avoided in order to prevent skin pigmentation. At least 20 min after the Sienna+® injection, transcutaneous detection was attempted with both devices (SM and GP) before incision. The existence of extraaxillary signal was also assessed transcutaneously with both methods. After incision, intraoperative detection (in the patient's armpit) was attempted with SM, and the positive spots were also measured intraoperatively using GP. All nodes with a positive reading with SM were excised as long as their reading was superior to 10% of the node with the highest SM reading. When no magnetic signal remained, the axilla was then verified using GP. All remaining nodes positive with GP were excised as long as their reading was superior to 10% of the node with the highest GP reading. Lymph nodes dyed blue or black, or suspicious by palpation were also excised. Finally, all excised nodes were measured again ex-vivo with both detection devices (SM and GP), and submitted to for either OSNA or histologic analysis, according to usual practice in each centre.

Surgeons participating in the study were trained in the use of the SM device during a single session held before the study began. In addition, support by trainers was also provided during the procedures for the first few patients recruited in each study centre.