

Sentimag® Technique for Sentinel Lymph Node Biopsy in Breast Cancer Patients: Evaluation of Effectiveness, Feasibility and Challenges

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Rezumat

Tehnica Sentimag® pentru biopsia ganglionului sentinelă la pacienții cu cancer de sân: evaluarea eficacității, fezabilității și provocărilor

Scop: Efectuarea biopsiei ganglionului sentinelă (Sentinel Lymph Node Biopsy - SLNB) are ca standard de aur tehnica duală ce implică utilizarea traserului radioactiv și a colorantului albastru. Scopul acestui studiu a fost de a evalua rata de identificare a ganglionilor și fezabilitatea acestei tehnici pentru SLNB la pacienții cu cancer de sân.

Metode: Au fost analizate date colectate retrospectiv de la 143 de paciente cu cancer de sân cu axila negativă clinic și radiologic. Procedurile SLNB au fost efectuate folosind nanoparticulele superparamagnetice de oxid de fier (SPIO). Ganglionii limfatici sentinelă au fost identificați vizual și utilizând magnetometrul Sentimag®.

Rezultate: Un total de 146 de proceduri SLNB au fost efectuate la 143 de pacienți. Rata de identificare a ganglionilor limfatici (RI) a fost de 97,9%. În cazul a treizeci și șapte de pacienți (25,3%) au fost detectați ganglioni limfatici invadați neoplazic, 19% au avut cel puțin o macrometastază, 6% cel puțin o micrometastază și 1% au avut ITC. Numărul mediu de ganglioni limfatici excizați a fost de 2,2 ganglioni per procedură. S-a observat o ușoară pigmentare maronie în jurul zonei de injectare. Nu a fost raportată nicio reacție alergică sau efect secundar al Sienna+® traser / Magtrace®.

Concluzie: Noua metodă de detecție magnetică a ganglionilor sentinelă (Sentimag®) este eficientă, fezabilă și comparabilă cu tehnica standard de aur a biopsiei ganglionului sentinelă la pacienții cu cancer de sân.

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Cuvinte cheie: cancer mamar, biopsie ganglion santinelă, tehnica Sentimag®, nanoparticule superparamagnetice de oxid de fier, Magtrace®

Abstract

Aim: The gold standard technique of Sentinel Lymph Node Biopsy (SLNB) is the dual technique of radioactive tracer with blue dye. The aim of this study was to assess the node identification rate and feasibility in terms of ease of use of this technique for SLNB in breast cancer patients.

Methods: Retrospectively collected data of 143 breast cancer patients with clinically and radiologically negative axilla were analysed. SLNB procedures were performed using the superparamagnetic iron oxide (SPIO) nanoparticles. Sentinel lymph nodes were identified using the Sentimag® magnetometer and visual aid.

Results: A total of 146 SLNB procedures were undertaken on 143 patients. Lymph node identification rate (IR) was 97.9%. Thirty seven patients (25.3%) were detected with cancer in their lymph nodes, 19% had at least one macrometastasis, 6% at least one micrometastasis and 1% had ITCs. The mean average lymph node retrieval was 2.2 nodes per procedure. Mild brownish discolouration was noted around the injection site. No allergic reaction or side effect of Sienna+® tracer / Magtrace® was reported.

Conclusion: The new magnetic detection method of sentinel lymph nodes (Sentimag®) is effective, feasible and comparable to the gold standard technique of sentinel lymph node biopsy in patients with breast cancer.

Key words: breast cancer, sentinel lymph node biopsy, Sentimag® technique, superparamagnetic iron oxide nano particles, Magtrace®

Introduction

The status of the axillary lymph nodes is the most significant prognostic factor in the management of breast cancer patients (1). SLNB is the standard technique for assessing the clinically and radiologically negative axilla in breast cancer patients (2). SLNB was introduced for the first time in breast cancer surgery for assessment of the axilla in 1994 (3). The National Surgical Adjuvant Breast and Bowel Project B-32 trial found that overall survival, disease free survival and loco-regional recurrence were equivalent between patients who were randomised to SLNB followed by routine axillary dissection compared with SLNB followed by axillary node dissection only in sentinel node positive patients (4). In the gold standard technique of SLNB, radioactive tracer (technetium-99-

labelled sulphur colloid) with blue dye is used. A prospective trial has shown that lymph node identification rates were 99% when dual tracer technique was used as compared to 93-95% in blue dye only and 96-96.2% in radioactive tracer only (5). The disadvantage of this technique is that blue dye carries risk of allergic reaction of about 1% including severe anaphylactic reaction requiring cardiopulmonary support (6). The Royal College of Anaesthetist's 6th National Audit Project (NAP6) has shown that patent blue dye was the fourth commonest cause of perioperative anaphylaxis. This is higher than suxamethonium and one of the highest in NAP6 (second only to teicoplanin) (7). Blue dye may result in prolonged discoloration of the skin at the injection site which can take 12 to 24 months and in some cases even more than 3 years to disappear (8). The disadvantage of utilization

of radioactive tracer in SLNB is radioactive exposure to patients, surgeon and theatre staff. There are also challenges with transfer, storage and handling of radioactive material due to strict regulations (9). An added drawback of radioactive tracer is lack of its availability and short half-life of 6 hours only (10).

Tracer is injected in the sub-areolar region and travels through the lymphatics to lymph nodes. Tracer also gives colour to the lymph node ranging from brown to greyish tinge which aids in identifying the lymph node. Superparamagnetic iron oxide (SPIO) nanoparticles also have a role as contrast agents for imaging (MRI) and as drug delivery for therapeutic purposes (11,12). The tracer is a dark brown suspension of organically coated, superparamagnetic iron oxide (SPIO) particles with a tight size distribution of around 60 nm (13). We conducted this study to evaluate the technique of SLNB in early breast cancer patients to assess node identification rate and feasibility in term of ease of use of this new technique.

Methods

We conducted a review of patients with breast cancer who underwent SLNB using Sentimag® technique from July 2018 to January 2020. Approval from local ethics committee was not required due to retrospective nature of the study. All the patients were fully informed about SLNB with Sentimag® technique and a written consent was obtained at the time of the procedure. A total of 143 patients had 146 SLNB procedures using Sentimag® technique during this time. Patients included in the study were breast cancer patients who had clinically and/radiologically (ultrasound) negative axilla.

Sentimag® SLNB Technique

Manufacturer's recommendations were followed for use of Sentimag® technique. Magtrace® tracer was injected in sub-areolar area on the side of SLNB after patient was anaesthetised

and moved on to the operation table. 2 mls of tracer was injected in the sub-areolar space as recommended by the manufacturer. After the injection the area was massaged gently for 5 minutes to facilitate the uptake of tracer by the lymphatics and migration to the axillary lymph nodes. Use of blue dye was kept as a back-up plan in case Sentimag® technique would not work during the surgery. Usually breast procedures were performed first followed by the SLNB which allowed more time for tracer to travel and concentrate in lymph nodes. According to the manufacturer the Magtrace® can be injected up to 7 days or as little as 20 minutes before surgery. We changed our practice to injecting 3 days before the operation. Three days before the operation was chosen as an average of recommended time of injection by the manufacturer (up to 7 days before surgery) to provide prolonged enough time for the tracer to travel to and concentrate in the nodes and make node identification easier. By using hand-held magnetometer probe (*Fig. 1*), we checked the signals at the injection site followed by scanning the axilla before making the skin incision to identify the area of maximum signal strength. After skin incision and opening the clavipectoral fascia, axilla was assessed visually. Presence of a brown colour guided the surgeon in identifying the sentinel node, which was then confirmed by using the magnetometer probe. If



Figure 1. The Sentimag® instrument (machine and probe) & a Magtrace® vial

no staining of node was seen initially, then using the magnetometer guided further dissection and identification of the sentinel lymph node both visually and with magnetic signals. Metallic instruments were removed from surgical field during use of magnetometer to avoid interference with magnetic signals. Once the lymph node was excised it was again checked for signal strength by placing the lymph node on the magnetometer probe to confirm that the correct node was removed. Further nodes with higher magnetometer signals were identified and removed according to rule of at least 10% signal strength. *Fig. 2* and *Fig. 3* show the sentinel lymph nodes with brown colouration.

Results

143 patients with breast cancer who underwent 146 sentinel lymph node biopsy procedures with Sentimag® technique were analysed. The age of patients ranged from 25 to 88 years with mean age of 65 years. The patient and pathology characteristics are shown in the *Table 1*.

The nodal identification rate (IR) was 97.9%. Thirty seven patients (25.3%) were detected with cancer in their lymph nodes, 19% (28 of 146) had at least one macrometastasis, 16% (9 of 146) had at least one



Figure 2. Brown coloured lymph node seen during the operation

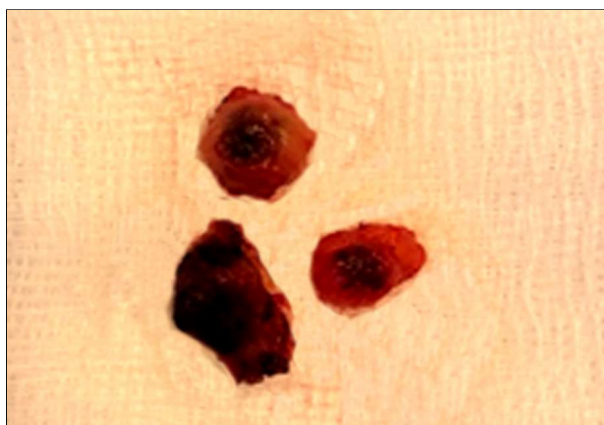


Figure 3. Three sentinel lymph nodes removed

Table 1. Patient and tumour characteristics of the study sample. Data is given as mean values or in %.

Characteristic	Value
Mean Age	63 y (range 25–88 y)
Screening Patients	6 (4%)
Symptomatic Patients	140 (96%)
Menopausal status	
Premenopausal	25 (17%)
Postmenopausal	121 (83%)
Tumour Type	
Ductal carcinoma in situ	7 (5%)
Invasive Carcinoma	139 (95%)
IDC (no special type)	120 (82%)
Invasive Lobular carcinoma	12 (8%)
Mucinous Type	5 (3%)
IDC + DCIS	44 (32%)
Metaplastic	1 (<1%)
No Tumour (Upfront SLNB)	1 (<1%)
Type of surgery	
Mastectomy	31 (21%)
Breast Conserving	114 (78%)
Magseed Guided	26 (18%)
Wire Guided	16 (11%)
Upfront SLNB	1 (<1%)
Tumour size	
1-10 mm	39 (27%)
11-20 mm	61 (41%)
21-30 mm	19 (13%)
31-40 mm	8 (5%)
41-50 mm	3 (2%)
> 50 mm / Extensive / Multifocal	16 (11%)
Pathological lymph node status	
pN0 (no mets)	109 (74%)
Nodes with Mets	37 (25%)
pNi+ (at least one ITC)	3 (2%)
pN1mi (at least one micromets)	9 (6%)
pN1ma (at least one macromets)	28 (19%)
Grading of Invasive Cancer	
G1	16 (11 %)
G2	81 (55%)
G3	40 (27%)
Receptor Status	
Estrogen receptor (ER) +	122 (83%)
Progesterone receptor (PR) +	80 (55%)
HER2+	16 (11%)
Triple Negative	13 (9%)

micrometastasis. 1% (2 of 146) had isolated tumour cells (ITCs).

A total of 334 nodes were assessed with Sentimag® technique and removed intra-operatively. The average number of lymph nodes removed per procedure was 2.2.

Subgroup analysis of patients with injection of tracer (Magtrace®) on the day of operation and three days before operation is provided in the *Table 2*. There were 24 patients who had their tracer injected three days before the operation and 119 patients had their Magtrace® injected on the day of operation. Statistical comparisons were made using Fisher Exact test for node identification rate and Mann-Whitney U Test (2 tailed) for average node retrieval. Significance was determined to be at $p \leq 0.05$. There was a significant difference in average node retrieval ($p=0.0348$) however there was no difference in node identification rate ($p=1$) between the two groups.

When looked at a median follow up of 20 months (range, 16 months to 24 month), no case of local axillary recurrence was reported.

In one patient the brown tissue (possible nodes) with high magnetic signals removed during SLNB showed no evidence of lymph nodes histologically. The histology of this

axillary tissue showed features of breast structure and fibrocystic changes consistent with ectopic breast tissue. In another two patients the tracer failed to concentrate in axillary lymph nodes resulting in no magnetic signals or brown discolouration. As a result, one patient had 4 node sampling and another patient who was in a trial (ROSCO Trial) underwent axillary node clearance, a part of the trial protocol.

No allergic reaction or side effect was reported in any of the patients underwent Sentimag® technique of SLNB. On postoperative review in clinic brown discolouration of the injection site was found in most patients.

Discussion

After implementing Sentimag® technique of SLNB we reviewed data of our breast cancer patients who underwent this new technique. The study assessed and analysed whether we were achieving the same performance with Sentimag® in our institution which has been seen in the Sentimag® trials and other studies with gold standard technique of SLNB (*Table 3*). Our study reported lymph node identification rate (IR) of 97.9% and average

Table 2. Subgroup analysis of patients who had tracer injected on the morning of operation and three days before operation

Tracer Injected	Numbers (%age)	Node Identification rate (IR)	Node Retrieval		
			Mean	Median (IQR)	Range
On the morning of operation:	119 (83%)	118 (99%)	2.25	2 (2-3)	1-5
3 days before operation:	24 (17%)	24 (100%)	1.8	2 (1-2)	1-3
P-Value		1 [†]	0.0348*		

*Mann-Whitney U Test (2 tailed). Z=2.10, [†]Fisher Exact Test, interquartile range (IQR)

Table 3. Sentinel lymph node identification rate and average node retrieval reported in the individual studies comparing the use of Sentimag® technique with a standard technique (technetium with or without blue dye)

Study/Author	Node IR*	Node IR*	ANR*	ANR*
	(Sentimag® Technique)	(Standard Technique)	(Sentimag Technique)	(Standard Technique)
SentiMAG Multicentre Trial	94.4%	95%	2.0	1.9
Ghilli et al	97.9%	99%	1.8 [†]	
The Nordic SentiMag Trial	97.6%	97.1%	1.83	1.79
The Central European SentiMag Study	98%	97.3%	1.9	1.8
The French Sentimag Feasibility Trial	97.2%	95.4%	2.01	1.94
Pinero-Madrone et al.	97.8%	98.3%	1.63	1.55
ALMANAC Trial		98%		2.0

*Node IR (Identification Rate). *ANR (Average Node Retrieval). [†]An average of 1.8 lymph nodes per patient was globally removed by both SP10 and 99mTc tracer

lymph node retrieval number of 2.2 which are comparable to other studies in the literature. The SentiMag multicentre trial reported no difference in IR between the standard SLNB technique and the Sentimag[®] technique (95.0% vs 94.4%) with comparable average lymph node retrieval of 1.9 nodes in standard technique and 2.0 nodes in magnetic technique (14). The IR in our study was even comparable to historical studies which used blue dye and radioactive tracer as their method of SLNB (4,6,15). Ghilli et al also showed no difference in IR between the standard technique 99mTc (99.0%) and Sentimag[®] technique (98%) (16). The Nordic SentiMag multicenter trial reported that sentinel node IR were similar between standard technique and SPIO per patient (97.1 vs. 97.6 %) and mean number of nodes were 1.79 nodes in standard technique and 1.83 nodes with Sienna (17). Similar results were shown in the Central European SentiMag study which reported IR of 97.35 in standard technique and 98% in magnetic technique with comparable mean number of lymph nodes (18). The French Sentimag[®] Feasibility Trial reported similar IR between standard and Sentimag[®] technique. In this trial the IR was 97.2% with magnetic technique and 95.4% for the standard technique. Average number of lymph nodes retrieved in this study was 2.1 nodes per patient (19). A meta-analysis of 1683 SLNBs by Teshome et al showed that Sienna mapping (magnetic technique) is non-inferior method for SLN detection in patients with clinically node negative breast cancer to a standard technique (20). A comparative non-inferiority study by Pinero-Madrona reported similar lymph node IR between the Sentimag[®] technique and radio-active isotope method (97.8% vs 98.3%). This study also showed that transcutaneous detection of lymph nodes is lower in Sentimag[®] technique as compared to radio-active isotope technique (21). Authors of current study had similar observation that transcutaneous detection of lymph nodes was not as effective with magnetometer and did not reach to the same depth as it has been

seen with gamma probe. Sentimag[®] manufacturers say that the depth perception for magnetometer probe is 3 cm which could be increased by firm pressure on the breast tissue with the probe. It was also noted that after dissection through the subcutaneous tissue and pectoralis fascia the detection with magnetometer improved significantly. However, with refined technique of injecting tracer 3 days before surgery did improve signal strength and it was much, much easier to locate sentinel nodes. A comparative study would be the way forward to evaluate this aspect further.

On Subgroup analysis, a higher node identification rate (100%) was noted in the patients who had injection three days before operation. The reason most likely being for tracer to have more time to travel to lymph nodes and concentrate as compared to the group who had injection on the day 20 minutes before surgery. It was also observed that average number of nodes retrieved was lower in the three-day group. Authors think this is due to the higher concentration of tracer in the nodes providing higher strength signals resulting in a sharp and clear identification of the sentinel nodes with less likelihood of removing closely associated non-sentinel or palpable nodes.

It was also found that in cases of Magseed[®] (localisation techniques which uses Sentimag[®] magnetometer probe) guided excision of breast lesions close to nipple areolar complex (NAC) the tracer (Sienna+[®]/ Magtrace[®]) had to be injected at least 3 cm away from Magseed[®] location to avoid signal interference from the tracer injection site which could hamper breast lesion localisation.

The skin staining from the tracer was a common problem and it has been reported that it disappears over time (22). It was observed that staining of injection site persisted in our patients even 15 months after the procedure. However, patients expressed better acceptance to brown discolouration than the blue around the nipple area.

Authors did not come across any case where postoperative MRI breast was required

however literature has reported that Sentimag® technique resulted in difficulty of MRI interpretation in postoperative breasts as persistence of tracer could create an artefact. Krischer et al conducted a small study in which for the first time MR feasibility after Sienna+® injection was investigated and concluded that Sienna+® impaired breast MRI after a mean follow-up time of 42 months in half of the cases however interpretation of the MRI scans using a 1.5T MR coil was still possible in 88% of patients (23).

The advantages of Sentimag® technique are that it is a non-radioactive method for SLNB, thus there is no risk of radiation exposure and no radioactive material control legislative framework to follow. The Sentimag® procedure has the flexibility of injecting tracer either in operation theatre or few days (up to one week) before in the clinic by the surgeon. The magnetic tracer does not require any special storage protocols and has a long shelf life of several years which allows the hospital to stock it and be readily available for use. No allergic reaction to the Sentimag® tracer was observed in our study and even not reported in literature so far.

The disadvantages and challenges with the use of Sentimag® technique are that metallic instruments cannot be used in the operation field during the scanning process with Sentimag® probe thus requiring use of plastic retractors and forceps instead of standard surgical instruments. Magnetometer requires regular recalibration during the procedure before each signal recording. Procedure time was not evaluated in this study however it was perceived that repeated recalibration did add more time to the procedure. The Sentimag® technology for SLNB is more expensive than using technetium 99m and blue dye in combination, but the company believe it could be resource releasing as it improves accessibility (no need for a nuclear medicine facility) and efficiency in radiology and theatre scheduling and capacity. Authors have observed that learning curve for this new technique is short (10-15 cases) however training would be needed and any breast

surgeon who is familiar with technetium-99m and blue dye used in SLNB would be able to adapt to the use of the Magtrace® and Sentimag® system fairly quickly.

Our study has an appropriate sample size and shows non-inferiority in node detection rate to other studies in the literature. Study has highlighted an interesting aspect of injecting Magtrace® on the day of operation versus 3 days before the operation which has shown a statistically significant difference between the two methods in terms of average node retrieval. Further studies with prospective design and bigger number are required to reinforce the current evidence. We recommend injecting Magtrace® 3 days before the operation as we found that signal strength and node colouration was much better than when tracer injected on the morning of operation.

We acknowledge that there are limitations of our study. In particular this is a retrospective analysis from a single center and moreover, there was no direct comparison with the gold standard technique.

Conclusion

Sentimag® technique has comparable results with the standard dual technique. Its advantages lie in the flexibility that it provides and especially non-reliance on nuclear medicine facilities, makes it an attractive option at places where radio-isotope availability is an issue. Our institutional experience adds to and re-enforce the already existing data about Sentimag® technique in breast cancer patients.

Disclosures

The authors have no related conflicts of interest to declare.

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