Breast Cancer (2020) 27:261–265
https://doi.org/10.1007/s12282-019-01016-8

ORIGINAL ARTICLE

The Turkish SentiMAG feasibility trial: preliminary results

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Received: 13 July 2019 / Accepted: 9 October 2019 / Published online: 16 October 2019

Abstract

Background Sentinel node biopsy (SNB) is the standard of care for staging of the clinically and radiologically negative axillary lymph nodes in breast cancer patients. Sentinel node biopsy, with using Technetium-sulphur colloid (99 m Tc) alone or with blue dye is standard technique for evaluating axillary lymph nodes. This technique has drawbacks such as radiation exposure. Superparamagnetic iron oxide nanoparticles (SPIO) can represent a valid option for SNB. In this study; we tried to evaluate feasibility of new magnetic technique in Turkish early breast cancer patients.

Material and methods The study sample consists of 143 women affected by early breast carcinoma with clinically negative axillary lymph nodes. Sentinel node localization was performed using magnetic technique. Detection rate of magnetic technique was calculated and postoperative complications were assessed.

Results Results are based on 104 patients. Sentinel node identification rate was 99% (103/104, 95% CI 0.97–1.01) for magnetic technique. A median of two SNs per patient was removed. Major adverse reaction was the permanent skin coloration (7.1%).

Conclusions The magnetic technique is a feasible method for detecting SN in breast cancer patients with minimal adverse effects. Magnetic technique may be alternative to standard technique especially in breast units, where nuclear medicine unit is not available.

Keywords Breast cancer · Sentinel lymph node biopsy · Magnetic technique

Introduction

Management of the axilla in patients with operable breast cancer is still one of the most controversial areas in clinical oncology. The best procedure to examine the lymph nodes is still standard axillary lymph node dissection; nevertheless, the morbidity associated with this procedure is well known [1]. Sentinel node biopsy (SNB) is the standard of care for staging of the clinically and radiologically negative axilla in breast cancer surgery. It should be the sole surgical procedure in the axilla when the sentinel node (SN) is proven negative or, in some cases even in the presence of metastases. Additionally, neoadjuvant treatment for breast cancer has further widened the indications of SNB [2].

The European Union has determined that breast cancer patients should be treated in Specialist Breast Units. These units must have the minimum standards for the quality indicators as defined by Eusoma. The existing standard for axillary lymph node staging in breast cancer is sentinel node biopsy (SNB), performed using Technetium-sulphur colloid (99 m Tc) alone or with blue dye [3]. The major limits of radioisotope consist of problems linked to radioactivity; the shortage of tracer and nuclear medicine units. The combined use of a radioactive isotope and blue dye is the standard technique of SNB. The standard technique has a SN identification rate of 96.4%, with a false-negative rate of 7.3% [4]. However, blue dye agents present some adverse effects; such as allergic reactions. Also, the blue dye can obscure the surgical field and frequently leaves a blue skin stain that can be permanent [4]. These adverse effects are reported in up to 2.7% of cases [5]. Recently, a new combined medical device using super paramagnetic iron oxide (SPIO) particles (Sienna + ®) associated with a hand-held magnetometer (Sentimag®) has been developed and first tested in the

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SentiMAG Multicentre Trial [2]. Sentimag method might be an alternative to standard technique [4, 6].

In this study, our aim was to evaluate the feasibility and safety of the sentimag technique (Sentimag®/Sienna + ®) in Turkish early breast cancer patients.

Material and methods

From 2013 to 2017, 143 patients with early breast cancer were enrolled in the study. Eligibility criteria were all adult female patients with clinical T0–T2 breast cancer proven by histopathology, clinically or radiologically node-negative and scheduled for sentinel node biopsy. Patients with clinically T3–T4 breast cancer were excluded from study. Patients with hypersensitivity to iron or dextran compounds and those with pacemakers or metal implants were excluded from the study.

Technique

Following anesthesia, injection of SPIO (2 ml Sienna + ® in 3 ml of NaCl) was given at least 20 min before surgery to the retro-areolar area, followed by a 5-min massage. Then, the massage was optional when SPIO was injected up to 4 weeks before the surgery. In the last part of the study period, SPIO was injected into the peritumoral area for non-palpable tumors [7]. SPIO has a dark brown color which can make the node visible and help the surgeon. Intraoperative SLN identification was performed using the Sentimag® probe. After axillary incision, all nodes identified with the probe and nodes colored brown were removed. The highest magnetic signal was recorded from the skin surface (percutaneous signal), in the depth of axilla after incision (in vivo signal) and after removing all SN(s) (residual signal). Each SLN removed was counted separately (ex vivo signal). Intraoperative SN analysis was performed by frozen section analyses. Immunohistochemistry was used in cases where no metastases were found with hematoxylin–eosin. It has previously been reported that SPIO does not affect routine histological examination.

The primary endpoint of this trial was the proportion of successful procedures for SN identification (identification rate per patient) by the Sentimag®/Sienna + ®.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corporation, Armonk, NY, USA). Median (interquartile range) and mean values (standard deviations), were used to summarize continuous variables when appropriate and frequency and percentage were used to summarize categorical variables. The identification rate is calculated for technique and presented with a 95% confidence interval (95% CI).

Results

Women diagnosed with primary early breast cancer, between 2013 and 2017 were initially analyzed. All malignancy-positive patients were diagnosed. Among the 143 patients enrolled, statistical analysis was performed on 104 patients with T0–T2. None of the patients included in the study received neoadjuvant therapy. 26 of these patients were excluded because of neoadjuvant therapy and 13 of them were T3 tumor. Median age was 51 years [range 34–82] and the median tumor size was 23 mm [2–45 mm]. A large majority of the women were in post-menopausal phase (67%). Fifteen cancers were DCIS (14%), while the others were invasive and various histopathologic types, in early stages of presentation. Median body mass index of the patients was 29.

One hundred and thirteen surgical procedures were performed in 104 patients. Breast conserving surgery was performed in 81 patients (71.6%); a particular oncoplastic approach was applied in 14 patients (12.3%). Mastectomy was performed in 12 cases (10.6%). Oncoplastic approach was applied in 6 patients who underwent mastectomy (5.3%). All characteristics of patients and tumors are shown in Table 1.

One patient had a complete failure of SN identification by sentimag technique. The median number of removed SNs was two (range 0–4). In total, 197 SNs were collected from 104 patients. The overall identification rate (IR) was 99% (103/104, 95% CI 97.1–1).

Axillary lymph node metastases were noted in 30 patients. The proportion of patients with pathologically positive results was 26.5% (30/10430/103, 95% CI 21.9–39.1).

No serious adverse event was observed with SPIO. In postoperative consultation, the surgeon noted brown dermo-pigmentation among 22 patients (20.4%). The skin pigmentation was attenuated in 66 patients (70.4%) and vanished in 37 patients (21.1%). In five patients (7.1%), the area was unchanged (Fig. 1).

Discussion

The highest rates of SN identification for breast cancer staging are observed using a combination of a radioisotope and a blue dye agent [4]. Standard technique is strongly recommended in current guidelines [8]. The motivation for the development of new techniques has risen from the drawbacks of the standard technique [4]. For example; radioisotopes are not available in all treatment centers, as

Table 1 Clinical characteristics of patients

Clinical variables	*N* (%)
Age	
< 65	90 (86.6)
≥ 65	14 (13.4)
BMI (kg/m^2)	
< 25	72 (69.2)
≥ 25	32 (30.8)
Side	
Right	45 (43.2)
Left	50 (48.0)
Right and left	9 (8.6)
Localization in the breast	
Upper outer quadrant	73 (64.6)
Upper inner quadrant	12 (10.6)
Lower inner quadrant	10 (8.84)
Lower outer quadrant	14 (12.3)
Central	4 (3.5)
Type of breast surgery	
Breast conserving surgery	81 (71.6)
Breast conserving surgery + reconstruction	14 (12.3)
Mastectomy	12 (10.6)
Mastectomy + oncoplasty	6 (5.3)
Histologic type	
Ductal invasive carcinoma	73 (64.6)
Lobular invasive carcinoma	7 (6.1)
Other	33 (29.2)
Nuclear grade	
Grade I	9 (11.25)
Grade II	28 (31.1)
Grade III	43 (47.77)
Estrogen receptor status	
Positive	79 (79)
Negative	21 (21)
pT (pathological tumour staging)	
pT1	84 (85.7)
pT2	12 (12.24)
pT3	2 (2.04)
pN (pathological nodal staging)	
pN(−)	83 (73.4)
pN(+)	30 (26.5)

their use requires licensing and a nuclear medicine department with strict legislative control, a preoperative visit, and effective coordination between the involved departments [5].

The use of sentimag technique has been tested clinically before [3, 9-12]. The detection rate of sentimag technique was 97.9% in Ghilli's study [3]. Similarly, the SN detection rate was 97.1% in Zada's study [4]. In French study detection rate was 97.2% [2]. The SN detection rate for sentimag technique was therefore noninferior to the standard technique [4, 6, 11].

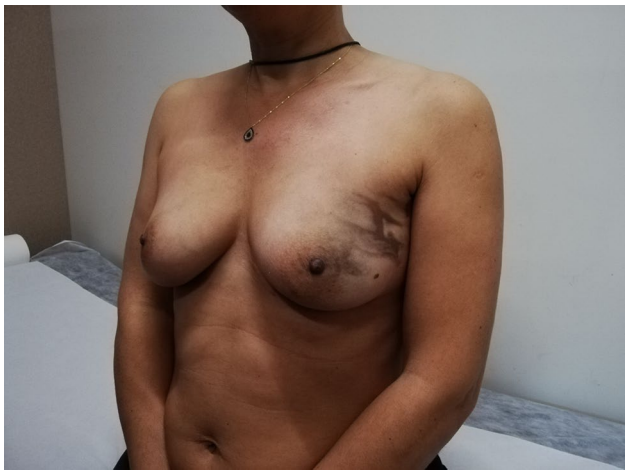

Fig. 1 Unchanged skin pigmentation observed 2 years after SPIO

Number of SNs identified has implications for the accuracy of the SN technique. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 study showed that the false-negative rate of SN dissection is 17.7% if one SN is identified compared with 10 and 6.9% if two or three SNs are found, respectively [13]. The mean lymph node retrieval rate per patient was 2.1 (range 1.8–2.5) for sentimag technique. The average number of SNs removed by sentimag technique is higher than standard technique [4]. Sentimag technique had the lower false-negative rate than the standard technique [4]. This finding could be explained by the higher lymph node retrieval rate. It should be emphasized that the overall analysis showed no statistically significant differences between sentimag technique and the standard technique with respect to the identification of SN(s) or malignant SN(s).

In our study, detection rate and retrieval SN rate were similar to literature [10].

Main advantage of sentimag technique over standard technique is the avoidance of radiation exposure. Radiation exposure may be a concern for patients and surgeons. The radioisotope is usually injected by nuclear medicine staff, often in a different location from the operating room, requiring scheduling coordination between the two departments. Other drawbacks of the radiation are strict legislative control, limitations on radiotracer availability and dependency on nuclear medicine units [14]. The SPIO tracer is not associated with radioactivity, easier to implement without the regulatory issues of radioisotope, available in around 30 countries. It can be stored conveniently because of the long shelf life [15]. Another advantage of sentimag technique is the timing between tracer injection and SNB. Surgeon is able to inject SPIO directly in the surgical theatre. This provides three beneficial effects: short preparation time, possibility

of performing a higher number of procedures per day and improved comfort for the patients [3].

Complications and adverse reactions were reported in all sentimag studies. Brown skin coloration was the most seen adverse effect [4]. In Ghilli's study; the skin pigmentation was attenuated in 70.4% and vanished in 21.1% but the staining remained unchanged or enlarged (6 of 150 patients) [3]. In another study, the average time needed for the discoloration to reduce by approximately 50% was 9 months and to disappear completely at approximately 18 months. The longest persisting discoloration observed took 22 and 24 months [16]. Other studies reported attenuation of skin coloration and there was no unchanged staining [2, 9-12]. We think that dermopigmentation is increased by the SPIO subdermal injection and an intense massage of the breast during 5 min. The same technical performance can be achieved with a deeper (glandular) periareolar injection and a softer massage. All future studies will have to focus more accurately on the dermopigmentation and monitor patients over a longer term. There was no other significant adverse reaction associated with the use of the SPIO, nevertheless Douek et al. described one patient with transient hypotension after SPIO injection [9].

The most common technique to detect breast cancer is mammography. However, the radiation dose emitted from the mammogram is harmful to the patients [17]. Additionally, SPIO may complicate subsequent magnetic resonance imaging (MRI) examinations [4]. An analysis of postoperative breast MRI in SentiMAG trial of one patient demonstrated that avoiding artifacts could potentially obscure important clinical findings (Fig. 2) [18, 19]. This is also true for mammography (Fig. 3) but, MRI has higher sensitivity

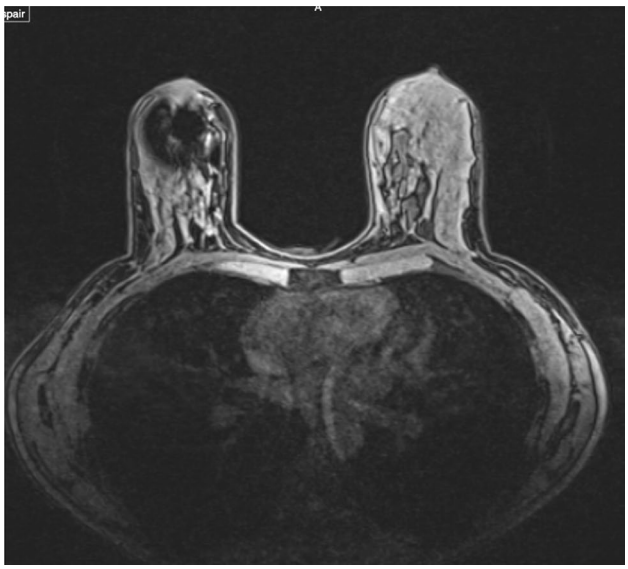

Fig. 2 MRI image revealed 2 years after SPIO

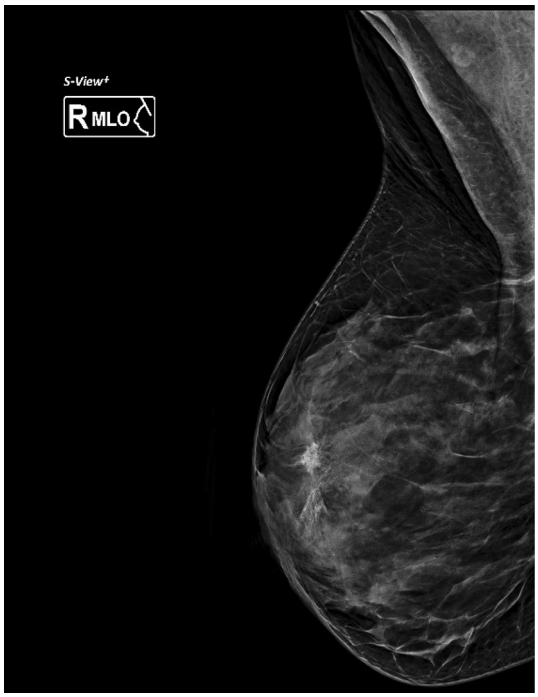

Fig. 3 Mammography image revealed 2 years after SPIO

to breast cancer than mammography in women with a 15% or greater lifetime risk of the disease [20]. Another potential limitation of mammography is the cumulative effects of breast tissue exposure to ionizing radiation. The revised 2007 International Commission for Radiological Protection estimated that the risk of breast cancer death due to breast tissue exposure to ionizing radiation doubled by 1977 and 1991 estimates [21]. Additional studies are needed regarding the use of SPIO in high-risk patients in whom follow-up MRI is clinically indicated. It should be remembered that patients with hypersensitivity to iron or dextran compounds and patients with pacemakers or metal implants were not suitable for using SPIO [6]. Other limitation already identified in the literature of the sentimag includes the need to use plastic surgical instruments. This may be a problem in obese patients especially who may require deep axillary dissection [6]. Another technical disadvantage of sentimag procedure is the large diameter of the handheld probe, which makes it necessary to enlarge the incision to insert the probe and to identify the magnetic SN, although this problem was in the first generation, this problem disappeared in the second generation [14].

In the literature, there is a lack of cost-effective studies comparing magnetic method with radioisotopes [3]. Specific studies are desirable in relation to a systematic cost assessment.

In conclusion, sentimag technique appears to be safe, and easy to perform with minimal adverse effects (skin

coloration). The sentimag technique may be an alternative to standard technique especially in breast units where nuclear medicine unit is not available. In addition, the sentimag technique can be quickly applied to the daily routine and can be minimized preoperative preparation by simple use. If more and more consistent results prove its effectiveness, it has the potential to become the standard of technical maintenance. Prior to this, it may be more appropriate to apply this technique only to patients who will undergo mastectomy given the fact that the pigmentation problem may not be well tolerated in some patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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