MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 3154-3160
DOI: 10.12659/MSM.912758

Received: 2018.08.15
Accepted: 2019.01.09
Published: 2019.04.29

Analysis of Postoperative Complications After 303 Sentinel Lymph Node Identification Procedures Using the SentiMag® Method in Breast Cancer Patients

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: Departmental sources

Background: The objective of this paper was to assess the complications following sentinel lymph node biopsy (SLNB) in breast cancer patients using the SentiMag® method.

Material/Methods: The study material consisted of 368 patients who had received the SLNB procedure in combination with wide local excision (WLE), simple mastectomy or who had an autonomous SLNB procedure in the period from January 2014 to September 2017. The final study group consisted of 303 patients who attended follow-up consultations.

Results: Sensory disturbances in the arm occurred in 12 patients (9.9%), including 3 patients (1.5%) after WLE and 9 patients (8.4%) after simple mastectomy. Restricted mobility in the upper limb was experienced by 9 patients (7.1%), including 3 patients (1.5%) after WLE and 6 patients (5.6%) after simple mastectomy. Minimal-degree lymphedema developed in 9 patients (7.5%), including 2 patients (1%) after WLE and 7 patients (6.5%) after simple mastectomy. A significant correlation was demonstrated between the incidence of these complications and the number of lymph nodes dissected. A significantly higher incidence of paresthesia and lymphedema was revealed for simple mastectomy with SLNB when compared to WLE with SLNB. Discolorations upon tracer administration were observed in 47 patients (15.5%).

Conclusions: SentiMag® is a safe sentinel lymph node identification method used in breast cancer and has a low risk of complications. The rate of complications increases together with the number of dissected lymph nodes and the extent of the surgery. The possibility of temporary discolorations on the skin should be communicated to the patients explicitly prior to surgery.

MeSH Keywords: Breast Neoplasms • Postoperative Complications • Sentinel Lymph Node Biopsy

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/912758

2613 4 2 40

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Background

The sentinel lymph node biopsy (SLNB) in breast cancer is a standard procedure for assessing the regional lymphatic confluence in patients with N(0) stage [1,2]. It allows for identification of patients who do not need to have their regional lymph nodes dissected, thereby reducing the risk of multiple complications [3–8]. Providing a correct oncological qualification, the procedure produces the same effects as regional lymphadenectomy and the risk of recurrence in the case of negative results is very low [9–11]. Common markers include radioactive colloids, which are used alone or in combination with a blue dye. Numerous studies have been conducted concerning postoperative complications associated with marker application, such as allergic reaction, a permanent tattoo or lymphedema [12–15]. Moreover, the use of a radioactive isotope has its limitations. It requires cooperation with a department of nuclear medicine, the very short half-life of Technetium-99m (^{99m}Tc) puts a severe time constraint on its shelf life and, most importantly, the isotope is not neutral for the patient and the personnel. As a result, it cannot be used in all cases.

As alternative, non-radioactive markers such as indocyanine green fluorescent dye can be used for sentinel lymph node identification [16–20]. Interestingly, in 2012 a novel method was introduced that uses an organically coated (dextran) colloid containing superparamagnetic iron oxide particles of 60 nm in diameter as a tracer (Sienna+®), which is detected by a handheld magnetic probe. These tracer nanoparticles are absorbed by the lymph node tissue and respond to the external magnetic field allowing for intraoperative localization using the SentiMag® probe. Moreover, in the absence of magnetic field it does not maintain residual magnetic induction while the nanoparticle size is optimized for retention by the sentinel node without travelling to the higher echelon nodes. Also, the colloid's dark brownish color makes it possible to visually identify the node in the operating field. Numerous clinical studies on patients in both European and nonEuropean countries have demonstrated equivalence between the SentiMag® method and the standard method using a gamma-camera and a 99m-technetium (^{99m}Tc) labeled radiotracer, either alone or in combination with a blue dye [21–24].

Study objective

The objective of this paper was to assess complications, including paresthesias, restricted upper limb mobility, lymphedema, and skin discolorations, following the sentinel lymph node biopsy (SLNB) in breast cancer patients using the SentiMag® method after 3.5 years from application.

Material and Methods

The initial study group comprised of a total of 368 patients with primary operative breast cancer who had received the SLNB procedure in combination with wide local excision (WLE) or simple mastectomy, or had autonomous SLNB prior to induction treatment based on the SentiMag® method in the period from January 2014 to September 2017 in the Department of Oncological Surgery at the Prof. Kornel Gibiński Independent Public Central Clinical Hospital of the Medical University of Silesia in Katowice (Poland). A total of 303 patients have attended the follow-up consultations at the Hospital's Oncological Surgery Outpatient Clinic. The longest observation period was 42 months while the shortest was 5 months, yielding 25.5 months of follow-up on average.

Prior to qualification for the SLNB procedure, each patient was assessed with a detailed medical history and a physical examination. The examination involved analysis of upper limb range of motion (ROM) and measurement of upper limb circumference, while the medical history was focused on the absence or presence of potential sensory disturbances in the limbs. Also, before qualifying for sentinel lymph node identification, all patients had their regional lymph nodes assessed by ultrasound. In cases of doubt, a fine-needle aspiration biopsy (FNAB) of the lymph node was performed under ultrasound control. Patients with cN0 status (qualifying) were selected for the SLNB procedure. As a standard, 2 mL of Sienna+® tracer dissolved in 3 mL of physiological saline was administered approximately 1–2 cm under the areola of the mammary gland. The SentiMag® probe was used intraoperatively to identify the sentinel lymph node (SLN) defined as that with the highest signal value (the signal range: 0–9999). Usually, 1 or 2 additional lymph nodes were collected as long as the signal reading was above 10% of the first node. The signal level of the identified sentinel lymph node(s) was recorded in the surgical operation note. The time from the administration of the ferromagnetic tracer to sentinel lymph node dissection ranged from 1 to 12 hours (average 3.8 hours) prior to surgery. Delays exceeding the manufacturer's recommendation resulted from the fact that some of the patients could not be accommodated within the daily plan of treatment procedures and were operated on the following day, while others required additional tests prior to the procedure due to concomitant diseases while the tracer had been administered earlier.

Follow-up visits were scheduled at the Hospital's Outpatient Clinic every 3 months for the first 2 years and encompassed: medical history, clinical examination, imaging and ultrasound examination of the regional lymphatic confluence. Patients who had their SLNB performed more than 2 years ago had their follow-up appointments every 6 months. Moreover, the post-surgery follow-up examination regimen encompasses assessment

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based on the following medical history and clinical examinations: 1) sensory disturbances in the form of paresthesias (including hyperesthesia on the skin of the arm); 2) restricted range of motion (ROM) in the upper limb; 3) presence of lymphedema; and 4) discolorations on the skin of the breast.

Restriction of upper limb range of motion of more than 20 degrees in comparison to the other limb was treated as significant. Lymphedema was determined on the basis of the arm circumference measured with a universal metric tape. A 10% difference between the limbs was defined as lymphedema, which was ranked into: minimal (a difference of <20%), moderate (a difference between 20% and 40%) and severe (a difference of >40%). All discolorations observed were recorded for their size (diameter in cm) and color intensity.

Statistical data were collected in the form of a database created in Excel 2013. The calculations were performed using Excel 2013 and Statistica 13.1 software. Before selecting the suitable comparative test to determine the statistical significance, analysis of data distribution was carried out using Shapiro-Wilk test. Due to the nature of the data distribution, non-parametric independent data comparison was performed using Mann-Whitney U test. The level of statistical significance was set at $P<0.05$. The remaining calculations were performed using Excel 2013 and included calculations of the average values for the particular data, medians and range of values.

Table 1. General characteristics of the study group.

Number of patients	303
Age of patients (average/median/range)	62.2/61/30–88
Observation time (average/median/range) [months]	25.5/25/5–42
Number of patients with diagnosed infiltrating cancer/Number of patients with diagnosed DCIS HG	275/28
Number of excised lymph nodes (average/median/range)	2.9/2/0–11
Total number of paresthesias	12
Total number of lymphedemas	9
Total number of restricted ROM in the upper limb	9

DCIS – ductal carcinoma *in situ*; HG – high grade.

Results

The study consists of a total of 303 patients after SLNB procedure. Range of age was 30–88 years with a median of 61 years old. In total, there were 191 SLNB procedures in combination with WLE, 107 procedures combined with simple mastectomy, and 5 autonomous SLNB procedures in patients prior to induction treatment. The total number of lymph nodes dissected in all the procedures was 808. The sentinel lymph node identification rate in the entire group was 99%.

The average number of dissected sentinel lymph nodes per procedure was 2.9 (median 2, 0–11). The average for autonomous SLNB procedure was 1.8 (median 1.5, 1–3), for wide local excision (WLE) with SLNB was 2.5 (median 2, 1–11) and for simple mastectomy with SLNB was 3.6 (median 3, 0–11). The median of follow-up observation was 25 months for WLE with SLNB, 26 months for simple mastectomy with SLNB, and 9 months for autonomous SLNB.

Complications in form of paresthesias in the shoulder region were recorded in 12 patients (9.9% of all patients), which include 3 patients (1.5%) after WLE with SLNB and 9 patients (8.4%) after simple mastectomy with SLNB. Limited range of upper limb ROM was observed in 9 patients (7.1%): 3 patients (1.5%) after WLE with SLNB and 6 patients (5.6%) after simple mastectomy with SLNB. Lymphedema of minimal severity was observed in 9 patients (7.5%), which include 2 patients (1%) after WLE with SLNB and 7 patients (6.5%) after mastectomy with SLNB (Tables 1 ,2).

The rate of complications was identified also in relation to particular procedure ie, in simple mastectomy with SLNB compared to WLE with SLNB. It showed a significantly higher incidence of

Table 2. General characteristics per particular procedure.

Type of procedure	WLE + SLNB	Simple mastectomy + SLNB	SLNB
Total of patients undergoing particular surgery	191	107	5
Age (average/median/range)	59.76/61/30–84	61.92/63/40–88	59/59/47–71
Number of excised lymph nodes (average/median/range)	2.53/2/1–11	3.61/3/0–11	1.83/1.5/1–3
Median of observation [months]	25	26	9

WLE – wide local excision; SLNB – sentinel lymph node biopsy.

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Table 3. Complication rate and the relationship with the type of surgery (WLE + SLNB versus simple mastectomy + SLNB).

Complications	WLE + SLNB	Simple mastectomy + SLNB	p Value
Paresthesias	3 (1.5%)	9 (8.4%)	0.004044
Restricted upper limb ROM	3 (1.5%)	6 (5.6%)	0.051449
Lymphedema	2 (1.0%)	7 (6.5%)	0.007999

WLE – wide local excision; SLNB – sentinel lymph node biopsy; ROM – range of motion.

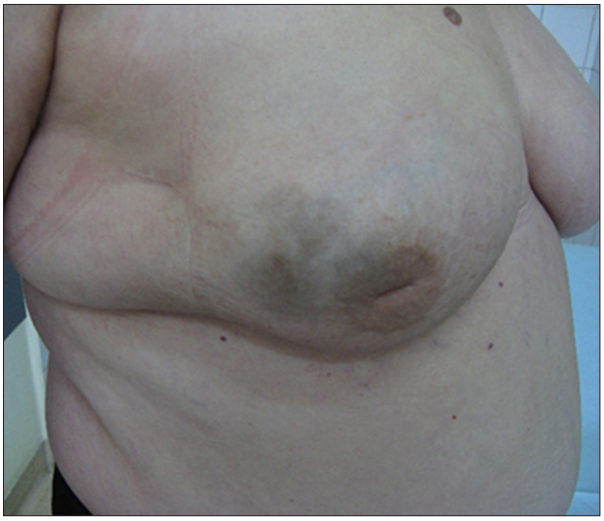

Figure 1. Skin discoloration following the administration of Sienna+®.

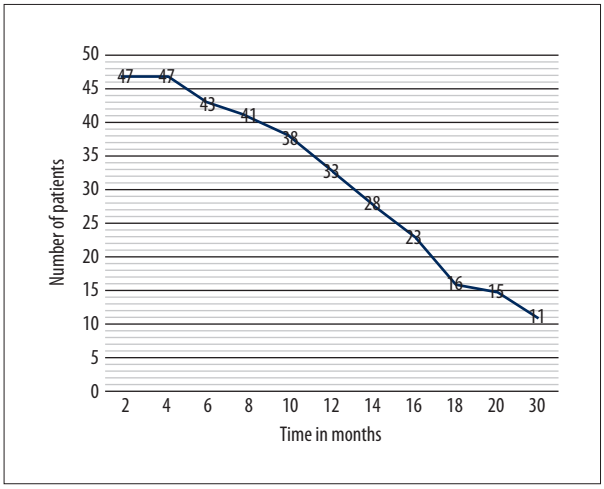

Figure 2. Number of patients with discoloration depending on the time from the surgery.

Table 4. Correlation between the incidence of complications and the number of lymph nodes dissected.

Type of complication	Number of lymph nodes dissected in patients with the complication symptom (average/median/range)	Number of lymph nodes dissected in patients without complication symptom (average/median/range)	Statistical significance (P) of the difference between the incidence of a given symptom and the number of dissected lymph nodes
Restricted upper limb ROM	5.55/4/3–11	2.82/2/0–11	0.001499
Paresthesias	5.08/4/2–11	2.81/2/0–11	0.000527
Lymphedema	7.33/8/2–10	2.76/2/0–11	0.000077

ROM – range of motion.

paresthesia (*P*=0.004) and lymphedema (*P*=0.007) after simple mastectomy with SLNB compared to WLE with SLNB. No significant difference was observed in the case of limited upper limb ROM in relation to the type of operation (*P*=0.051) (Table 3).

Skin discoloration following the administration of Sienna+® tracer took the form of an irregular grey-brown bruise resembling a hematoma (Figure 1). Discolorations were observed in 47 patients (15.5%), predominantly after WLE of the tumor with SLNB. They were predominantly located in the periareolar area in the upper outer quadrant. The observations made during consecutive follow-up examinations revealed a gradual decrease in both the diameter and the intensity of the discoloration. 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 (Figure 2).

The rate of complications was assessed also in relation to the number of excised lymph nodes. A significant correlation was demonstrated between the incidence of complications and the number of lymph nodes dissected in the SLNB procedure (Table 4).

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Following the SLNB procedure, a total of 34 patients (9.2%) were found to have macrometastases in sentinel lymph nodes with infiltration of the lymph node capsule or with tumor cells in the perinodular adipose tissue. All of them underwent lymphadenectomy of the regional lymphatic confluence. The sentinel lymph node identification failed in 2 patients (0.5%). In all these cases, the first and second level lymph nodes were dissected, thereby excluding these cases from analysis.

Discussion

The sentinel lymph node biopsy (SLNB) is the basic diagnostic procedure in the surgical treatment of breast cancer. To date, the "golden standard" to localize the sentinel lymph node has been a method involving the use of a gamma-camera on a 99m-technetium (^{99m}Tc)-labeled radiotracer alone or in combination with a dye. Yet, for the last few years sentinel lymph node identification has been performed by means of the SentiMag® method where a superferromagnetic colloid is injected in search of the sentinel lymph node. The results of the sentinel lymph node identification with this method have been shown to be comparable with the conventional technique using a gamma-camera with a ^{99m}Tc-labelled radiotracer [25–27].

Complication in the form of a bruise-like, grey-brown discoloration resembling a hematoma was noted in 47 patients (15%). During consecutive follow-up visits, it was observed that the discoloration faded away systematically to approximately 50% of its initial diameter and intensity within 9 months from injection, to disappear completely after 18 months in the majority of cases. Similarly, Rubio et al. [23] noted that 19% of patients experienced skin discoloration, which subsided after 6 months. In our study, the relatively small number of discolorations could be attributed to a quite deep injection of the tracer, at approximately 1–2 cm under the areola, the technique that has been performed in our center since the implementation of the SentiMag® method. In fact, Ghilli et al. [27] proposed that the tracer be injected more deeply, which might then reduce the size of discolorations or minimize their occurrence. The possible development of a temporary bruise should be considered and communicated to patients prior to the procedure.

Lymphedema is one of the main postoperative complications associated with axillary lymph node dissection (ALND). It may lead to restricted mobility, pain, asthenia (weakness), or rigidity in the upper limb [28,29]. Lymphedema following ALND has been described in numerous reports in the literature and its incidence rate is estimated to range from 5% to 25% [30,31]. Compared to ALND, the SLNB procedure brings substantial benefits by limiting the occurrence of such complications. In the first extensive prospective ALMANAC trial, the number of arm edema noted 18 months post-surgery was almost twice as high in the ALND group as compared to the SLNB group (14% compared to 7% respectively). The same was true of numbness (19% compared to 8.7% respectively) [32]. A multicenter Swiss study on a group of 635 patients revealed the complication rate after SLNB in comparison to ALND was 3.5% versus 19.1% for lymphedema, 3.5% versus 11.3% for limited ROM of the arm, 8.1% versus 21.1% for pain in the arm/upper arm, and 10.9% versus 37.7% for numbness, respectively [33]. In our study, a minimal degree lymphedema occurred in 7.5% of the patients and was directly related to the type of surgery i.e., 6.5% in simple mastectomy with SLNB compared to 1% in WLE with SLNB (P=0.007), and to the average number of dissected lymph nodes i.e., 3.6 in simple mastectomy with SLNB and 2.5 in WLE with SLNB (P=0.0007). The recommendations concerning the number of lymph nodes to be dissected in the SLNB procedure currently indicate to remove 1 node with the highest signal reading and, additionally, 1 or 2 nodes with a signal value of at least 10% of the first one. Such an approach minimizes the risk of false negative results [34–36]. Yet, dissection of a larger number of lymph nodes during SLNB does not increase the sensitivity of the examination and may lead to a potentially greater number of postoperative complications [37–39]. Another troublesome postoperative complication, besides lymphedema, is restricted mobility and paresthesia in the upper limb on the operated side. The incidence of these complications and the difference in their occurrence in the SLNB procedure compared to ALND has already been mentioned. In our study, restricted upper limb mobility and paresthesias affected 7.1% and 9.9%of the patients, respectively. Mobility restriction in the upper limb was associated significantly with a higher number of dissected lymph nodes (P=0.001) and so was the occurrence of paresthesia (P=0.0005). No significant difference was observed in the case of restricted upper limb mobility in relation to the type of surgery. A significantly higher incidence of paresthesias was observed in the group of patients after simple mastectomy compared to post-WLE patients (P=0.004). Generally, the obtained results showed a similar rate of complications when compared to the conventional method of sentinel lymph node identification based on a radiotracer, whether used alone or in combination with a dye. Moreover, the extensive ACOSOG Z0010 study concerning early complications in 5327 patients followed 30 days and 6 months after SLNB demonstrated the rates of lymphedema, upper limb mobility restriction, and paresthesia following SLNB alone to be very similar to our results obtained by means of the SentiMag® method [40].

In the group analyzed, during the procedure, 2 patients had post-CNB (core-needle biopsy) hematoma in the upper outer quadrant (median age 65.5 years, median time from tracer administration 4.5 hours). In neither case could the sentinel lymph node be identified since the probe provided no reading whatsoever for the axillary lymph nodes. In both cases,

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lymphadenectomy was performed in the first and second level of the axillary fossa. No metastases were found in the dissected lymph nodes in a postoperative histopathological examination. It is hypothesized that the extravasated blood around the hematoma with rich hemosiderin deposits have absorbed the entire Sienna® tracer and prevented it from travelling further along the lymphatic vessels. The SentiMag® method of sentinel lymph node identification seems to be safe and well-tolerated since no early or delayed hypersensitivity reactions have occurred in the group under analysis.

Conclusions

SentiMag® is a safe sentinel lymph node identification method used in breast cancer and has a low risk of complications. The rate of complications increases together with the number of dissected lymph nodes and the extent of the surgery. The possibility of temporary discolorations on the skin should be communicated to the patients explicitly prior to surgery.

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