



Skin Staining After Injection of Superparamagnetic Iron Oxide for Sentinel Lymph Node Dissection: A Retrospective Study of Two Protocols for Injection and Long-Term Follow-Up

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ABSTRACT

Objective: Sentinel lymph node (SLN) dissection is a highly accurate surgical procedure allowing detection of lymph node invasion in patients with clinically negative axilla in early breast cancer. Superparamagnetic iron oxide (SPIO) is a marker used during SLN procedure, allowing the same detection rate as isotopes (Tc-99). A drawback of SPIO is skin staining that can occur around the injection site. The goal of this retrospective study was to assess the frequency of skin staining after oncological breast surgery with SPIO, and the impact of two different injection protocols on the rate of skin staining.

Materials and Methods: Data from breast cancer patients undergoing magnetic tracer SLN detection (SLND) procedure in a single department between 2020 and 2022 was reviewed. Injection protocol P1 consisted of retro-areolar injection of Magtrace 0.8 mL. Injection protocol P2, consisted of retro-tumoral injection with 1 mL. Presence of skin staining was assessed at day 10 after surgery. The evolution and satisfaction of the patients was assessed at six and 12 months.

Results: In total 175 sentinel lymph node biopsy procedures were performed (P1: 141/P2: 34), consisting of breast conservative surgery (BCS) (P1: 70%/P2: 53%) or mastectomy (P1: 30%/P2: 47%) with SLN. SLN detection rate was 97.7%. Skin staining was reported in 23% and occurred more often after BCS (31.6%) compared to mastectomy (6.8%). When BCS was performed, peritumoral injection was associated with a decreased risk of skin staining compared with retro-areolar injection (22.2% *vs.* 33.3%, respectively). When present skin staining persisted for 12 months, but most of the patients described only a slight discomfort. The low rate of discoloration after mastectomy, as previously reported, can be explained by the removal of skin and glandular tissue in which the tracer accumulates. Less skin staining in P2 may be because of a shorter interval between injection and surgery and the removal of the excess of SPIO during the lumpectomy.

Conclusion: SPIO injection is a safe surgical technique. After mastectomy, the rate of discoloration was low. Despite the persistent skin discoloration in 58.6% in our study, patient satisfaction was high. Deeper injection, reduced doses, massage of the injection site and peritumoral injection may reduce skin staining.

Keywords: Axillary lymph node dissection; body image; breast cancer; breast conserving surgery; mastectomy; quality of life; risk factors; sentinel lymph node dissection; surgery; women

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Key Points

- Axillary lymph node dissection
- Breast conserving surgery
- Sentinel lymph node dissection

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Introduction

Breast cancer is the leading form of cancer among women worldwide (1, 2). Sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection as the standard surgical procedure for staging clinically tumor-free regional nodes in patients with early-stage breast cancer. SLNB staging considerably reduces surgical morbidity in terms of shoulder dysfunction and lymphedema, without affecting diagnostic accuracy and prognostic information (detection rate >97%) (3-6). Tracking of the sentinel lymph node (SLN) can be made by injection of different tracers such technetium-99m, blue dye, indocyanine green (ICG) or superparamagnetic iron oxide (SPIO). Radioactive agents have several disadvantages, such as the need for a nuclear radiology unit, radiation exposure, cost, and time-limited effectiveness. Meanwhile, blue dye injection can be done less than one hour before surgery, is cheap, but carries a risk of anaphylactic reaction, skin staining and tissue necrosis (7). ICG seems to be the most efficient tracer to identify metastatic lymph nodes and is detectable 10 minutes after injection, but this technique has not yet been standardized (8). Large studies reported non-inferiority of SPIO compared to standard techniques, with the same detection rate as other techniques (8-11). Detection of the SLN is feasible 20 minutes after injection, and even up to one month after injection, which improves scheduling, benefitting both the patient and the surgical team (11, 12).

However, side effects of SPIO, such as skin staining can develop around the injection site, corresponding to a persistent gray/black skin pigmentation (11). Incidence rate of discoloration seems to be similar to blue dye injection, at 30.8%, but with a large range from 0% to 84.4%, depending on the source (12-14). Another disadvantage of SPIO is accumulation of the iron residual nanoparticles, which leads to magnetic resonance imaging (MRI) artifacts.

In this retrospective study, two protocols of two different injection sites and dilution of SPIO are described together with associated side effects. The goal of this retrospective study was to assess the frequency of skin staining after mastectomy or breast conserving surgery (BCS), and the impact of the two different protocols on the rate of skin staining after BCS.

Materials and Methods

Data were retrospectively analyzed from patients suffering from early breast cancer undergoing SLNB with an SPIO procedure in a single

department between January 2020 and December 2022. Injection protocol P1 consisted of pre-operative retro-areolar injection of 0.8 mL Magtrace (EndoMagnetics, Cambridge, UK) from November 2020 until March 2022. In order to reduce the rate of skin staining, it was decided, from April 2022 to December 2022, to introduce injection protocol P2, which consisted of retro-tumoral injection of 1 mL Magtrace. The detector probe was Sentimag (Sysmex GmbH, Hamburg, Germany). Presence of skin staining was assessed at day 10 after surgery. If present, clinical re-evaluation of the discoloration and the satisfaction of the patients was assessed at six and 12 months postoperatively. Demographic characteristics of the patients and type of surgery (BCS vs mastectomy), were collected from patient records.

Results

In total, 175 SLNB procedures were performed [141 (80.6%) using P1, 34 (19.4%) using P2] (Table 1). Mean age was 64.7 years in P1 and 62.4 years in P2. Types of surgeries performed were BCS (70% in P1/53% in P2) versus mastectomy (30% in P1/47% in P2) with SLN. The waiting period between injection and surgery was 9.4 days in P1 and 3.6 days in P2. Sentinel node detection rate after Magtrace injection was 97.7% overall (171/175). There were four procedural failures consisting of an absence of signal detection, which led to axillary sampling.

Skin staining was reported in 23% (41/175) of the cases and occurred more often after BCS 31.6% (37/117) than after mastectomy 6.8% (4/58). When BCS was performed, peritumoral injection (P2) was associated with a decreased risk of skin staining occurring in 22.2% (4/18) compared to retro-areolar injection (P1) at 33.3% (33/99). Skin staining was less common after mastectomies and only reported in four cases, of which three did not undergo breast reconstruction, and one had a skin-sparing mastectomy with breast reconstruction.

For long-term follow-up, we were able to recall 37 of 41 patients (90.3%) in March 2024. When confirmed, skin stainings remained persistent from one month up to four years (Figure 1). The overall patient experience was good, with 73% describing no discomfort at all, 24% a slight discomfort and only one case describing a major impact on the way she perceived herself (Chart 1). While 56.8 % had persistent skin staining 2-4 years after surgery, the remaining 43.2% described complete disappearance of the stain (Chart 2). Even when skin staining remained, all these patients described a progressive fading since surgery (Figure 1).

Table 1. Demographic and surgical data			
	Protocol 1 retro areolar injection	Protocol 2 peritumoral injection	Total
Number of cases	141	34	175
Mean age (years)	64.7	62.4	64.2
Proportion of tumorectomia	70.2% (99)	52.9% (18)	66.9% (117)
Proportion of mastectomies	29.8% (42)	47.1% (16)	33.1% (58)
Time lapse between injection and surgery (days)	9.4	3.6	8.9
Number developing skin staining	34	7	41
Skin staining and BCS	33.3% (33/99)	22.2% (4/18)	28.2% (37/117)
Skin staining and mastectomy	2.4% (1/42)	18.8% (3/16)	6.9% (4/58)
BCS: Breast conservative surgery			



Figure 1. Picture of a skin staining, one month after surgery

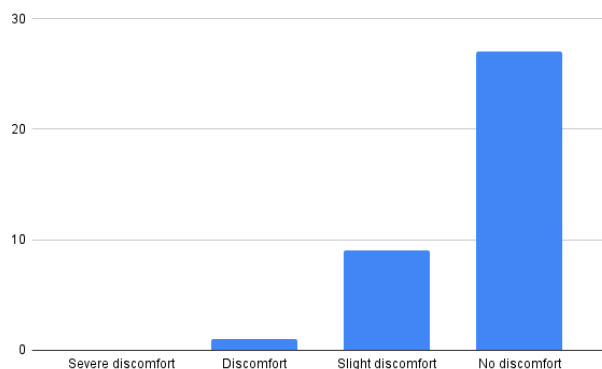


Chart 1. Self image

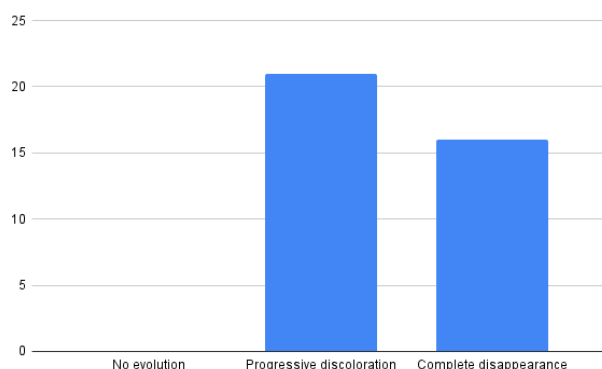


Chart 2. Clinical evolution

Discussion and Conclusion

Sentinel node identification rate after SPIO injection was similar, regardless of the injection site and was similar to that previously reported (15). Failure to detect SLN in the four patients led to axillary sampling (between 3-6 lymph nodes) without axillary dissection because they were elderly patients with low grade tumors. Although

metastatic lymph nodes are associated with a lower SLN detection rate, none of the four patients with failure to detect SLN showed tumoral cells on histopathological examination (8).

The principal drawback of SPIO is skin discoloration around the injection site (16). The type of surgery, the localisation of injection and probably the time lapse between the injection and surgery may influence the rate of skin staining (14). The low rate of skin staining after mastectomy (6.8%) may have been due to the removal of the skin and the glandular tissue in which the tracer accumulated (17, 18). More skin staining was observed in P2 (18.8%) compared to P1 (2.4%) after mastectomy. This may be due to sample size effects as we collected more patients with mastectomy than BCS, and a higher dilution of SPIO. A meta-analysis performed in 2023 of 12 case series regarding skin staining concluded that 95% of skin staining were described after BCS (14). After BCS, protocol P2 was associated with a decreased risk of skin staining compared to P1. This difference, although not statistically significant, could be explained by the different injection sites, a shorter interval between injection and surgery and the removal of the excess magnetic tracer in the breast during lumpectomy.

Wärnberg et al. (17) showed that peri-tumoral injection significantly reduced the discoloration compared to retro-areolar injection in BCS (37.8% compared with 67.8%). Retro-tumoral injection could even reduce the size of the staining and lead to a more radiant regression (18). Other ways to reduce the rate of skin staining may be by injecting at least 15 mm under the skin or by reducing the dose of SPIO (21). A study by Rubio et al. (12) compared 1 mL to 1.5 and 2 mL and showed that 1 mL of SPIO significantly decreased the rate of skin discoloration (84.4% to 60%) and its size, with no effect on the SNL detection rate (8). Mirzaei et al. (19) concluded that even an ultralow dose of 0.1 mL SPIO, showed the same efficiency.

A recent meta-analysis from Pantiora et al. (14) showed that the common rate of skin staining is usually described as 30.8%, but ranged widely from 0 to 84.%. In the meta-analysis regression, taking each potential factor separately, such as the injection site, the injection volume or applying massage to the area, reported that none of these factors significantly reduced skin staining. The authors suggested that achieving less skin staining was probably only due to the combination of these factors (14).

It is known that SPIO injection may result in residual tissue nanoparticles and lead to MRI artifacts when this modality is needed for medical follow-up (20). About half of the patients showed postoperative accumulation of iron oxide particles on MRI (21). Therefore it is important to specify to the radiologist that the patient was injected with SPIO tracers. Christenhusz et al. (20) showed that a 0.1 mL intra tumoural dose did not result in MRI residual remnants and reduced the difficulty of reading subsequent MRIs. However, some specific protocols improve the MRI image quality when artifacts are observed (20, 22).

Despite persistent skin staining up to four years after surgery, a majority of the patients in the present study were satisfied with the procedure, since it only slightly affected their self-image. This has already been described by other studies with a maximum follow-up of three years (9, 14, 17). During the consultation, patients often mention less interest in the aesthetic result in comparison to the oncological issue, primarily justified by advanced patient age. Most of the time, complete disappearance takes at least a year, but it is important to reassure the patient about the fading of the stain, even if it does not totally

disappear in about half of cases. When breast cancer affects a young patient in whom BCS and SLN is planned, it seems wise to discuss the potential risk of skin discoloration and perhaps to use another type of tracer, such as a radioactive marker or ICG. SLN detection with SPIO markers shortens the preoperative care pathway, and it also seems that SPIO tends to reduce costs because of avoidance of nuclear medicine charges (10). In order to reduce medical charges and iatrogenicity, preoperative SPIO injection could also minimize unnecessary SLNB, in case of preoperative diagnosis of ductal carcinoma *in situ*, and enable SLNB to be performed later if invasive breast cancer was found post-operation (23).

SPIO injection is a safe surgical method for detecting SLN which facilitates logistics at surgery. After mastectomy, the rate of skin staining was low at less than seven percent with good patient satisfaction. In the presented series, the rate of skin staining after BCS was 31.6%. Peritumoral injection was associated with a decreased risk of skin discoloration after BCS compared to retroareolar injection. Despite the persistent skin discoloration in 58.6% of cases in the present study, patient satisfaction was high. Deeper injection in the subcutaneous tissue, reduced doses, massage of the injection area and peritumoral injection were correlated with less skin staining.

Ethics Committee Approval: No ethical statement is mandatory because the dose and the localisation of the injection are decisions dependant on an internal service protocol, without deviating from the guidelines for respecting the use of the product.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.P.M., C.S., D.H.; Concept: M.P.M., C.S., D.H.; Design: M.P.M., C.S., D.H.; Data Collection and/or Processing: M.P.M., C.S., D.H.; Analysis and/or Interpretation: M.P.M., C.S., D.H.; Literature Search: M.P.M., C.S., D.H.; Writing: M.P.M., C.S., D.H.

Conflict of Interest: The authors have no conflicts of interest to declare.

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