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A combined, totally magnetic technique with a magnetic marker for non-palpable tumour localization and superparamagnetic iron oxide nanoparticles for sentinel lymph node detection in breast cancer surgery

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ABSTRACT

Background: Surgery for non-palpable breast cancer may often be a challenging procedure. Recently, a magnetic seed (Magseed®) used for tumour localization has been developed. Superparamagnetic iron oxide nanoparticles (SPIO) for sentinel lymph node (SN) detection is a novel tracer that may be injected up to four weeks preoperatively. This study is the first combining the magnetic seed and SPIO.
Material and methods: Patients planned for breast conserving surgery and SN-biopsy (SNB) were recruited from two units in Sweden. Patients underwent lesion localization with Magseed® and SPIO injection (Magtrace™) by the breast radiologist in the preoperative period. Feasibility of successful lesion localization and excision together with a successful SNB detection was evaluated. Seed migration, number of SNs, specimen volume and calculated resection ratio (CRR) were reported.A survey of the physicians' experience was conducted.
Results: Localization was performed at a median of three days before surgery (range 0–25). All 32 patients underwent microscopically radical resection with a CRR of 1.49. No seed migration was noticed. SNB was successful in all patients. A median of two SNs was retrieved. Radiologists and surgeons reported the procedure easy to learn and outperformed guidewire localization in terms of localization and excision time. They thought the technique facilitated planning localization and surgery.
Conclusions: The combined magnetic technique provided accuracy in tumour localization and SN detection without excess tissue excision and with promising results for flexibility in delivery of care. Larger studies are needed to confirm these findings.

Introduction

Breast cancer is the leading form of cancer among women worldwide and with a rising incidence [1–3]. The introduction of mammography screening has led to diagnosis of tumours at an earlier clinical stage, often with a clinically negative axilla [4]. In Sweden, about 50% of breast cancers diagnosed annually are screening-detected [5]. These cancers are often asymptomatic at clinical examination, as they either are too small in size or seated too deep in the breast parenchyma to be detected at clinical examination as a palpable lump and are often referred to as non-palpable lesions.

Surgical treatment of non-palpable lesions is an example of interdisciplinary dependence in surgical oncology. The breast

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surgeon is called to excise a part of the breast, guided solely by the localization performed by the radiologist. A variety of techniques have been developed, with guidewire localization being viewed as the default method [6]. However, guidewire localization poses certain challenges. The guidewire is placed preferably on the day of surgery to minimize risk for dislocation. Furthermore, a guidewire case is hard to postpone and, if the theatre list only includes cases requiring localization, the first case can be delayed, which may have an impact on utilization of resources and costs. Guidewires may also limit alternatives for incision placement, thus affecting the possible aesthetic outcome [7].

A paramagnetic steel seed (Magseed®, Endomagnetics Ltd, Cambridge, U.K.) for localization of breast lesions has recently gained interest. The Magseed® is inserted under ultrasonographic or stereotactic guidance. At surgery the seed is localized with a magnetic detector probe (Sentimag®, Endomagnetics Ltd, Cambridge, U.K.). The probe is also used for sentinel lymph node (SN) detection when using superparamagnetic iron oxide nanoparticles (SPIO) at SN-biopsies (SNB). Reports from the U.K. [8] and U.S.A. [9] on the Magseed® use demonstrate safety, efficacy and ease of implementation and suggest that the preoperative insertion of the seeds may facilitate logistics. However, in the study where breast conserving surgery (BCS) was performed, there was a concern regarding magnetic transcutaneous probe detection of lesions located deeper than 3.5 cm [9]. On the other hand, if the primary is detected with the magnetic probe, but SNB is performed using radioisotope, then nuclear medicine facilities are still necessary, two different probes are used and therefore increased resources are required, exposure to radiation is not avoided and the flexibility that seems to be provided by the Magseed®, compared to the guidewire, is not fully capitalised on.

SPIO-guided SNB has been the standard at the breast unit at Uppsala University Hospital since 2014. Our research group has demonstrated comparable results to the isotope and blue dye (BD) combination as well as feasibility of a preoperative SPIO injection, up to one month before surgery [10]. Subsequently, SPIO-guided SNB was combined with tumour localization with the Magseed® for patients with occult breast lesions in a totally isotope-free technique with magnetic guidance both for the resection of the primary and for SNB. Aim of this study is to report initial outcomes, feasibility and implementations of this standardized, combined method.

Patients and methods

Patient selection

Patients with non-palpable, screening-detected lesions with a core cut biopsy diagnostic for breast cancer that were planned for BCS and SNB were identified at the multidisciplinary meetings at the two centres. Exclusion criteria were hypersensitivity to dextran compounds or SPIO, iron overload disease, pregnancy, or mental condition rendering the patient incapable of giving written informed consent. The study was approved by the Regional Ethics Board in Uppsala (Dnr: 2017/508).

Technique

Consecutive patients meeting the inclusion criteria, such as depicted in Fig. 1, were recruited for the study and scheduled for an operation during their visit at the outpatient clinic. At any time-point between that visit and the day of surgery, an appointment for tumour localization was booked at the mammography unit. The tumour was located with ultrasound or mammography. SPIO (Magtrace™,1.0–2.0 ml, Endomagnetics Ltd, Cambridge, U.K.) was injected on the dorsal surface of the tumour (Fig. 2a), or divided in four doses at the periphery of the lesion in cases with micro-calcifications, larger lesions seated deeply in the breast or lesions with diffuse growth pattern. A MagSeed® was placed at the ventral surface of the tumour (Fig. 2b). It is known from the manufacturer that the MagSeed® gives maximum signal on the Sentimag® detection system at a distance of five mm, meaning that placing the

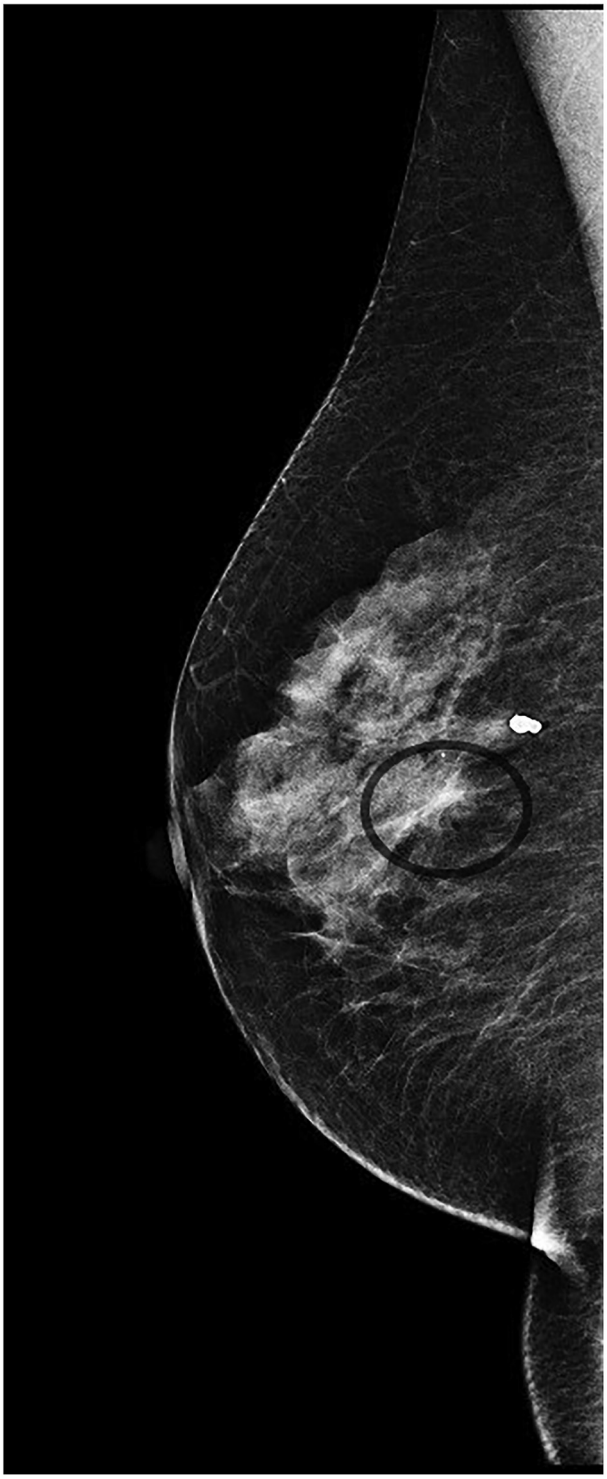


Fig. 1. Screening mammogram. Mediolateral oblique view of a right breast depicting a 15 mm invasive ductal cancer, oestrogen positive, in the lower outer quadrant, marked with a circle.

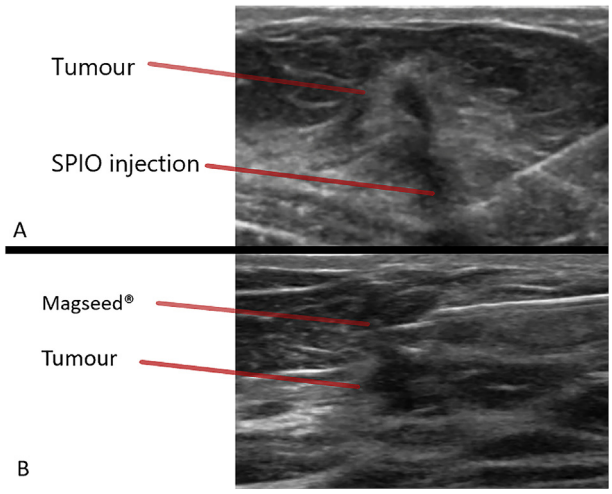


Fig. 2. A. Breast Ultrasound with the lesion and SPIO injected dorsally. B. The Magseed® is injected and left on the ventral surface of the tumour.

seed on the ventral surface of the tumour would allow for safe margins. Accordingly, SPIO injection at the periphery would result in the creation of a rim of maximum magnetic signal behind and around the tumour, both enhancing transcutaneous magnetic signal and surrounding the lesion, but without losing the focal signal of the MagSeed® on the anteroposterior axis of the breast, when the probe is accordingly placed. Mammography was conducted to confirm successful localization (Fig. 3) and the distance between seed and tumour was documented The optimal resection volume (ORV) for a given tumour size was calculated as described by Krekel et al. [11], including suspected areas of DCIS described by the radiologists. The distance between ultrasound probe or skin, in cases of stereotactic localization, and tumour was documented.

On the day of surgery, the seed was localized with the Sentimag® probe after imaging review. The axilla was scanned with the probe and BD was injected at the surgeon's discretion. Resection of the tumour was performed with help of the Sentimag® probe. Resection was guided by the maximum magnetic signal of the Sentimag® probe, without the need to resect all the tissue with magnetic signal. It is known from the manufacturer that maximum magnetic signal responds to a distance of five mm from the clip or the SPIO injection site. Time-to-specimen-excision and cavity residual signal counts were registered. Specimen radiography was obtained and radiologic margins were documented (Fig. 4). Distance between seed and tumour was also documented, to allow for comparison with the post-localization mammogram so as to see if there is seed migration. Cavity shavers were not routinely obtained. Specimen volume was obtained after weighing the specimen and assuming a molecular weight of 0.958 g/cm^3, which is known to correspond to a 1:1 proportion of gland-fatty-tissue [12]. SNB was subsequently conducted using the probe and detection rate, number of SNs and presence of metastases were documented. The calculated resection ratio (CRR) was calculated by dividing the ORV to the surgical specimen volume, to allow for an objective estimate of the outcome. A background comparison with the "true" resected volume (TRV) was also performed, using the formula of the ellipse volume, as previously performed in the literature [11] and the estimated CRR (eCRR) was defined as TRV/ORV. Finally, surgeons and radiologists undertook a survey to assess the ease of the method in comparison to the use of guidewires and their experiences on the method. No learning curve patients were operated prior to the study.

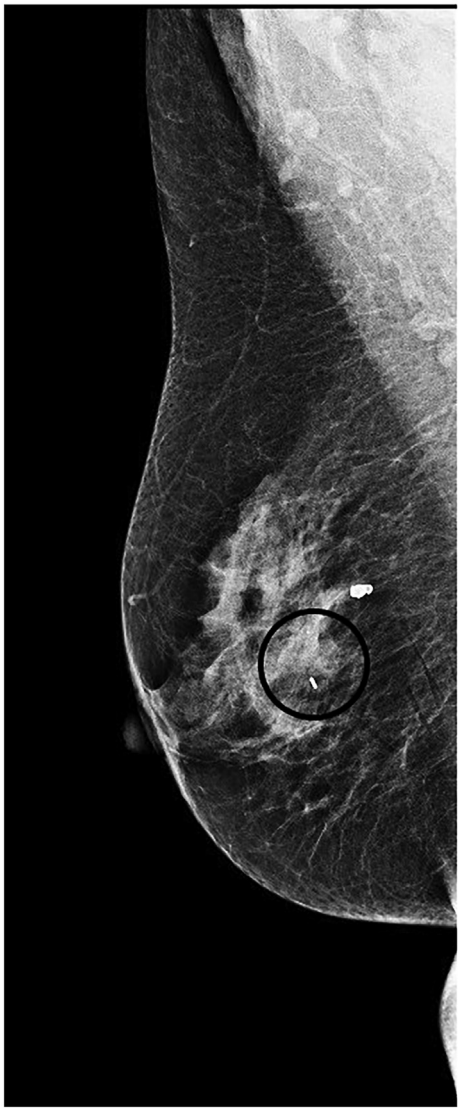


Fig. 3. Mediolateral oblique view of the mammogram confirming successful tumour localization.

Study endpoints

Primary endpoint was successful lesion localization and excision and successful SN detection. Secondary endpoints were Magseed® migration, number of SNs, localization time, excision time, CRR and a survey of the physicians' views on the technique.

Results

Thirty-two patients were included in the study. Patient demographics and tumour characteristics are presented in Table 1. Patients underwent localization and SPIO injection at a median of three days before surgery (range 0–25). The median minimum distance from the tumour to the skin was 17.5 mm (range 5–65). The most usual modality for localization was ultrasound (30 of 32 patients). Median time required for seed placement and SPIO injection per patient was six minutes (range 2–50); this time increased to twelve minutes (range 5–60) when the time required for the post-localization mammogram was added. Primary tumour resection was radical in all patients, with a median

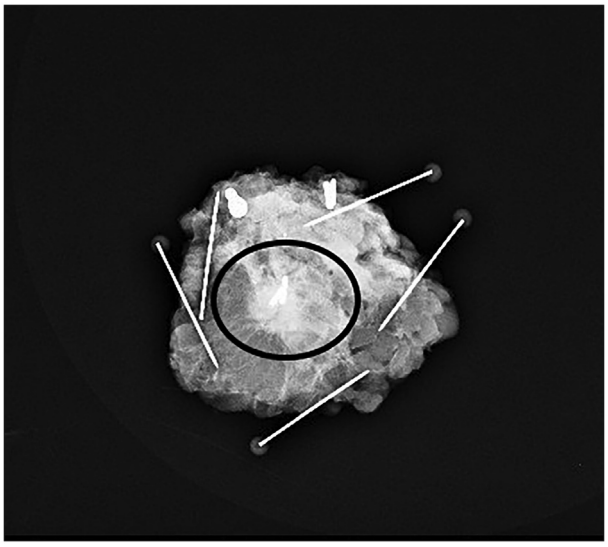


Fig. 4. Specimen radiography, anteroposterior view with the tumour and the Magseed® centrally located with adequate radiologic margins.

histopathological margin of 6.5 mm (0–14 mm). No seed migration was noted. Median time for specimen excision was eight minutes (range 4–35). SNB was successful in all cases with median of two retrieved (range 1–5). Blue Dye was added in eight cases, but did not prove to be necessary in any. Median operative time for tumour excision together with SNB was 64 min (range 38–113).

The comparison of medians for the different methods for specimen volumetry (direct volume estimate vs TRV) did not demonstrate any differences (42.19 vs 41.75 cm^3, Wilcoxon signed rank test, $p = 0.466$). Subsequently, no difference was seen between the medians of the "true" and the estimated CRR (1.82 vs 1.49, Wilcoxon signed rank test, $p = 0.681$).

The views of the physicians involved in the procedures are illustrated in Table 2. The response that everybody would be positive to use this technique and recommend it to others was unanimous. The operation theatre co-ordinators experienced that the combined method was an improvement, allowing for more flexibility in the schedule of the mammography unit and the theatre lists without delayed start. Finally, neither the SPIO nor the seed affected specimen pathology.

Discussion

The present study is the first report of a novel technique combining a magnetic seed for non-palpable lesion localization and SPIO for SNB, allowing for a totally magnetic, isotope and wire-free technique. Results and clinical outcomes are promising and seem to have the potential to improve current practice, providing flexibility in delivery of care as well as simplified logistics.

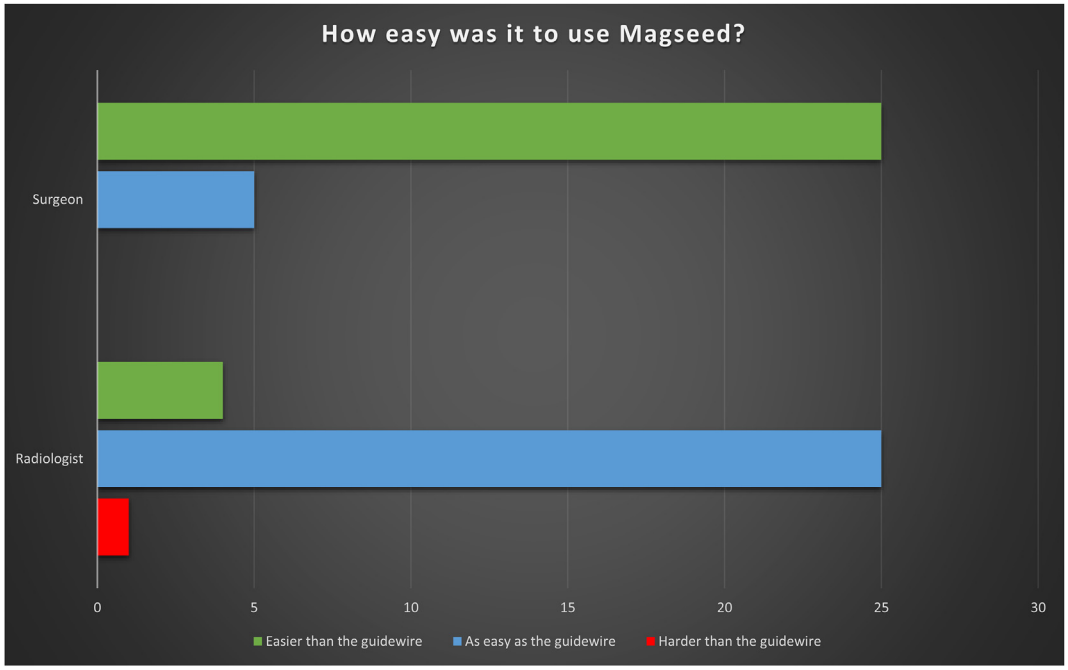
Three previous reports on the use of magnetic seeds have described safety and feasibility [8,9,13] but only Price et al. describe Magseed® in clinical use and focus on the advantages in logistics, the reliability in deployment and, the comparable re-excision rate to the use of guidewires [9]. Harvey et al. conducted a safety and feasibility study in mastectomy cases and concluded that the seeds could be placed accurately [8]. A Dutch group conducted a feasibility study using a similar magnetic marker comparing it to radioactive seeds and all fifteen cases could be identified with participating radiologists and surgeons reporting positive views of the technique [13]. The intratumoural injection of SPIO, both for

Table 1
Clinicopathological data of study patients (N = 32).

Age (years)		66 (41–82)
BMI (kg/m^2)		26.6 (19.2–39.9)
Side	Right	16
	Left	16
Localization in the breast	Upper Outer Quadrant	13
	Upper Inner Quadrant	9
	Lower Inner Quadrant	5
	Lower Outer Quadrant	4
	Central	1
Primary Systemic Treatment	No	30
	Yes	2
Primary tumour size*		13.5 (6, 47)
Histological type	DCIS	3
	IDC	27
	ILC	2
Nuclear grade	In situ, grade 2	3
	1	7
	2	17
	3	5
Receptor status	ER + HER2-	23
	ER + HER2+	2
	ER-HER2+	2
	ER-HER2-	2
	Not assessed (DCIS)	3
T-stage	T_{is}	3
	T_1	21
	T_2	8
Transcutaneous magnetic signal before incision	Yes	30
	No	2
Ex vivo signal on SN (median, range)		4300 (200,9999)
SNs retrieved (median, range)		2 (1,4)

Descriptives are presented as median (range), for continuous variables and numbers for nominal or ordinal variables. *: Based on the size of the largest focus. DCIS: Ductal Cancer In Situ, IDC: Invasive Ductal Cancer, ILC: Invasive Lobular Cancer, ER: Oestrogen Receptor, HER2: Human Epidermal growth factor Receptor 2.

Table 2
Bar plot with the views of the physicians who partook in the study.



tumour localization and SNB have been described [14]. Using a dose of 0.5 ml Sienna+ (Endomagnetics Ltd, Cambridge, UK), a SN was detected in 28 of 33 patients with SPIO only and in 32 of 33 in combination with BD. The CRR was 2.5 using and in two of 20 cases with non-palpable lesions the BCS was not radical.

The combination of magnetic marker and SPIO seems to be an improvement;, SPIO injected dorsally or around a lesion seems to amplify the transcutaneous magnetic signal in tumours located deep in the breast; the surgeon may intraoperatively be guided by the maximum focal signal provided by the Magseed® placed ventrally to the lesion and SPIO diffusion creates a “halo” of magnetic signal around the tumour. In other words, the radiologist uses the SPIO and the seed to demarcate the dissection plane for the surgeon with the additional benefit of simultaneously injecting the tracer for SNB. Injecting the SPIO on the lesion margins is additionally expected to result in surgical removal of the majority of the SPIO in the breast resulting in turn to less skin staining or artefacts in a postoperative MRI. This technique may account for the fact that all resections in the cohort were microscopically radical with satisfactory pathological margins, without removing a large excess of breast tissue. In fact, the estimated CRR was only 1.49, which is markedly lower than CRRs reported for other techniques, ranging from 2.5 for the MagSNOLL[15] up to 3.8 for the radioiodine seeds[12]. The low CRR obtained implies that the totally magnetic technique may yield promising results for smaller resection volumes and therefore potential for improved cosmesis [15]. That was particularly useful for larger, deep seated tumours in the present series, where the demarcation of tumour spared the resection of excess tissue. No seed migration was noted, nor did the SPIO spread diffusely the breast tissue. The exact association of SPIO volume injected and grade of diffusion at the area of injection as well as the minimum dose for a successful SNB is a question of clinical interest currently investigated by our group.

In this study, SPIO-guided SNB was successful in all patients. Blue Dye was injected either due to a low transcutaneous magnetic signal or the surgeon's decision. However, in all cases the SN was clearly magnetic when entering the axilla, and blue dye injection could have probably been avoided, a finding which is in agreement with previous findings of our group [10]. As far as the timeframe of the Magseed® insertion and the SPIO injection is concerned, a maximum of 40 days prior to the operation has been previously reported for the Magseed® insertion [9] and successful SPIO-guided SNB up to 47 days after SPIO injection have been conducted by our group [16], implying that long-term application may be feasible, which may be of interest for the marking of primary tumour and SN prior to primary systemic therapy, in cases that MRI during that period is not required. Results from the ongoing SentiDose trial, regarding the effectivity of a lower SPIO dose are expected to further refine the parameters of this combined technique.

Breast radiologists almost unanimously felt that localization was faster with the combination of Magseed® and SPIO compared to guidewire and that the procedure was comparable or easier to guidewire placement, despite the lack of experience with the seeds. There was no steep learning curve and overall, the technique seemed to be more comfortable for the patients. Moreover, there was no difficulty in identifying the Magseed® and the lesion on specimen imaging. The surgeons felt that the combined magnetic technique was easier than the guidewire and reported shorter time for excision, even when oncoplastic procedures were performed with incisions not right over the seed, the explanation being that dissection and raising of skin flaps all the way to the guidewire entrance under the skin was not necessary. Additionally, guidewire displacement or tip anchoring in the fascia were avoided by using the magnetic technique. Planning was more flexible both for the mammography unit and for the operating theatres, whereas late starts or rescheduling could be avoided. The implication of this technique on health economy related to the procedure was not an endpoint in the study due to small number of participants and lack of a control arm, but possibly shorter operating times and avoidance of late starts may be of value.

The present report demonstrates that the totally magnetic technique with a combination of Magseed® and SPIO is feasible for non-palpable breast cancer localization and SNB. This novel technique seems to overcome the limitations of wire- or radioiodine seed-guided surgery, to provide radical excisions without the removal of excess breast tissue. Simplification of logistics and reduction of resources seems to make it attractive for the global setting, where co-ordination of radiologists and surgeons or access to nuclear medicine departments maybe very challenging. Additionally, no skills in intraoperative ultrasound are required, which is mandatory for ultrasound guided excisions. Finally, both the primary tumour and the SN can be excised by the use of a single-principle technique, diminishing the need for complex procedures that would involve steep learning curves. Albeit very promising, these first results need to be tested in larger randomized trials. Therefore, our research group is currently accruing data within the MagTotal trial [17], in order to reach to more robust conclusions on the implementations and advantages of this novel technique.

Role of the funding source

The study was sponsored by Uppsala University. EndoMagnetics Ltd (Cambridge, UK) provided the Magseed® and the SPIO (Magtrace™) for the study. The sponsor and the funding source had no role in study concept and design, data acquisition, analysis and interpretation, manuscript preparation or decision to submit for publication.

Conflict of interest

Authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2018.10.064.

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