European Journal of Surgical Oncology 45 (2019) 2016–2021

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Is the future magnetic? Magseed localisation for non palpable breast cancer. A multi-centre non randomised control study

Konstantinos Zacharioudakis [a, *], Sue Down [b], Zaheerah Bholah [a], Sum Lee [a], Taherah Khan [a], Anthony J. Maxwell [a, c], Miles Howe [a], James Harvey [a]

[a] The Nightingale Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Southmoor Road, Manchester, M23 9LT, UK
[b] James Paget University Hospitals NHS Foundation Trust, Lowestoft Road, Gorleston-on-Sea, Great Yarmouth, NR31 6LA, UK
[c] Division of Informatics, Imaging & Data Sciences, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, M13 9PT, UK

ARTICLE INFO

Article history:
Received 13 March 2019
Received in revised form
21 June 2019
Accepted 24 June 2019
Available online 26 June 2019

Keywords:
Magseed
Seed localisation
Wide local excision
Non palpable breast cancer
Lumpectomy
Magnetic

ABSTRACT

Introduction: Magseed is an alternative method of localising non-palpable breast lesions that has addressed many of the limitations of wire guided localisation (WGL). It consists of a paramagnetic seed that can be visualised on mammography and ultrasound. Intraoperative localisation of the seed is achieved with the use of the Sentimag probe. The aim of this study was to prospectively compare localisation in patients undergoing wide local excision (WLE) for non-palpable lesions between Magseed and WGL.
Methods: We prospectively collected data on all patients undergoing image-guided WLE between October 2017 and September 2018 in two academic breast units with a planned accrual of 100 consecutive patients undergoing Magseed localisation. Data was also collected on a cohort of 100 consecutive patients undergoing WGL in the same time period.
Results: Demographic and disease characteristics were well balanced between the two groups. 4/104 patients were converted preoperatively from Magseed to WGL (2 misplaced Magseeds; 2 undetected Magseeds). Intraoperative identification and excision of the localised lesion was successful in all patients as confirmed with specimen radiography. Overall no significant differences were observed in the proportion of patients requiring re-excision between the two groups (Magseed 16% vs. WGL 14% $p = 0.692$). Specimens size by weight and volume was similar for both groups (Magseed 39.6 g vs. WGL 44.5 g $p = 0.206$ and 90.1 cm^3 for Magseed vs. 95.6 cm^3 for WGL $p = 0.579$).
Conclusions: In our series Magseed localisation proved to be as reliable and effective as WGL in terms of lesion identification, excision with tumour free margins and specimen weight.

Introduction

Although preoperative wire guided localisation (WGL) is the standard of care for non-palpable breast lesions in most centres, this procedure has several limitations; most notably wire migration which can occur in up to 3% of patients [1]. Furthermore, as there may be some distance between the entry site and the tip of the wire, accurately ascertaining the position of the lesion intra-operatively and ensuring optimal incision placement may be challenging, thus leading to extensive dissection. In order to minimise patients' discomfort and the risk of dislocation, wire localisation is usually performed on the day of surgery. This requires close co-ordination between the radiology department and theatres and can lead to delays and cancellations in the operating schedule. Despite its limitations, wire localisation remains the default method of localisation in most breast units given the long term data supporting its effectiveness [2].

Alternative methods such as Iodine (^{125}I) radioactive seed localization (RSL) and Radio Occult Lesion Localisation (ROLL) are equally reliable and are used in a number of centres in order to overcome some of the disadvantages of wire localisation [3]. Iodine seed localisation can be performed prior to the day of surgery. The position of the seed can be confirmed on mammography preoperatively, and the lesion can be accurately localised intra-

Abbreviations: WGL, wire guided localisation; RSL, radioactive seed localization; ROLL, Radio Occult Lesion Localisation.

* Corresponding author.
E-mail address: kzacharioudakis@yahoo.gr (K. Zacharioudakis).

https://doi.org/10.1016/j.ejso.2019.06.035

operatively with a handheld gamma probe, and in the specimen X-ray ex-vivo. Despite the advantages of this technique the nuclear medicine regulatory requirements have limited its widespread implementation [3]. Although ROLL does not require the same stringent radiation safety precautions as iodine seeds, patients need to be injected within 24 h of surgery. Furthermore, the accuracy of localisation cannot be confirmed unless radio-opaque contrast medium is also injected [4].

Magseed is an alternative method of localising breast lesions that may address many of these limitations (Fig. 1). It consists of a non-radioactive paramagnetic seed that can be visualised on mammography and ultrasound. Intraoperative localisation of the seed is achieved with the use of the Sentimag probe. The feasibility and safety of this technique had been previously assessed in an open label cohort study of patients undergoing mastectomy where we demonstrated that magnetic seeds can be accurately placed without displacement and can be detected in all breast sizes and depths [5]. The aim of this study was to prospectively compare Magseed and wire-guided localisation in patients undergoing wide local excision for non-palpable lesions.

Material and methods

Data were prospectively collected on all patients undergoing image-guided wide local excision for non-palpable invasive breast cancer or ductal carcinoma-in-situ in this multi-centre non-randomised control trial in two academic breast units between October 2017 and September 2018, with a planned accrual of 100 consecutive patients undergoing Magseed localisation and a cohort of 100 consecutive patients undergoing wire guided localisation in the same time period. All clinical decisions and treatment recommendations were made following consensus within the multidisciplinary team meeting. During this period assignment to localisation technique was initially by consultant rather than by individual case as some consultants were using magseed for localisation and some where using wire guided localisation. As we moved forward and our experience increased, Magseed was gradually adopted by all consultants and the majority of our cases were performed using Magseed localisation. WLE were performed by consultant breast surgeons or trainee breast fellows.

The Magseed device consists of a 5 mm x 1 mm cylindrical non-radioactive paramagnetic steel and iron oxide seed with no barbs that can be visualised on mammography and ultrasound. The seed was deployed via a preloaded 18—gauge, 12 cm long needle prior to surgery under ultrasonographic or mammographic guidance. Following insertion, mediolateral oblique and craniocaudal full field digital mammography was performed in order to confirm accurate lesion localisation. Intraoperative localisation of the seed was achieved with the use of the Sentimag probe in the same way as the Sienna dye is localised in sentinel lymph node biopsy [6]. The probe generates an alternating magnetic field which transiently magnetises the iron oxide within the Magseed. The magnetic signature of the seed is then detected by the Sentimag probe and a numerical count is displayed by the Sentimag unit along with an audio tone, the frequency of which varies according to the intensity of the magnetic field produced by the Magseed, thus allowing the surgeon to gauge the distance of the seed from the probe and accurately localise the lesion.

In our study, detectability of the Magseed was confirmed using the Sentimag device in the anaesthetic room prior to induction. If the Magseed could not be accurately localised prior to induction, the patient returned to the radiology department and wire localisation was performed. Exclusion criteria for Magseed localisation were the presence of a pacemaker or an implanted device in the chest wall, and allergy to nickel. Patients requiring bracketing localisation were not included in our study.

The primary outcome of our study was successful localisation of the lesion (removal of the index lesion) using the predetermined localisation technique. Secondary outcomes were successful identification and excision of the lesion, re-excision rate, specimen weight, specimen size, and lesion to specimen size ratio. We calculated tumour volume based on its maximum diameter and specimen volume using the three dimensions reported by the pathologist. When comparing specimen size and weight we excluded those from patients undergoing therapeutic mammoplasty as in these cases the specimen weight and size were not proportional to the size of the lesion. We also collected data on patient age, presentation (symptomatic vs. screen detected), lesion size (based on the final histopathology report) and mode of localisation (ultrasound vs. stereo guided). All unplanned events that took place in the radiology department during localisation, in the anesthetic room prior to induction and during surgery were documented (appendix A). Any margin <1 mm was deemed positive and patients underwent re-excision as appropriate.

Statistical methods

Descriptive statistics were used to generate means and medians to describe the two cohorts (Magseed vs. wire localisation). Associations were analysed with Student's *t*-test and Chi-square test using IBM SPSS statistics version 25. P values that were less than 0.05 were considered significant.

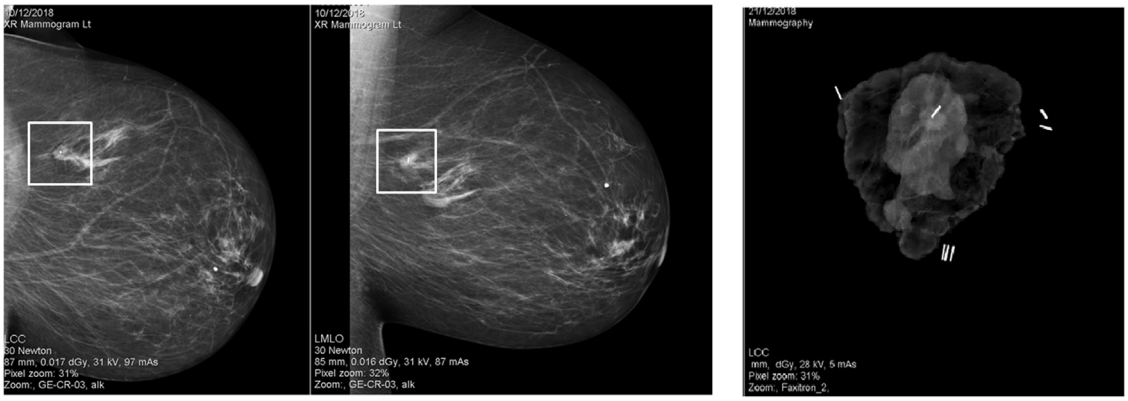

Fig. 1. Stereo-guided Magseed localisation of a non palpable lesion and X-ray of the WLE specimen.

Results

Patient characteristics

Demographic and disease characteristics were well balanced between the Magseed and wire-guided group (Table 1). Mean patient age was 60.9 years in the Magseed group and 61.7 years in the wire-guided localisation groups ($p = 0.586$). Mean tumour size, based on final pathology, was also similar in the two groups (16.3 mm for Magseed vs. 15.8 mm for wire-guided localisation; $p = 0.774$). Invasive breast cancer was seen in 81.5% and DCIS in 18.5% of cases with no significant difference between the two groups ($p = 0.284$). The majority of patients underwent ultrasound guided localisation (67% US guided vs. 33% stereo guided). There were no significant differences regarding the mode of detection between the two groups; in the wire-guided cohort 75% of cancers were screen detected vs. 80% in the Magseed cohort ($p = 0.397$).

Primary outcome

I. Successful localisation of the index lesion using the pre-operatively planned technique for patients undergoing Magseed localisation

In total there were 104 patients booked for Magseed localisation. Two patients were converted to wire-guided localisation because the device was deployed at a distance from the target lesion and placement of a second Magseed was not feasible as the surgeon may have been unable to distinguish between the two signals. Two patients were converted to wire-guided localisation because the surgeon was unable to localise the lesion using the Sentimag prior to induction in the anaesthetic room (0.96–95% CI 0.91–0.99) Fig. 2.

Secondary outcomes

I. Successful identification and excision of the lesion intra-operatively

Intraoperative identification and excision of the localised lesion was successful in 100% of patients in both groups (after the above exclusions), as confirmed with specimen radiography.

II. Re-operation rate – positive excision margins

Overall no significant differences were observed in the proportion of patients requiring re-excision between the two groups. Complete excision after the initial procedure with at least 1 mm disease free margins was achieved in 84% of patients in the Magseed cohort and 86% of patients in the wire localisation cohort (Table 2; $p = 0.692$).

Table 1
Patients characteristics in the WGL and Magseed cohort.

	Magseed	WGL
Age	60.9 years	61.7 years $p = 0.586$
Tumour size	16.3 mm	15.8 mm $p = 0.774$
Screen detected	80%	75%
Symptomatic	20%	25% $p = 0.397$
Invasive	86%	77%
DCIS	14%	23% $p = 0.101$
Neodajuvant therapy	18%	13% $p = 0.329$
US guided localisation	74%	60%
Stereo guided localisation	26%	40% $p = 0.015$

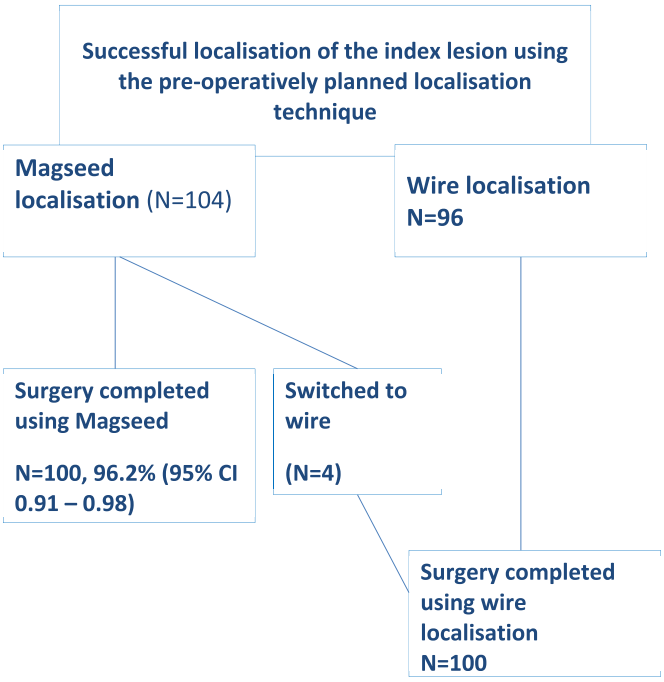

Fig. 2. There were four cases (4/104) where a Magseed was deployed but the procedure was converted to WGL, either because the Magseed could not be identified in theatre prior to induction (2/104) or because the Magseed was deployed at a distance from the target lesion.

Table 2
Clinical outcomes in the Magseed and WGL cohort.

	Magseed	WGL
Re-excision rate	16%	14% $p = 0.692$
Specimen weight	39.6 g	44.5 g $p = 0.206$
Specimen volume	90.1 cm^3	95.6 cm^3 $p = 0.579$
Tumour/specimen volume ratio	0.598	0.519 $p = 0.769$

III. Specimen weight

Specimen weight was similar for both groups. There were three patients from the Magseed cohort and two patients from the wire-guided cohort that underwent therapeutic mammoplasty and were excluded from our analysis. The mean weight was 39.6 g in the Magseed cohort and 44.5 g in the wire localisation cohort (Table 2; $p = 0.206$).

IV. Specimen volume

There was no significant difference between the Magseed and wire localisation groups (Table 2; $p = 0.579$). The mean specimen volume for the Magseed group was 90.1 cm^3 whereas the mean specimen volume for the wire-guided localisation group was 95.6 cm^3.

V. Tumour to specimen volume ratio

There was no significant difference between the Magseed and wire localisation groups (Table 2; $p = 0.769$). The ratio for the Magseed group was 0.598 whereas the ratio for the wire-guided localisation group was 0.519.

VI. Unplanned events

There was one patient in the Magseed cohort that developed a

haematoma following localisation and the seed was dislodged and contained within the haematoma. In a second patient with a lesion located adjacent to the skin the Magseed was dislodged during dissection. In both cases the WLE was completed with negative margins.

Discussion

The advent of screening mammography has resulted in an increase in the proportion of detected invasive or in-situ carcinomas measuring less than 2 cm from 36% to 68% [7]. Wire-guided excision of non-palpable cancers is associated with an increased risk of positive margins. Although this can be partly attributed to the inherent differences in the growth pattern and biology of non-palpable, often pre-invasive cancers, the technical challenges of accurately locating a small non-palpable tumour deep within a large breast are a contributing factor [8].

Our series is the first study that included exclusively non-palpable invasive and in-situ carcinoma, comparing a cohort of patients undergoing Magseed localisation with wire-guided wide local excision. Our results have shown that Magseed is an effective alternative to wire-guided localisation. Although 4/104 patients that were initially allocated to Magseed localisation had to be converted to wire guided localisation prior to surgery, intra-operative identification and excision of the index lesion was 100% in the Magseed cohort.

When compared to wire-guided localisation there were no significant differences across all surgical outcomes including identification rate, re-excision rate, specimen size and weight and lesion to specimen size ratio, suggesting that Magseed localisation demonstrated equivalence to wire localisation. There has been only one published study evaluating the use of Magseed for preoperative localisation of non-palpable breast lesions [9] in which Price et al. reported their initial clinical experience in a cohort of 73 patients undergoing Magseed localisation under ultrasound or mammographic guidance for non-palpable breast lesions. In their cohort all Magseeds were successfully identified and retrieved and the re-excision rate for the 58 cases with malignant lesions was 12%.

Our findings appear to be comparable to those reported for other non wire localisation devices. The re-excision rate in the Magseed cohort was 16% whereas the re-excision rate in the WGL cohort was 14%. In a systematic review of studies comparing localisation techniques for non palpable breast lesions by Chan et al. [10] the re-operation rate for wire guided localisation was 13.5% which is comparable to our outcomes. In total the Magseed was dislodged in two patients during the WLE (2%) although this did not affect the outcome and in both cases the excision was completed to clear margins. Although all unplanned events were recorded prospectively for the Magseed cohort and reported to the Chief Investigator as this is a new technique undergoing evaluation, it may be that there was under-reporting of unplanned events within the wire cohort. McGhan and colleagues reviewed their outcomes in 1148 consecutive patients undergoing Iodine (^{125}I) radioactive seed localization (RSL) [11]. Re-excision rates were 9% for patients with invasive carcinoma and 19% for patients with DCIS. Reported adverse events included 30 seeds that were displaced from the breast specimen during wide local excision (2.61%). Lovrics et al. compared RSL to WGL in a multicentre randomised control trial that showed similar re-excision rates between the two groups (RSL 10.5% vs. 11.8% WGL) [12].

In our study, there were four cases (4/104) where a Magseed was deployed but the procedure converted to WGL, either because the Magseed could not be identified in theatre prior to induction (2/104) or because the Magseed was deployed at a distance from the target lesion (Fig. 2). Lovrics et al. reported similar outcomes for RSL [12]. In their series, 12/152 patients randomised for RSL were converted to WGL due to failure of seed placement, either because the seed could not be deployed or because the seed was displaced. In three patients a wire was used in addition to the Magseed in order to bracket larger lesions.

Our results did not show any significant differences between the two groups regarding specimen weight, specimen volume and lesion to specimen volume ratio. Although earlier studies comparing WGL with ROLL had showed favourable outcomes for the ROLL procedure [13,14], including excision of smaller tissue volumes in one non-randomised study [15], most of these studies included patients requiring excisional biopsy for diagnostic purposes and were performed in a non-randomised setting. A randomised controlled multicentre trial conducted by the ROLL study group [16] comparing the efficacy of ROLL vs. WGL for non-palpable invasive breast cancer showed that the total amount of tissue excised was significantly larger in patients treated with ROLL compared to the WGL group (71 cm^3 vs. 64 cm^3; $p = 0.017$). Although the authors could not provide a straightforward explanation for this outcome they hypothesized that a guide wire can more accurately pinpoint the centre of the lesion than the more diffuse radioactivity detected in the ROLL procedure. Magseed addresses this limitation of ROLL as it permits continuous intra-operative re-orientation without signal diffusion as the intensity of the magnetic signature rapidly decreases as the distance increases. Furthermore, it allows the surgeon to visualise the centre of the targeted lesion on post excision specimen X Ray. As this is an exploratory comparative study that is not powered to detect small differences in specimen weight, re-excision rate or tumour to specimen volume there may be a true difference in these outcomes when a larger cohort is studied.

Although this was not a randomised controlled trial the patients' characteristics were well balanced in the two groups (Table 1). Furthermore, our cohort reflected the demographics of patients with breast cancer (in situ and invasive) treated at a tertiary screening breast unit. All decisions regarding treatment were made within a multidisciplinary team meeting and there were no specific set criteria to choose one localisation technique over the other. Even allowing for possible selection bias during the initial patients' allocation, as we moved forward the majority of our WLE were performed using Magseed localisation.

One limitation of our study was the comparison of outcomes of wire-guided localisation, a technique in which all surgeons taking part in the study had many years of experience, with a novel localisation technique. In fact, the Magseed cohort comprised the first 10 Magseed cases for most of the surgeons involved in the study. We were therefore comparing the outcomes of surgeons that were in different stages of their learning curve for the two techniques. Although efficiency should be optimised within a fairly narrow temporal window we would expect on-going improvement in efficiency over the course of time as surgeons gain further experience. This important factor should be considered and accounted for in order to make accurate, equitable and comparable measurement of outcomes between the two cohorts. This was demonstrated by Pieri et al. in a series of 233 consecutive cases localised by RSL where an improvement in re-excision rate was observed following the initial learning curve [17].

In the majority of patients who underwent Magseed guided WLE in our study localisation was performed on the day of surgery; we have now moved to performing the seed placement in advance. This allows more flexibility to our scheduling and may reduce overall cost, unnecessary delays and cancelations, improve theatre utilisation while allocating personnel more effectively. As Magseed localisation is significantly more expensive than wire localisation this may be a barrier to wider uptake of this procedure and data

from a cost effectiveness analysis is necessary in order to justify a change of practice.

As a National UK group we plan to prospectively collect data from units in the United Kingdom adopting Magseed localisation through the i-BRA network. This will allow breast surgeons to collaborate and ensure device safety and efficacy within the safe governance of a formalised evaluation. The iBRA-net study of Magseed will aim to describe the current practice of breast localisations and evaluate the outcomes of 1000 Magseed localisations with 1000 wire-guided localisations.

Conclusion

Magseed localisation is an innovative technique that allows continuous intraoperative re-orientation with target centering. In our series Magseed localisation proved to be as reliable and effective as wire-guided localisation in terms of lesion identification, excision with tumour-free margins, re-operation rate and specimen weight and size. Compared to wire localisation, surgical approach and incision placement is independent of the localisation access. Moreover, Magseed can be placed in advance allowing disassociation of radiology and surgical schedule. As with any new technical procedure prior to acceptance and adoption by healthcare professionals potential barriers need to be overcome and a large scale evaluation of the clinical outcomes and cost-effectiveness needs to be performed.

Conflict of interest

Endomag sponsored a separate feasibility study for which James Harvey was Chief Investigator.

Ethical approval for research

Not required.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.06.035.

Appendix A

Feedback Form

Ibra-net Magseed feedback form (please enter as much relevant information as possible)

Surgeon initials	Click here to enter text.
Date of surgery	Click here to enter a date.
Hospital	Click here to enter text.

1. Was there a problem during localisation in the Radiology department: What was the nature of the localization problem? What was done to rectify the problem?

Click here to enter text.
Click here to enter text.
Click here to enter text.
Click here to enter text.

2. Was there a problem prior to induction of anaesthetic: e.g.inability to localise Magseed prior to induction? Case cancelled? Switch to wire?

Click here to enter text.
Click here to enter text.
Click here to enter text.
Click here to enter text.

3. Was there a problem intraoperatively: Was the excision completed? Was the lesion identified? Was the Magseed identified?

Click here to enter text.
Click here to enter text.
Click here to enter text.
Click here to enter text.

Doctor:	
Date:	Click here to enter a date.

References

[1] Rahusen FD, et al. Ultrasound-guided lumpectomy of nonpalpable breast cancer versus wire-guided resection: a randomized clinical trial. Ann Surg Oncol 2002;9(10):994–8.

[2] Frank HA, Hall FM, Steer ML. Preoperative localization of nonpalpable breast lesions demonstrated by mammography. N Engl J Med 1976;295(5):259–60.

[3] Langhans L, et al. Radioactive seed localization or wire-guided localization of nonpalpable invasive and in situ breast cancer: a randomized, multicenter, open-label trial. Ann Surg 2017;266(1):29–35.

[4] Rampaul RS, et al. Randomized clinical trial comparing radioisotope occult lesion localization and wire-guided excision for biopsy of occult breast lesions. Br J Surg 2004;91(12):1575–7.

[5] Harvey JR, et al. Safety and feasibility of breast lesion localization using magnetic seeds (Magseed): a multi-centre, open-label cohort study. Breast Canc Res Treat 2018;169(3):531–6.

[6] Thill M, et al. The Central-European SentiMag study: sentinel lymph node biopsy with superparamagnetic iron oxide (SPIO) vs. radioisotope. Breast 2014;23(2):175–9.

[7] Welch HG, et al. Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. N Engl J Med 2016;375(15):1438–47.

[8] Skinner KA, et al. Palpable breast cancers are inherently different from non-palpable breast cancers. Ann Surg Oncol 2001;8(9):705–10.

[9] Price ER, et al. Initial clinical experience with an inducible magnetic seed system for preoperative breast lesion localization. AJR Am J Roentgenol 2018;210(4):913–7.

[10] Chan BK, et al. Localization techniques for guided surgical excision of non-palpable breast lesions. Cochrane Database Syst Rev 2015;(12):CD009206.

[11] McGhan LJ, et al. Radioactive seed localization for nonpalpable breast lesions: review of 1,000 consecutive procedures at a single institution. Ann Surg Oncol 2011;18(11):3096–101.

[12] Lovrics PJ, et al. A multicentered, randomized, controlled trial comparing radioguided seed localization to standard wire localization for nonpalpable, invasive and in situ breast carcinomas. Ann Surg Oncol 2011;18(12):3407–14.

[13] Lovrics PJ, et al. Systematic review of radioguided surgery for non-palpable breast cancer. Eur J Surg Oncol 2011;37(5):388–97.

[14] van der Ploeg IM, et al. 'Radioguided occult lesion localisation' (ROLL) for non-palpable breast lesions: a review of the relevant literature. Eur J Surg Oncol 2008;34(1):1–5.

[15] Zgajnar J, et al. Radioguided occult lesion localization (ROLL) of the non-palpable breast lesions. Neoplasma 2004;51(5):385–9.

[16] Postma EL, et al. Efficacy of 'radioguided occult lesion localisation' (ROLL) versus 'wire-guided localisation' (WGL) in breast conserving surgery for non-palpable breast cancer: a randomised controlled multicentre trial. Breast Canc Res Treat 2012;136(2):469–78.

[17] Pieri A, et al. The introduction of radioactive seed localisation improves the oncological outcome of image guided breast conservation surgery. Breast 2017;36:49–53.