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REVIEW ARTICLE

Innovations in image-guided preoperative breast lesion localization

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ABSTRACT

Screening mammography increases detection of non-palpable breast lesions requiring image-guided localization prior to surgery. Accurate preoperative localization is crucial for successful surgical outcomes. Wire-guided localization is currently the most widely used localization method for non-palpable breast lesions; however, this technique has multiple disadvantages including patient discomfort, possible wire transection and migration, suboptimal surgical incision placement due to wire location and limited scheduling flexibility decreasing operating room efficiency. As a result, promising new techniques including radioactive seed localization, non-radioactive radar localization and magnetic seed localization have been developed as alternatives. In this article, we provide an overview of these techniques and discuss their advantages, drawbacks and currently available outcome data.

INTRODUCTION

Screening mammography and improvements in imaging have increased detection of non-palpable clinically occult breast lesions which require preoperative localization.[1–5] In females with non-palpable breast cancer, various randomized trials showed that breast conserving surgery is the treatment of choice.[6–8] The main challenge when resecting non-palpable tumours is to obtain clear margins while minimizing resection of healthy breast tissue with associated good cosmetic outcomes.[9]

Currently, wire-guided localization (WL) is the most widely used method for localization of non-palpable breast lesions. The limitations of WL include patient discomfort, potential need to perform localization the day of surgery creating logistic challenges which limit operating room (OR) efficiency, possible wire migration and transection, lack of a point source for reorientation during surgery and suboptimal cosmetic outcome.[10–13] These disadvantages have led to the development of alternative approaches, such as radioactive seed localization (RSL), non-radioactive radar localization (SAVI SCOUT), magnetic seed (Magseed) localization (MSL), radiofrequency identification (RFID) and haematoma ultrasound-guided (HUG) localization.

In this article, we provide an overview of currently available breast preoperative localization techniques and recent innovations with discussion of advantages and disadvantages of various approaches (Table 1). We review the current data available for each technique.

WIRE-GUIDED LOCALIZATION

The first breast lesion localization, reported in 1966, involved a bent-wire implanted through a needle placed in a breast lesion utilizing fluoroscopic guidance.[14] The use of a needle combined with a hook wire was later introduced in 1976.[15] WL is currently considered the standard localization method for non-palpable breast lesions. Localization wires range in length, 3–15 cm, and are preloaded in a 16–21 G needle introducer. Depending on the manufacturer, wires can include a hook, barb, or pigtail designed to anchor the wire. When accurate needle placement is confirmed, with the tip just beyond the target, the wire is deployed through the needle. Following wire insertion, a post-procedure mammogram is obtained to confirm accurate placement (Figure 1). The wire's external component is taped to the skin or covered in order to stabilize its position and the patient is transferred to the OR. The surgeon removes the breast tissue around the wire guided by the wire and preoperative images.[15] Some wires have a thicker reinforced

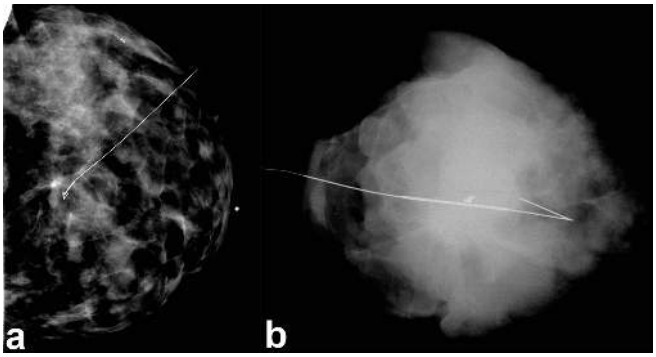
Table 1. Summary of localization methods

Localization technique	System components	Advantages	Disadvantages
Wire-guided localization	• Wire • Needle delivery system	• Safe • Effective • Well established • Inexpensive • Can be placed under mammogram, ultrasound or MRI guidance	• Depending on practice setting often same day procedure (limited scheduling) • Wire external to patient (wire may dislodge, migrate, kink, fracture, or become transected) • Patient discomfort • Potential worse cosmesis due to suboptimal incision placement depending on wire location
Radioactive seed localization	• Iodine-125 labeled titanium seed implant • Needle delivery system • Detector: gamma probe/ion chamber	• Scheduling flexibility (half life I-125 = 59 days) • No external component limits the possibility of displacement or transection • No depth limitation • Compatible with sentinel lymph node mapping • Better cosmesis	• Radiation safety precautions • Radiation exposure to patient and staff • No repositioning once deployed • Cannot be placed under MRI guidance (gamma probe not MRI compatible)
Non-radioactive radar localization (SAVI SCOUT)	• Implantable non-radioactive reflector • Needle delivery system • Detector • Console	• Scheduling flexibility (FDA long-term implant clearance) • No external component limits the possibility of displacement or transection • No radiation exposure • No radiation safety precautions • Better cosmesis	• Cost • Depth limitation • No repositioning once deployed • No MRI compatible needle delivery system • Interference with older halogen lights in OR • Contain nickel (possible nickel allergy) • Limited published data
Magnetic seed (MagSeed)	• Stainless steel seed implant • Needle delivery system • Detector probe magnetizes the seed and temporarily converts it to a magnet	• Scheduling flexibility (placed up to 30 days in advance) • No external component limits the possibility of displacement or transection • No radiation exposure • No radiation safety precautions • Stainless steel seed (no issue with nickel allergy) • Better cosmesis • Count indicates distance to the seed	• Cost • Depth limitation • No repositioning once deployed • No MRI compatible needle delivery system • No published data • Need for non-magnetizable surgical instruments • MRI bloom up to 4 cm (depending on sequence used)

portion which provides an additional palpable indication to the surgeon that the target has been reached.

WL is a safe, cost-effective and well-established technique for preoperative localization of non-palpable breast lesions. WL may be performed under mammographic, ultrasound or MRI guidance. Wires can be placed in the setting of a post-biopsy haematoma and in some cases wire position may be slightly adjusted once deployed.

Figure 1. A 34-year-old woman with IDC. (a) Craniocaudal mammogram view confirms appropriate wire placement with the thicker reinforced portion of the wire immediately adjacent to the target mass and clip. (b) Specimen radiograph demonstrates successful removal of the wire, marker clip and mass. IDC, invasive ductal carcinoma.

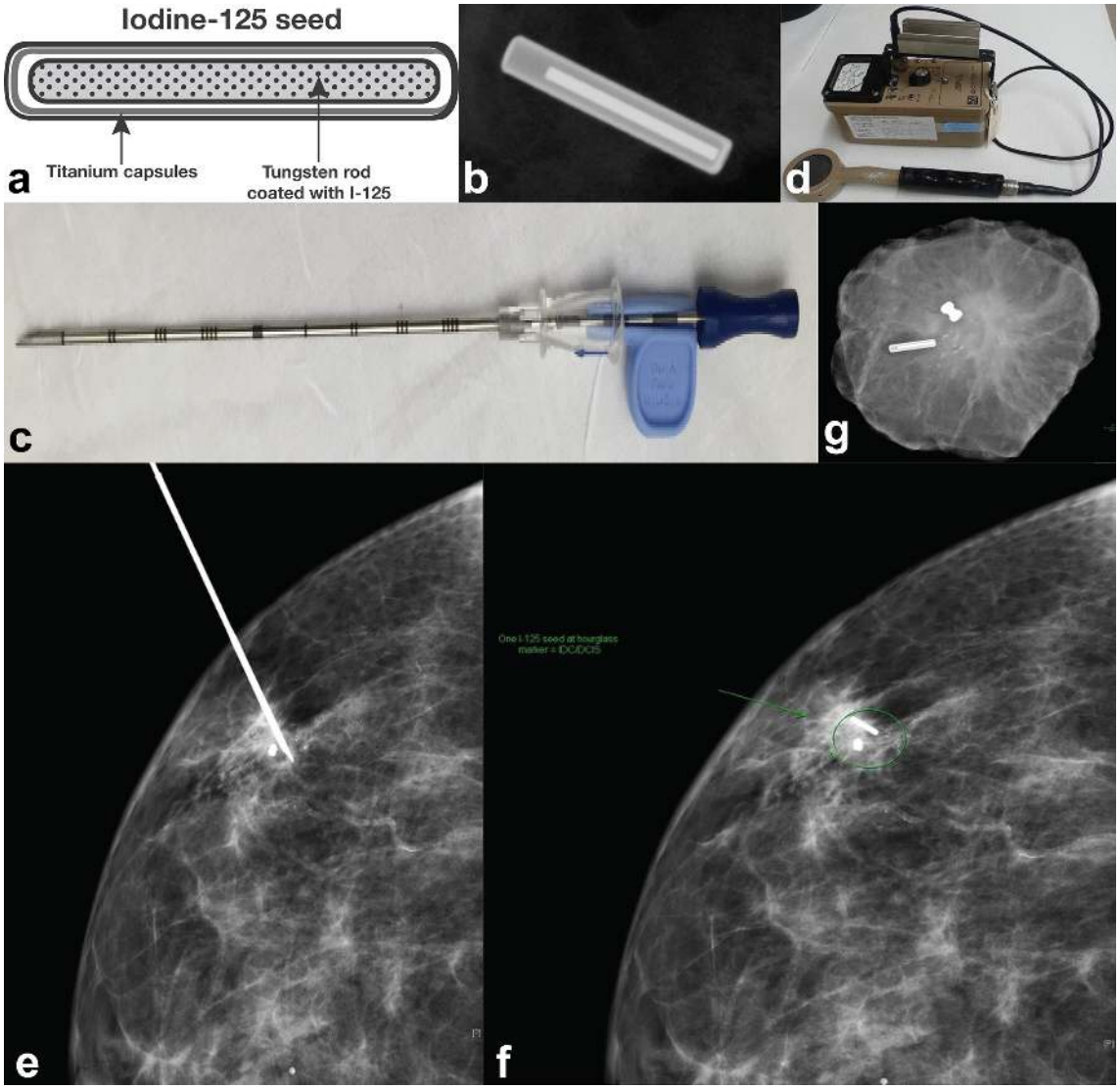


WL has a number of disadvantages. Because part of the wire is external, it can dislodge, migrate, kink, fracture or be transected before or during surgery.[5,12] Vasovagal reactions are reported in 10–20% of patients.[16–19] Additionally, the wire entry site determined by the radiologist may not correspond to the surgeon's ideal skin incision site. This compromises incision positioning, impacting extent of surgical dissection and cosmesis.[5,11,18,20,21] In the United States, wire placement typically takes place the day of surgery, limiting scheduling flexibility and OR efficiency. In the United Kingdom, it is accepted practice to place a localization wire the day prior to surgery. Following placement, the wire is secured with tape and covered with a dressing. The patient is sent home with the wire in place and returns for surgery the next day. Clear margins with WL are reported in 70.8–87.4% of cases.[22–26]

RADIOACTIVE SEED LOCALIZATION

In 1999, Dauway et al reported the first pilot study with RSL as an alternative to WL.[27] This technique utilizes an ^{125}I radioactive seed composed of titanium containing 0.075–0.3 mCi of ^{125}I ($T_{1/2}$ 59 days and 27 keV gamma radiation).[28] The tip of an 18 G

Figure 2. A 72-year-old woman with IDC/DCIS. Components of radioactive seed localization system (a–d). Diagram (courtesy of Best Medical International, Inc.) (a) and radiographic view (b) of the radioactive seed, delivery needle (c) and Geiger counter (d). Mammographic-guided localization of the microcalcifications and marking clip with the delivery needle tip positioned at the targeted clip (e). Radioactive seed deployed adjacent to the clip within the group of microcalcifications(f). Specimen radiograph shows the microcalcifications, mass, radioactive seed and clip (g). DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma.



needle is occluded by bone wax and can be purchased pre-loaded with the seed or manually loaded by the user. A stilette is loosely placed into the needle containing the seed. Once the needle is advanced to the desired location under mammogram or ultrasound guidance, the seed is deployed through the bone wax by advancing the stilette. Mammography confirms accurate placement (Figure 2). The gamma probe used to detect the seed, should it be inadvertently dropped or extruded, is not MRI compatible thus RSL is not performed under MR guidance. During surgery, the seed/lesion are localized using a gamma probe set for ^{125}I. Due to the different energy peak of technetium-99 (^{99}Tc), the isotope used for sentinel lymph node mapping (SLNB), surgeons can differentiate ^{125}I from ^{99}Tc by altering detector settings.[29]

The long half-life of ^{125}I is one advantage of RSL. RSL can theoretically be performed weeks preoperatively which allows scheduling flexibility; although to minimize radiation exposure the procedure should be done within 7 days of surgery per Nuclear Regulatory Commission (NRC) guidelines.[30] In contrast to WL, the ^{125}I seed is a point source that enables more precise surgical localization. Surgeons receive constant audible feedback from the gamma probe allowing continuous reorientation in real time, a strategically placed incision, and potentially a better cosmetic outcome.[30,31]

The use of radioactive seeds in the United States is regulated by the NRC and an NRC state license for medical use of radioactive materials is required as well as an authorized user at the facility with specialized training. The seeds must be carefully tracked from acquisition, deployment, excision, transport, storage and disposal. Licensure and safety precautions for handling radioactive seeds adds complexity to utilizing RSL.[30] Another limitation

is the inability to reposition the seed once deployed. If incorrectly positioned, a second seed (or wire) must be placed to accurately localize the lesion.[32] Radiation exposure is another potential drawback. However, the activity levels of the radioactive seeds are low and considered safe for human exposure.

Non-controlled trials: RSL

RSL studies demonstrate relatively low placement failure ranging from 0 to 3% and negligible seed migration rate ranging from 0 to 0.1%.[31,33–35] The negative margin rates range from 73.5 to 96.7% (Table 2). Cox et al prospectively studied 142 lesions in 124 patients who underwent RSL. 64 lesions in 60 patients with proven malignancy received RSL-guided lumpectomy with 47 of 64 lumpectomies (73.5%) demonstrating negative margins on final pathology.[33] In 2010, van Riet et al performed a prospective study including 325 patients with proven malignancy. They reported a negative margin in 95.4% of patients.[31] McGhan et al retrospectively reviewed 1000 RSL in 978 patients and showed negative margins in 742/767 (96.7%) malignant lesions.[35]

RSL VS WL

Current literature comparing RSL and WL margin status shows variable results, with some studies favouring RSL and more recent studies suggesting no difference between the two methods (Table 3). Overall the negative margin rates range from 70 to 93% with RSL and 43 to 95% with WL.[29,38–45] In 2001, Gray et al reported the first randomized trial comparing RSL with WL involving 97 females. Negative margin rates were significantly better for RSL than WL (74.3 *vs* 42.3%; $p = 0.02$).[29] Of note, a large percentage of patients (53%) underwent excisional biopsies and only 61% of patients had a confirmed diagnosis of malignancy after surgery (26 patients in the WL group and 35 patients in the RSL group). The number of ductal carcinoma in situ (DCIS) cases was not matched between the RSL and WL groups (11% had DCIS in the RSL group and 19% had DCIS in the WL group). These could be potential confounders as previous literature suggested that a preoperative diagnosis, the presence of DCIS or invasive lobular cancer, and large tumour size are associated with increased positive margin rates.[49, 50] Gray et al subsequently performed a prospective cohort study comparing 100 RSL and 100 WL patients.[38] They reported the patient characteristics of RSL and WL groups were similar (19 *vs* 12% DCIS; $p = 0.17$ and 16 *vs* 13% invasive lobular carcinoma; $p = 0.55$). Again, negative margin rates were significantly better in RSL than WL (90.4 *vs* 75.9%, $p = 0.01$). Hughes et al prospectively compared the negative margin rate between a group of 99 patients with WL and 383 patients with RSL with RSL demonstrating a significantly higher rate of negative margins (73.1 *vs* 53.5%, $p = 0.001$).[39]

Since then, multiple studies have shown no statistically significant difference in negative margin rates between RSL and WL.[41–45] These include 3 randomized control trials (RCTs), 2 prospective and 1 retrospective cohort study. In 2011, Lovrics et al performed the first multicentre randomized trial comparing 152 patients treated with RSL (124 invasive cancer, 29 DCIS) and 153 patients treated with WL (129 invasive cancer, 22 DCIS). There was no statistical difference in negative margin rates

Table 2. Studies evaluating different localization methods for non-palpable breast cancer

Reference	Study design	Year of publication	Method	Malignant lesions	Mean/range time to operation (days)	Placement failure (%)	Reoperation rate (%)	Negative margins (%)	Seed/reflector migration (%)
Cox et al[33]	Prospective	2003	RSL	64/134	0–5	4/134 (3.0)	17/64 (26.5)	47/64 (73.5)	0/134 (0)
van Riet et al[31]	Prospective	2010	RSL	325/325	4	3/325 (0.9)	15/325 (4.6)	310/325 (95.4)	0/325 (0)
Alderliesten et al[34]	Prospective	2011	RSL	46/48	59.5 (3–136)	0/100 (0)	2/46 (4.3)		0/35 (0)
McGhan et al[35]	Retrospective	2011	RSL	767/978	0–5	3/978 (0.3)	118/767 (15.4)	742/767 (96.7)	1/978 (0.1)
Cox et al[36]	Prospective	2016	SAVI SCOUTt	101/153	1.8 (0–7)	1/154 (0.6)	17/101 (16.8)	86/101 (85.1)	
Mango et al[37]	Retrospective	2017	SAVI SCOUT	54/110	0–8	0/123 (0)	4/54 (7.4)	50/54 (92.6)	5/110 (4.5)

RSL, radioactive seed localization; SAVI SCOUT, non-radioactive radar localization.

Table 3. Studies comparing localization methods for non-palpable breast cancer

Reference	Study design	Year of publication	Methods compared	Malignant lesions, *n*	Mean/median specimen volume or weight	*p*-value	Negative margins (%)	*p*-value
Gray et al[29]	RCT	2001	WL RSL	26/46 35/51	73.5 ml 55.7 ml	0.48	11/26 (42.3) 26/35 (74.3)	0.02
Gray et al[38]	Prospective cohort	2004	WL RSL	79 83			60/79 (75.9) 75/83 (90.4)	0.01
Hughes et al[39]	Prospective cohort	2008	WL RSL	79/99 306/383			42/79 (53.5) 224/306 (73.1)	0.001
Rao et al[40]	Retrospective cohort	2010	WL RSL	33 33			24/33 (72.7) 23/33 (69.7)	0.20
Lovrics et al[41]	Multicentre RCT	2011	WL RSL	153 152	184 ml 191 ml	0.61	135/153 (88.2) 136/152 (89.5)	0.99
Murphy et al[42]	Prospective cohort	2013	WL RSL	256 431	21 ml 19 ml	0.07	242/256 (94.5) 398/431 (92.3)	0.38
Sung et al[43]	Retrospective cohort	2013	WL + RSL RSL	24 232			21/24 (87.5) 216/232 (93.1)	0.40
Bloomquist et al[44]	RCT	2015	WL RSL	59 72	77.2 cm^3 88.8 cm^3	0.67	50/59 (84.7) 58/72 (80.6)	0.53
Langhans et al[45]	Multicentre RCT	2017	WL RSL	185 194	26.0 g 29.0 g	0.54	169/185 (86.7) 172/194 (88.2)	0.65
Patel et al[46]	Retrospective cohort	2017	WL SAVI SCOUT	42 42	15.2 cm^3 16.3 cm^3	>0.05	37/42 (88.1) 39/42 (92.9)	>0.05
Thompson et al[47]	Retrospective cohort	2007	WL HUG	19/63 58/123			5/19 (26.3) 39/58 (67.2)	0.0001
Arentz et al[48]	Retrospective cohort	2010	WL HUG	38/126 177/329			20/38 (52.6) 135/177 (76.3)	0.045

HUG, haematoma ultrasound-guided; RCT, randomized control trial; RSL, radioactive seed localization; SAVI SCOUT, non-radioactive radar localization; WL, wire-guided localization.

between the two groups (89.5 *vs* 88.2%; $p = 0.99$).[41] Bloomquist et al reported another smaller randomized trial comparing RSL and WL (48 invasive cancer, 24 DCIS *vs* 43 invasive cancer, 16 DCIS; $p = 0.33$). They found no statistical difference in negative margin rates (80.6 *vs* 84.7%; $p = 0.53$).[44] Recently, Langhans et al performed another multicentre randomized trial comparing 194 patients with invasive breast cancer treated with RSL and 185 patients with invasive breast cancer treated with WL (22 *vs* 28 invasive lobular carcinoma; $p = 0.13$).[45] They found similar negative margin rates in RSL and WL (88.2 *vs* 86.7%; $p = 0.65$). A recent Cochrane review concluded that RSL is an equivalent alternative to WL, but the evidence was insufficient for supporting one as superior to the other.[51]

Studies have suggested that the key determinant for cosmetic outcome is the total volume of breast tissue removed.[52,53] Multiple studies comparing RSL with WL in females undergoing BCS consistently showed no difference in specimen volume or weight.[29,41,42,44,45] Sharek et al compared cosmetic outcome at 1-year follow-up and found no difference in clinical cosmesis score for patients treated with RSL *vs* WL (98.6 *vs* 97.1%; $p = 0.5$).[54] In 2014, Parvez conducted the first multicentre, randomized trial comparing cosmetic outcome between RSL and WL. They found no difference in patient self-assessment cosmesis ratings. 25 out of 33 patients (75%) in RSL group and 25 out of 31 patients (81%) in WL group rated their overall cosmesis as good or excellent ($p = 0.636$).[53]

When comparing patient satisfaction, multiple studies showed procedure convenience was rated higher in the RSL group.[29,40,44] However, data regarding patient pain perception comparing RSL and WL vary. Lovrics et al demonstrated higher pain ratings during WL ($p = 0.038$).[41] Bloomquist et al suggested similar results with fewer patients in the RSL group experiencing moderate to severe pain ($n = 8$, 12% *vs* $n = 12$, 26%; $p = 0.058$).[44] Langhans et al did not show any difference in pain perception between RSL and WL ($p = 0.28$).[45] Multiple studies reported no difference in surgical procedure time and localization procedure time comparing RSL and WL.[29,43,45] Lovrics et al suggested shorter mean operative times for RSL (RSL 19.4 *vs* WL 22.2 min; $p < 0.001$).[41]

Fung et al carried out the first RCT comparing breast cancer recurrence following RSL and WL. They compared the local recurrence rate in 146 patients who received RSL and 152 patients who received WL at 5-year follow-up. They found no statistical difference in local recurrence between two groups (2/146 in RSL *vs* 6/152 in WL; $p = 0.28$).[55] However, small sample size and low event rate were the major limitations with this study.

In summary, RSL is a safe and effective procedure for preoperative localization of non-palpable lesions. Current data on margin status, cosmesis, procedure time and recurrence rate are insufficient to judge RSL as superior to WL. Localization several days prior to surgery is a major logistic advantage. Required radioactive safety restrictions remain a significant drawback.

Non-radioactive radar localization (SAVI SCOUT localization—SSL)

In 2016 initial studies evaluated SAVI SCOUT radar localization (SSL) as an alternative localization method (Table 2).[36,56] SAVI SCOUT (Cianna Medical, Aliso Viejo, CA) is a novel technique utilizing non-radioactive micro-impulse radar technology to provide surgical guidance. The system consists of an implantable 12 mm reflector preloaded in a 16G delivery needle, a hand piece and a console (Figure 3). The reflector is U.S. Food and Drug Administration (FDA) approved for long-term implantation.[56] The reflector consists of an IR light receptor, resistor switch and two antennae which is placed into or near the target through a 16 G needle under mammographic or sonographic guidance. The handpiece and console system emit pulses of infrared (IR) light and radar wave signals, and receives signals back from the reflector to provide real-time localization and target proximity information to the surgeon.[36,56]

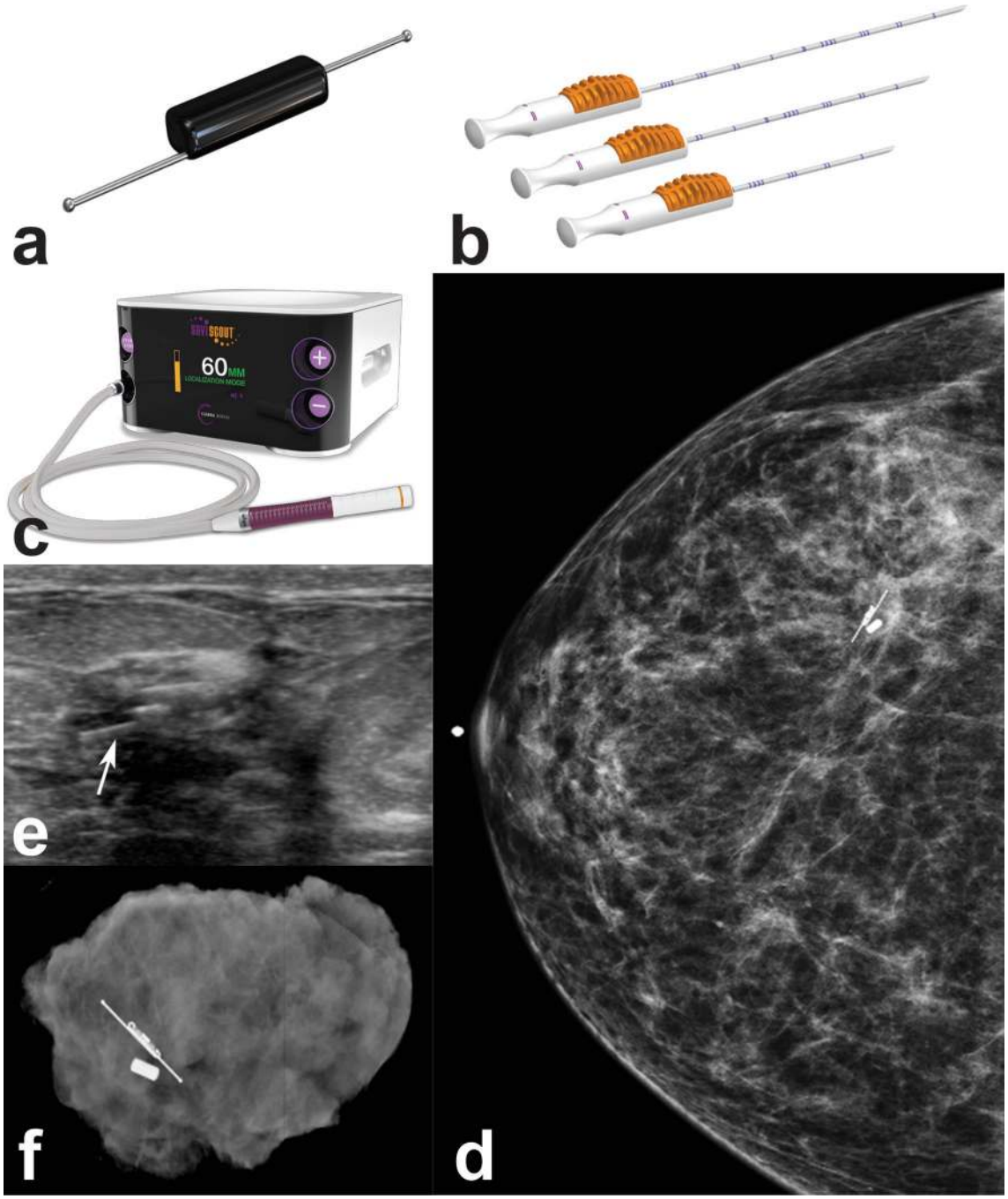
An advantage of SSL is reflector placement many prior to surgery, enabling scheduling flexibility. The lack of an external component limits possible displacement or transection. The reflector provides a point source allowing for continuous surgical reorientation and the newer generation of detector offers real time distance measurement with accuracy within 1 mm shown on the console display. Surgeons determine the ideal skin incision site which can potentially improve cosmesis. In contrast to RSL, SSL bypasses radiation safety precautions.[36,37,56,57] Additionallywith long-term implant clearance from the FDA, the reflector could potentially be placed at the time of biopsy if a lesion is highly likely to need excision, potentially skipping the preoperative localization procedure completely. This is an area of future research. Given there are no concerns about radioactive decay over time as with RSL, this could provide a unique advantage to this localization technique.

Limitations of SSL include limited repositioning once deployed which could damage the reflector and potential reflector migration, particularly in the setting of a haematoma.[56] Placement of the reflector deeper than 6 cm may interfere with detection. The reflector can only be placed with ultrasound or mammographic guidance. Although no MRI compatible needle delivery system is currently available, the reflector itself is MRI conditional and patients can be scanned safely (at 3T or less) after reflector placement with no significant surrounding MRI artefact.[56] Another potential drawback is that older technology halogen OR lights emit infrared radiation which could impact reflector detection. The reflector contains nickel and caution is recommended in patients with nickel allergy. Finally, it is substantially more expensive than WL and RSL including an initial capital purchase and disposable purchase per procedure, although at the time of this publication disposable reflector and delivery system costs are reimbursed.[37,56]

Non-controlled trials: SSL

Cox et al performed a multicentre prospective study including 154 patients who underwent SSL (52 excisional biopsies and 101

Figure 3. SAVI SCOUT surgical guidance system. (a-c, Images courtesy of Cianna Medical, Inc.) (a) Diagram of the reflector (b) Preloaded 5-, 7.5- or 10-cm 16-gauge needle. (c) Handpiece and console system. (d) Reflector deployed within the mass adjacent to the marker clip. (e) Sonographic image shows a linear echogenic reflector within the targeted mass. (f) Radiograph of the specimen demonstrates successful removal of the clip, mass and reflector. SAVI SCOUT, non-radioactive radar localization.



lumpectomies).[57] 153 out of 154 (99.4%) reflectors were successfully placed up to 7 days before surgery and all were successfully surgically excised. For 101 cases with a preoperative diagnosis of cancer, 86 out of 101 (85.1%) had clear margins and 17 out of 101 (16.8%) required reoperation for close or positive margins. Patient satisfaction was assessed. 75 out of 101 patients reported "very satisfied" and 14 out of 101 reported "somewhat satisfied" with the procedure. 97% patients would recommend SAVI SCOUT to other patients.[57]

In 2017, Mango et al reported a single institution retrospective review of 100 females who underwent preoperative localization using SSL.[37] 123 reflectors were successfully placed in 110 lesions, 0–8 days prior to surgery. 20 patients had 2–3 reflectors placed for bracketing or for localizing multiple lesions, with reflectors placed as close as 2.6 cm for bracketing. All 123 reflectors were successfully excised. 50 out of 54 (92.6%) malignant cases demonstrated negative margins and 4 out of 54 (7.4%) required re-excision. 5 out of 110 (4.5%) specimen radiographs

showed increased target-reflector distance >1 cm compared to the post-procedure mammograms, suggesting reflector migration in those cases. Three out of these five cases were associated with post-biopsy haematoma while the remaining two had no identifiable cause.[37] Migration in the setting of a haematoma is a concern for seeds and reflectors and may be prevented by placing a reflector adjacent to rather than within a haematoma when possible.

SSL VS WL

Recently Patel et al reported the first retrospective study comparing 42 patients who underwent SSL and 42 patients who underwent WL, all with a preoperative malignant diagnosis (Table 3).[46] Clinical and pathological features including mean age, tumour size, invasive cancer rate, and receptor status were matched between the two groups. They found no statistical difference in mean tumour volume (15.2 cm^3 in SSL *vs* 16.3 cm^3 in WL; $p > 0.05$), negative margin rate (92.9% in SSL *vs* 88.1% in WL; $p > 0.05$) and re-excision rate (7.1% in SSL *vs* 9.5% in WL; $p > 0.05$).[46]

Initial outcome data suggest that SSL is a safe and reliable technique to localize breast lesions preoperatively and does not require radiation safety precautions. Depth limitation and cost are potential limitations. Although it may overcome many of the limitations of other localization methods, further study of SSL is warranted.

MAGNETIC SEED LOCALIZATION

The utilization of magnetic tracers to localize occult breast lesions and concurrent SLNB was recently investigated by Ahmed et al in a feasibility study, the MagSNOLL trial.[58] 32 patients (1 patient with bilateral disease, 13 with palpable breast cancer, and 20 with non-palpable breast cancer) were enrolled in this study. Within 24 h prior to surgery, all patients received an intratumoral injection of 0.5 ml magnetic tracer containing 27 mg iron per ml (Endomagnetics, Inc., Cambridge, UK), placement of a radiopaque marker clip, followed by skin marking directly over the lesion. Patients also received the standard SLNB with radioisotope and blue dye. A handheld magnetometer (SentiMAG, Endomagnetics, Inc., Austin, TX) was used to localize the centre of lesion and confirm the peak magnetometer count corresponded to the skin marking placed. Once the lesion was excised, magnetometer counts were repeated on the excised specimen. Peak magnetometer counts were retained in all resected lesions. An intraoperative specimen radiograph confirmed the targeted lesion and marker clip were removed. Two patients with non-palpable breast cancers required re-excision due to positive margins. This study confirmed that magnetic lesion localization is feasible which led to subsequent development of Magseed (Endomagnetics, Inc., Austin, TX).[58]

Magseed is another novel alternative method to localize and excise non-palpable breast lesions which received FDA 510(k) clearance March 2016.[59] This technique uses the magnetization of a seed containing a magnetic iron alloy to localize lesions. The system consists of a stainless steel implantable seed preloaded in a 18 G needle introducer and a detector probe (Figure 4). The seed is 5 mm long, non-radioactive and approved for placement up to 30 days before surgery.[59] The seed is introduced through a sterile needle using ultrasound or mammogram guidance. The detector probe magnetizes the iron within the seed and transiently converts the seed to a magnet. The probe then detects the magnetization produced by the seed to provide real-time localization.

The advantages of MSL are similar to SSL including OR scheduling flexibility, limited possibility of displacement or transection, and no radiation safety requirements. Similar to RSL and SSL, Magseed provides a point source which enables continuous reorientation during surgery. In addition, Magseed is made of low nickel stainless steel so there is no concern for nickel allergy.

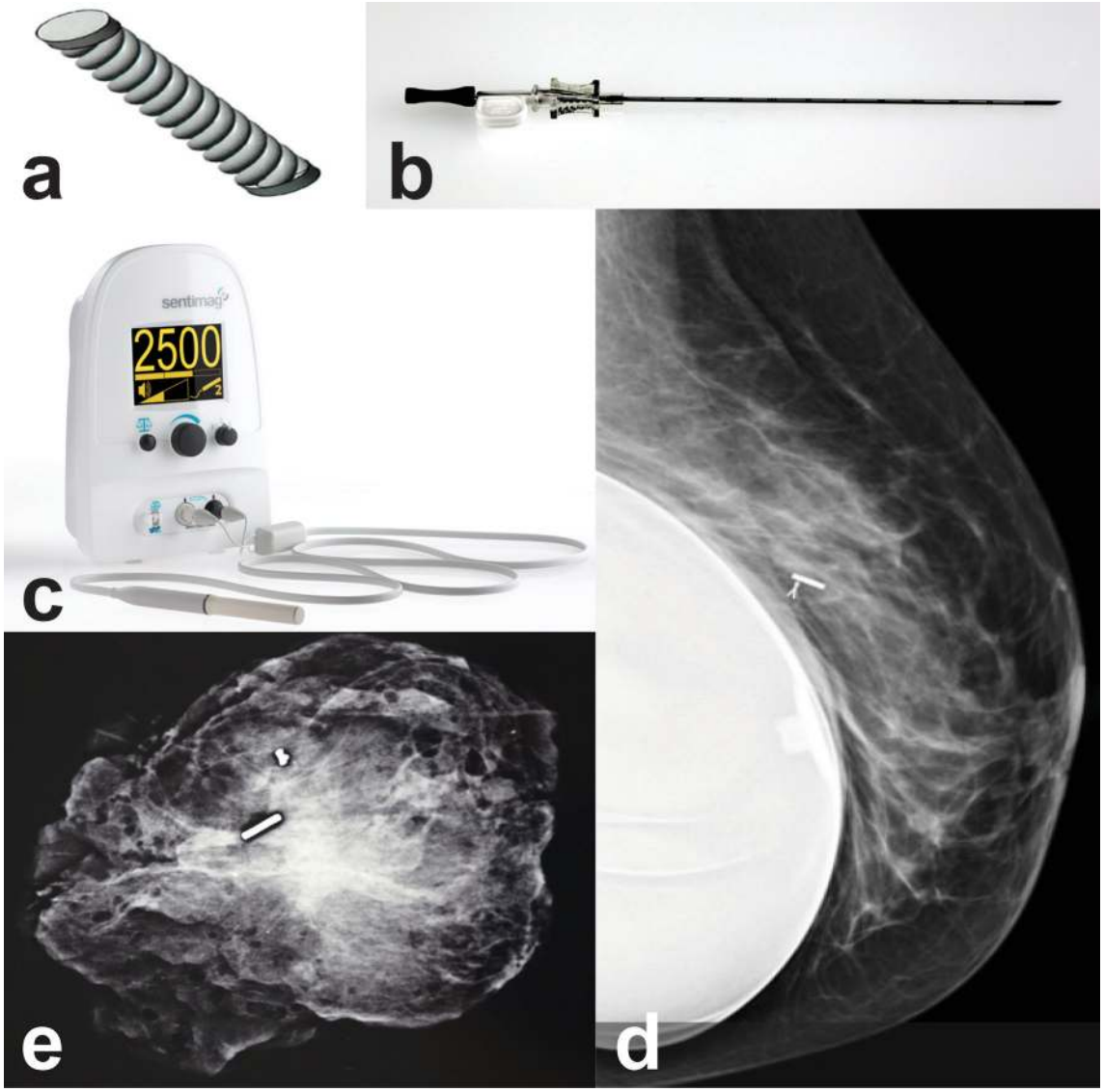
Similar to RSL and SSL, drawbacks of MSL include inability to reposition once deployed and both MSL and SSL lack an MRI compatible needle delivery system. The seed itself is MRI conditional and can be safely scanned after placement; however, the bloom artefact surrounding the seed can measure up to 4 cm depending on the MRI sequence, sequences may need to be optimized to reduce associated artefact.[59] The seed can be detected up to 4 cm away from the probe. The manufacturer reports detection of seeds up to 12 cm from the skin surface by compressing the breast tissue with the probe, to decrease distance between the seed and probe, improving detectability. The numerical count on the display also accurately indicates distance to the seed. Surgeons must use caution in the OR as magnetizable instruments must be away from the probes sensing zone while scanning, thus conversion to non-magnetic (*i.e.* titanium or polymer) surgical instruments may be necessary. Currently Magseed has no published outcome data but clinical trials are ongoing for lesion and axillary lymph node localization (NCT03020888 and NCT03038152).

While magnetic seeds are currently FDA approved for placement up to 30 days preoperatively, they do not inherently expire at 30 days and theoretically could be placed for a longer time. Manufacturers are pursuing long-term implantable status by the FDA. This could be particularly useful in patients undergoing neoadjuvant chemotherapy particularly for marking the breast or a positive axillary lymph node prior to treatment. Studies are underway in this area. This can be another potential advantage of SSL or MSL beyond scheduling efficiency.

RADIOFREQUENCY IDENTIFICATION TAGS

RFID involves percutaneous placement of a 12 mm RFID tag utilizing ultrasound or mammogram guidance up to 30 days preoperatively with information stored in the tag retrieved by a handheld reader device placed on the skin up to 6 cm away.[60] While the FDA has approved radiofrequency tag implantation in humans, FDA clearance is pending for intraoperative use of the RFID pencil probe system and clinical data for this technique are limited.[59] An initial feasibility study of 20 patients utilizing both a wire and RFID provided promising results with additional studies underway.[60] This study excluded patients with cardiac pacemakers and defibrillators as radiofrequency signals may interfere with function of these devices. Pending further clinical

Figure 4. Magnetic seed localization system. (Images courtesy of Endomagnetics, Inc.) (a) Diagram of the magnetic seed. (b) Picture of the preloaded 18-gauge delivery needle. (c) Detector probe and console. (d) Mediolateral Oblique mammogram image confirms placement of the magnetic seed adjacent to the marker clip. (e) Specimen radiograph shows a seed, clip and targeted mass.



research, RFID may provide a unique advantage in that tags can be distinguished from one another based on an identification number enabling surgeons to differentiate multiple lesions in the same breast.[59] Although a patient can safely have an MRI once the tag is in placed (MR conditional), associated 2 cm MRI artefact may limit MRI evaluation.[59]

HAEMATOMA ULTRASOUND-GUIDED LOCALIZATION

The previously described innovations can be costly and not available in low resource settings. HUG was first described in 2001 utilizing haematoma as a surrogate marker for breast lesion localization.[61] After vacuum assisted biopsy, the biopsy cavity often has a haematoma that can be sonographically visible for up to 5 weeks. On the day of surgery, mammograms are obtained to triangulate the position of the lesion within the breast. The haematoma is localized and lesion depth determined using ultrasound in the same sitting position as the mammogram and in the supine position. After making an incision over the haematoma, a block of tissue is excised by dissecting to the predetermined depth. Specimen ultrasound and mammograms are obtained to confirm excision.[47]

Unlike other techniques, HUG requires no additional procedure. In places with limited resources, this technique can be the most cost effective option compared to other localization methods. Other advantages include OR scheduling flexibility and no additional radiation exposure or safety requirements.[47] One major drawback is that some mammographic lesions are not sonographically visible. Another potential drawback of HUG is utilization within a narrow time window before haematomas reabsorb.[47]

HUG VS WL

In 2007, Thompson et al retrospectively compared 123 patients undergoing HUG and 63 patients undergoing WL. They found a significantly higher negative margin rate in the HUG group (39/58, 67.2% in HUG *vs* 5/19, 26.3% in WL; $p = 0.0001$).[47] However, only 58 out of 123 (47%) lesions were malignant lesions and microcalcification cases between HUG and WL were not matched. Arentz et al later reported another retrospective study comparing 329 HUG cases and 126 WL. In this study, the negative margin rate was higher in HUG (135/177, 76.35% in HUG group *vs* 20/38, 52.6% in WL group; $p = 0.045$), only 47% of cases (215 out of 417 cases) were malignant lesions.[48]

A limited number of studies suggest HUG may have higher negative margin rate compared to WL. Although HUG has many advantages including no additional procedure, minimal cost, and OR scheduling flexibility, there is a time limitation for surgery, many lesions may not be sonographically visible and further RCTs are warranted to determine appropriate utilization in a resource limited context.

CONCLUSION

In summary, despite numerous exciting advances in preoperative localization of non-palpable breast lesions no one perfect localization method exists. Wires are often placed the day of surgery and may move/be transected but can be utilized at any depth, may be slightly repositioned once deployed, are sometimes better in the setting of haematomas and can be placed under MR guidance. Non-wire alternatives can be placed prior to the day of surgery offering unique scheduling advantages but cannot be placed under MR guidance, cannot be repositioned once deployed and may migrate in the setting of a post-biopsy haematoma. Specific limitations of non-wire alternatives such as need for radiation safety precautions/exposure (RSL), need for non-magnetizable surgical instruments (MSL), associated MR artefact (MSL and RFID), potential depth limitations and increased cost must be weighed carefully. FDA approval for long-term implantation enables future research directions to involve placing a localizer instead of a clip at the time of biopsy in a lesion highly suspicious for cancer thus potentially foregoing a separate localization procedure altogether. Associated MRI artefact may become increasingly important in this setting as patients may subsequently undergo MR to evaluate extent of disease or neoadjuvant chemotherapy response.

Ongoing technological developments, clinical outcomes research and regulatory decisions will provide more information as radiologists and surgeons assess which method is best for patients in their particular clinical setting.

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