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ORIGINAL ARTICLE

Randomized controlled trial comparing magnetic marker localization (MaMaLoc) with wire-guided localization in the treatment of early-stage breast cancer

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Abstract

Wire-guided localization (WGL) is the standard of care in the surgical treatment of nonpalpable breast tumors. In this study, we compare the use of a new magnetic marker localization (MaMaLoc) technique to WGL in the treatment of early-stage breast cancer patients. Open-label, single-center, randomized controlled trial comparing MaMaLoc (intervention) to WGL (control) in women with early-stage breast cancer. Primary outcome was surgical usability measured using the System Usability Scale (SUS, 0–100 score). Secondary outcomes were patient reported, clinical, and pathological outcomes such as retrieval rate, operative time, resected specimen weight, margin status, and reoperation rate. Thirty-two patients were analyzed in the MaMaLoc group and 35 in the WGL group. Patient and tumor characteristics were comparable between groups. No in situ complications occurred. Retrieval rate was 100% in both groups. Surgical usability was higher for MaMaLoc: 70.2 ± 8.9 vs. 58.1 ± 9.1, $p < 0.001$. Patients reported higher overall satisfaction with MaMaLoc (median score 5/5) versus WGL (score 4/5), $p < 0.001$. The use of magnetic marker localization (MaMaLoc) for early-stage breast cancer is effective and has higher surgical usability than standard WGL.

KEYWORDS
breast carcinoma, magnetism, nonradioactive, patient satisfaction, surgery, surgical usability, trial registration, tumor localization

1 | INTRODUCTION

Breast cancer screening programs increasingly detect tumors at an early stage.[1,2] For these tumors, breast-conserving surgery(BCS) with adjuvant radiotherapy is equivalent to mastectomy in terms of local control and overall survival.[3,4] BCS aims at complete tumor removal, while limiting the resected volume, which is associated with a good cosmetic outcome.[5-8] Therefore, accurate localization of these small and often nonpalpable lesions is standard of care to guide the surgeon during surgery.

Gerson M. Struik and Bram Schermers contributed equally to this work.

The trial was prospectively registered in October 2017 at the Netherlands Trial Register (NL6553).

Since the 1970s, wire-guided localization (WGL) has been the standard tumor localization technique.[9,10] In WGL, a metal anchor wire is placed within or near the tumor, under radiologic guidance. Typically, the procedure takes place on the day of surgery. During surgery, the wire guides the surgeon to excise the tissue surrounding the wire tip. Although widely used, WGL has several disadvantages, of which the most reported are (1) patient distress and discomfort from the protruding wire; (2) interference with the ideal surgical approach; and (3) limited scheduling flexibility.[11,12]

Alternative localization techniques have been developed to overcome the disadvantages of WGL. In radioactive seed localization (RSL), a 4.5 × 0.8 mm Iodine-125 seed is implanted in or near the lesion and an intraoperative gamma probe is used for guidance. This technique has gained 40% adoption in the Netherlands.[13] Advantages of RSL compared to WGL are (1) real-time three-dimensional guidance toward the lesion[14]; (2) logisticflexibility[15,16]; and (3) improved patient satisfaction.[17] In 2015, a Cochrane review concluded that RSL could be offered as an alternative to WGL.[12]

Unfortunately, RSL is associated with considerable challenges as well. Governmental regulations on radiation safety require strict management of the chain of custody of each individual seed, which leads to high operational burden. Consequently, the adoption of RSL outside the Netherlands is low, and to our knowledge, WGL is still the standard of care internationally.

Magnetic marker localization (MaMaLoc) was proposed by the Netherlands Cancer Institute (Amsterdam, the Netherlands) as an alternative to RSL.[18,19] Similar to RSL, a magnetic marker is implanted in or near the lesion and a clinical magnetic detector is used for intraoperative guidance. Its proposed advantage would be to provide the similar benefits as RSL, but without the use of radioactivity. Although interference with the surgical approach is mentioned as a drawback of WGL,[20] surgical usability has never been compared between WGL and any of the new techniques.

The objective of the current study was to compare MaMaLoc with the standard of WGL in the treatment of early-stage breast cancer. The primary outcome was surgical usability. Secondarily, clinical, pathological, and patient-reported outcomes were explored for both techniques. It was hypothesized that MaMaLoc has a higher surgical usability and better patient-reported outcomes than WGL, while clinical outcomes are expected to be comparable.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This study was an open-label, parallel-group randomized controlled trial, comparing MaMaLocto WGL. All study procedures were performed in a single large secondary teaching hospital. The study protocol was approved by the regional research ethics committee[1] and registered at the Netherlands Trial Register[2]. The study was conducted according to the principles of the Declaration of Helsinki (version 10, October 2013).

The study methodologist prepared 72 opaque sealed envelopes that allocated patients in a 1:1 ratio to either the MaMaLoc group (interventional) or the WGL group (control). Random group allocation was performed by an independent nurse by opening an envelope.

Eligible patients included women aged 18 years or above with a unifocal breast lesion (either invasive carcinoma, carcinoma in situ, or high suspicion of malignancy) that were indicated for BCS. Patients were excluded if an MRI was planned between marker placement and surgery, if the lesion was ultrasound occult or in case of a pregnancy. Palpability was not an exclusion criterium, as in this clinic preoperative tumor localization is standard procedure for both palpable and nonpalpable breast lesions.

2.2 | Intervention

2.2.1 | Localization

Patients allocated to the control group received standard ultrasound-guidedhook-wire localization(Duo-System, 20G needle, Somatex, Berlin, Germany) without local anesthesia at maximum one day before surgery. Due to practice variation, 5%–10% of patients nevertheless received local anesthesia in this group.

Patients allocated to the experimental group received ultrasound-guided placement of the MaMaLoc marker(1.6 × 3.5 mm, provided by the Netherlands Cancer Institute, Amsterdam, NL, Figure 1A) at a maximum of 30 days before surgery using a custom 14G needle. After application of local anesthesia, which is standard protocol in our institution when using a large bore needle, the marker was placed. Due to practice variation, 25% of patients nevertheless received no local anesthesia in this group.

Localization procedures were performed by 6 experienced senior breast radiologists (caseload >50 per year). The distance from skin to the center of the lesion was recorded from ultrasound images. A two-way mammography was obtained to confirm correct placement of wire tip or marker (Figure 1B).

2.2.2 | Surgery

Surgical procedures were performed by two senior surgeons having experience in WGL (case load>50 per year) but not with MaMaLoc or other marker-based localization techniques. A MaMaLoc specific training, including a short introduction of the use of the Sentimag system and a simulated surgery on a phantom, was followed twice by each surgeon before start of the trial.

Patients allocated to the control group received standard of care which was wire-guided lumpectomy. Patients allocated to the experimental group received lumpectomy guided by a commercially available magnetic detector (Endomag Sentimag, Cambridge, UK). This system functions as a magnetic proximity sensing system with a reported detection range of approximately 30mm that displays a count value and provides audible feedback for the user.[18] The detector was used several

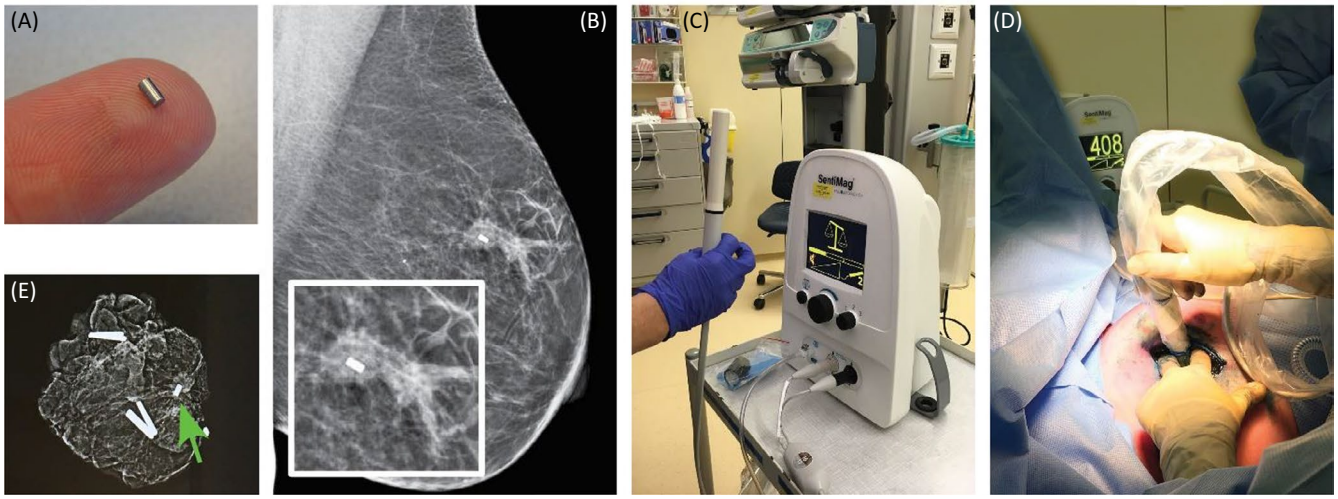


FIGURE 1 Procedural overview for patient allocated to the MaMaLoc group. A: MaMaLoc Marker on finger. B: Mammography after implantation of MaMaLoc marker (inset: zoom of lesion with marker). C: Calibrating the Sentimag prior to use. D: Detecting the MaMaLoc marker during surgery. E: Postoperative specimen x-ray with MaMaLoc in situ (green arrow). In this case, additional vascular clips were used for 3D orientation of the specimen

times during the procedure to guide the dissection (Figure 1C-D). Due to interference from metal surgical instruments, polymer instruments were available(SUSI, B. Braun Aesculap, Tuttlingen, Germany).

Successful retrieval (wire or marker confirmed in the specimen and no fallback technique needed) and operative time (time from first skin incision to skin closure) were recorded. All specimens were sent for x-ray imaging directly after surgery (Figure 1E). Intraoperative re-excision of additional cavity margins was allowed at the surgeon's discretion if macroscopic evaluation, the magnetic signal, and/or the specimen x-ray suggested that the resection was incomplete. All tissue was then transferred to the pathology department and the wound was closed.

2.3 | Outcomes

The primary outcome of this study was surgical usability as measured using the System Usability Scale (SUS)after each procedure (see Appendix A). This 10-item, 5-point scale is converted into a single score between 0 and 100. It is a simple and valid tool to measure and directly compare usability of new technology or products,[21,22] even in small sample sizes,[23,24] and has been used in medical research before.[25,26] A SUS score ≥68 is widely recognized as usability being above-average.[21,23,27] This binary outcome is analyzed as secondary outcome measure.

Additionally, surgeons were requested to complete a tumor localization specific questionnaire after each procedure (see Appendix B); were asked if they would have preferred WGL or MaMaLoc for that patient; and were invited to provide qualitative remarks using a retrospective think aloud (RTA) method.

Secondarily, radiologists scored the usability of the technique on the same SUS per procedure (Appendix A). Patient pain scores prior to, during and in the period between implantation and surgery (if applicable) were recorded using a visual analog scale (VAS, Appendix C). Patient satisfaction with the implantation procedure and the overall satisfaction with the localization technique were recorded (Appendix C).

Pathology assessment included recording of weight, maximum tumor diameter and estimated volume(using the mathematical formula of an ellipsoid[28]) of the resected specimen. Tumor grade, dominant tumor histology, and presence of extensive intraductal component were recorded.[29-31]

Margin status was scored as the most unfavorable margin of invasive cancer and/or DCIS component, defined as (1) free, with minimal margin ≥2 mm; (2) close, with minimal margin <2 mm; (3) focally positive margin (< 4mm cumulative positive margin); or 4) more than focally positive margin.[32] Re-operation was defined as a separate surgical procedure where breast tissue was excised to remove a close or positive margin in the same breast within 3 months of primary surgery.

2.4 | Sample size and statistical analysis

In literature, no data are available on SUS scores of breast tumor localization techniques. In quality of life and utility research, 5% is commonly considered as a minimal important (absolute) difference.[33,34] We opted for a more conservative approach and determined a 10-point mean absolute difference on the surgical SUS score to be clinically relevant. Based on this expected mean difference with a standard deviation (SD) of 5, we would be able to estimate a mean difference in SUS score of 10 within a 95% confidence interval (CI) of [8.83–11.17] using a sample size of 70 (35 in each group). This CI was deemed acceptable.

Statistical analysis was performed according to the intention-to-treat principle. Numbers of missing data were small and not imputed.

Descriptive statistics are reported for baseline characteristics. Differences in the primary and secondary outcome measures between the study groups were analyzed with the Fisher exact or chi-squared test for nominal/ordinal variables; independent Student's *t* test for continuous variables with normal distributions; and the nonparametric Mann-Whitney U test for continuous variables with skewed distributions.

A *p*-value <0.05 (two-sided) was considered to be significant for the primary outcome. For the secondary outcomes, Bonferroni correction for multiple testing (n = 10) was applied; an adjusted *p*-value of <0.005 was considered significant. Statistical analyses were performed using IBM-SPSS version 24 (IBM Corporation).

3 | RESULTS

Between October 2017 and December 2018, 70 patients were included, 34 in the MaMaLoc group and 36 in the WGL group (Figure 2). Two patients were excluded in the intervention group and one in the control group after randomization but before any study procedure was performed (Figure 2). There was no loss to follow-up, resulting in 67 patients being analyzed. We were not able to continue inclusion up to the planned sample size in the intervention group as threeof the supplied markers became unsterile during the aseptic preparation of the localization procedure. Inclusion was stopped when no markers were left. Therefore, all randomized patients received the allocated treatment in both groups, and protocol compliance was 100%.

Table 1 shows the patient and tumor characteristics, which were all comparable between groups. Also, tumor characteristics that may specifically influence the surgical usability of the localization technique (such as tumor depth, microscopic tumor diameter, and palpability) and factors known to impact the risk of positive surgical margins (tumor grade, histology, and intraductal component) were comparable.

Median tumor depth was comparable: 16.0 mm (range 7–26) in the WGL group and 13.5 mm (range 7–30) in the MaMaLoc group, $p = 0.102$, Table 2. Slightly more subjects in the WGL group had lobular carcinoma (4 cases; 11%) than in the MaMaLoc group (1 case, 3%), although this difference was not significant ($p = 0.054$). Most patients underwent a lumpectomy with sentinel node procedure in both groups (89% of WGL and 69% of MaMaLoc procedures).

Table 2 includes the primary outcome of this study. The mean SUS-score was significantly higher for MaMaLoc (70.2 ± 8.9) than for WGL (58.1 ± 9.1), $p < 0.001$. In the MaMaLoc group, 56% of cases showed above-average usability (SUS score>68), as opposed to only 9% in the WGL group, $p < 0.001$. Radiological usability was very high for both WGL (median SUS score of 100) and MaMaLoc (median SUS score of 97.5), $p = 0.036$ (Table 2).

Patients reported significantly less pain during implantation of a MaMaLoc marker (median VAS score =1.5) than a wire (median VAS=3), $p = 0.005$, Table 2. Four patients reported pain after the wire implantation procedure and one after the MaMaLoc marker implantation. Patients were comparably satisfied with the implantation procedure. Overall satisfaction with the localization technique was rated significantly better for MaMaLoc (median score 5 of 5) than for WGL (4 of 5), $p = 0.001$, Table 2.

Figure 3 depicts additional surgical satisfaction scores measured using a procedure-specific questionnaire. There was a significant difference in favor of MaMaLoc for all procedure-specific surgical usability questions, except for questions 5and 7. Additionally, surgeons would have preferred the MaMaLoc technique in 34/61 (56%)

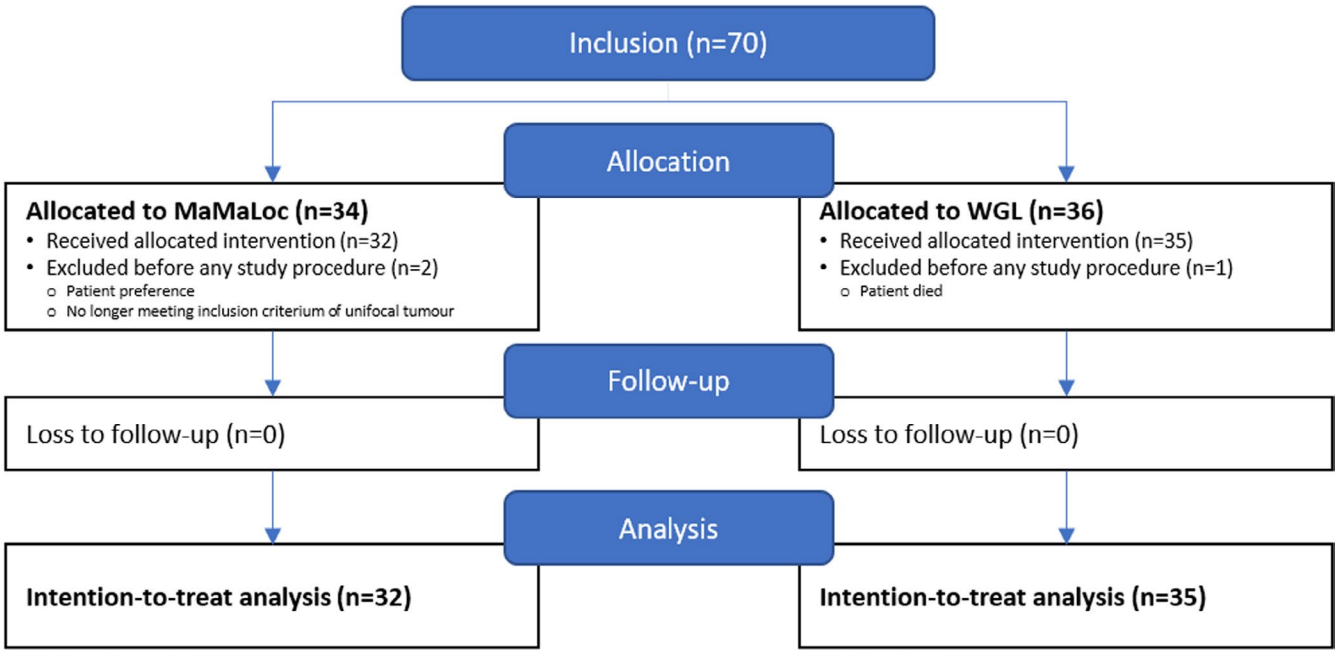


FIGURE 2 Patient inclusion flow

TABLE 1 Patient and tumor characteristics

	Control (WGL) n = 35	Intervention (MaMaLoc) n = 32	*p*-value
Patient			
Age (years; mean ±SD)	64.9 ± 9.2	65.5 ± 9.7	0.925
BMI (kg/m2; median (IQR))	26.5 (24.6–31.4)	27.4 (23.7–31.8)	0.543
Tumor laterality (n, %)			
Left	15 (43%)	17 (53%)	0.401
Right	20 (57%)	15 (47%)	
Previous ipsilateral breast surgery (n, %)	3 (9%)	3 (9%)	>0.999
Neo-adjuvant chemotherapy (n, %)	1 (3%)	2 (6%)	0.603
Screening detected tumors (n, %)	25 (71%)	23 (72%)	0.968
Tumor (Clinical)			
Palpable (n, %)			
No	16 (46%)	15 (47%)	0.994
Uncertain	11 (31%)	10 (31%)	
Yes	8 (23%)	7 (22%)	
Tumor depth (mm; median (range))	16.0 (7–26)	13.5 (7–30)	0.102
Type of surgical procedure (n, %)			
Lumpectomy only	1 (3%)	6 (19%)	0.076
Lumpectomy +SLNB	31 (89%)	22 (69%)	
Lumpectomy +ALND	2 (6%)	1 (3%)	
Lumpectomy +oncoplastic procedure +SLNB	1 (3%)	3 (9%)	
Tumor (Pathology)			
Receptor status (n, %)[a]			
ER+	30 (94%)	23 (77%)	0.077
PR+	27 (84%)	21 (70%)	0.176
Her2-neu+	0	2 (7%)	0.230
Invasive tumor grade (Bloom-Richardson; n,%)[b]			
1	15 (43%)	10 (33%)	0.672
2	12 (34%)	14 (47%)	
3	8 (23%)	6 (20%)	
Tumor diameter (mm; median (range))	14.0 (1–40)	14.0 (4–35)	0.989
Postoperative tumor histology (n, %)			
Ductal carcinoma	26 (74%)	24 (75%)	0.054
Lobular carcinoma	4 (11%)	1 (3%)	
Pure DCIS	3 (9%)	0	
Other malignant	1 (3%)	3 (9%)	
Complete response after NAC	1 (3%)	2 (6%)	
Benign	0	2 (6%)	
Extensive intraductal component (n, %)[a]	7 (23%)	2 (7%)	0.150

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index; DCIS, ductal carcinoma in situ; ER+, estrogen receptor positive; NAC, Neo-adjuvant chemotherapy; PR+, progesterone receptor positive; SLNB, sentinel lymph node biopsy.

[a]For invasive tumors only.

[b]Only available for malignant tumors.

cases. There was no preference in 23/61 (38%) cases, and WGL was preferred in only 4/61 (7%) of cases, $p < 0.001$.

Based on the RTA data, surgeons reported that freedom of surgical skin incision and dissection was the main advantage of the MaMaLoc technique. Main reported disadvantages of the MaMaLoc technique were (1) relatively large diameter of the Sentimag probe; (2) incompatibility with standard surgical instruments; and (3) poor directional sensitivity.

TABLE 2 Surgeon and radiologist satisfaction measured on the system usability scale and patient satisfaction and pain scores

	Control (WGL) n = 35	Intervention (MaMaLoc) n = 32	*p*-value
Surgery			
SUS-score (0–100; mean ±SD)	58.1 ± 9.1	70.2 ± 8.9	**<0.001**
Above-average SUS score (>68; n, %)	3 (9%)	18 (56%)	**<0.001**
Radiology			
SUS-score (0–100; median (IQR))	100 (97.5–100)	97.5 (93.1–100)	0.036
Patient pain			
Score before implantation[a] (0–10, median (IQR))	0 (0–1)	0 (0–0.75)	
Score during implantation[a] (0–10, median (IQR))	3 (1.5–4.0)	1 (0–3.0)	**0.005**
Any pain experienced in period between implantation and surgery[b]			
Yes(n (%))	4/24 (17%)	1/23 (4%)	
Maximum pain score (0–10, median (IQR))	7 (4.5–8.0)	3 (3.0–3.0)	
Time after implantation (hours, median(IQR))	3.5 (2.3–8.5)	2 (2.0–2.0)	
No (n (%))	20/24 (83%)	22/23 (96%)	
Patient satisfaction			
With implantation procedure (1–5, median (IQR))	4 (4–4); *satisfied*	4 (4–5); *satisfied*	0.032
Overall (1–5, median (IQR))	4 (3–4.75); *satisfied*	5 (4–5) *very satisfied*	**0.001**

[a]Data missing in 7 WGL patients.

[b]Data missing in 11 WGL patients and 9 MaMaLoc patients.

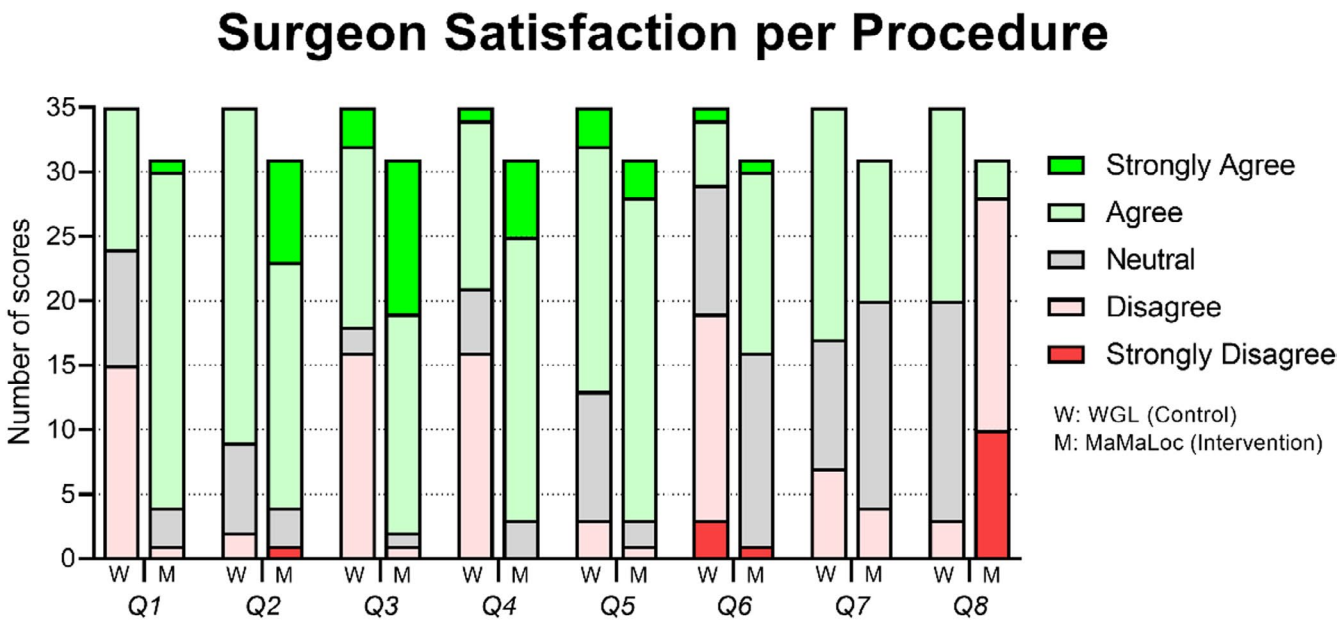
Table 3 shows surgical and pathological outcomes. The median time in situ was 10.5 days for the MaMaLoc marker and 1 day for the wire. No in situ complications occurred in both groups, and postoperative complication rates were comparably low and all ClavienDindo grade 1. Successful retrieval was achieved in all cases in this study. An intraoperative re-excision of additional cavity margins was performed in 11/35of WGL cases (31%) and 8/32 of MaMaLoccases (25%), $p = 0.560$. Median resected specimen weight and volumes were comparable between groups.

More patients had positive margins in the WGL group (6/34 (18%)) than in the MaMaLoc group (2/28 (8%)) and negative margins were more often close (<2 mm) with WGL (13/28 (46%)) than with MaMaLoc (4/26 (15%)). However, after correction for multiple testing, there was no significant difference in margin status between both groups ($p = 0.017$). One patient in the MaMaLoc group and two patients in the WGL group required a re-operation.

4 | DISCUSSION

In this paper, we report the results of a randomized controlled trial comparing magnetic marker localization (MaMaLoc) with wire-guided localization in the surgical treatment of early-stage breast cancer. This study demonstrates that the surgical usability is scored significantly higher for MaMaLoc (SUS score of 70) than for WGL (SUS score of 58), $p < 0.001$. Additionally, in retrospect, surgeons would have preferred MaMaLoc in 56% of procedures, while WGL was the preferred method in only 7% of cases ($p < 0.001$).

This was a single-center study performed by a selected team of surgeons without prior experience with any marker-based localization technique. The study population was representative for the general breast cancer population and randomization resulted in comparable groups (Table 1). Depth of tumors was comparable between groups and all within the 30 mm limits of detection of the magnetic technique.



	P-Value
Q1. This localization technique is intuitive to use	< 0.001
Q2. The marker or wire was easy to identify	0.002
Q3. This localization technique gives me the freedom to choose the location of skin incision	< 0.001
Q4. This localization technique gives me the freedom to choose my surgical approach	< 0.001
Q5. I am confident that this localization technique leads me to the correct location	0.064
Q6. The localization technique allowed me to choose exactly the size of my resection	< 0.001
Q7. The localization technique influenced the size of my resection	0.167
Q8. I think this localization technique is uncomfortable for the patient	< 0.001

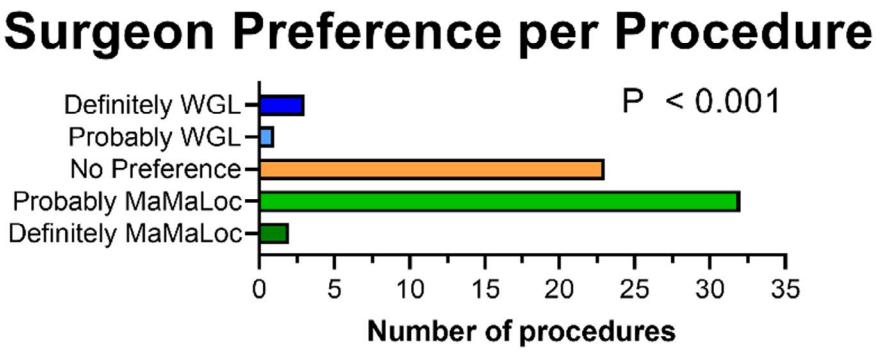


FIGURE 3 Surgeon satisfaction measured using a procedure-specific questionnaire and surgeon preferenceper procedure

Better surgical usability for MaMaLoc was further confirmed using a procedure-specific questionnaire, in which MaMaLoc scored significantly higher than WGL in on all but two questions, including intuitiveness and allowing freedom of surgical incision approach. In question 5, surgeons were more often confident that the technique led to the correct location with MaMaLoc (28/31 = 90%) than with WGL (22/35 = 63%), but not significantly. Question 7 on resection size was deemed ambiguous, as it could both mean an increased or decreased size of the resection, and therefore, it probably did not detect a difference between techniques.

Several secondary clinical outcome parameters were explored. Median resected specimen weight and volume were not different between the MaMaLoc group (36 g and 39.5cc) and the WGL group (39 gram and 42.9cc). In contrast, comparable studies found slightly higher resected specimen weight[16,35] and volume[15,35] in an RSL

TABLE 3 Surgical and pathological outcomes

	Control (WGL) n=35	Intervention (MaMaLoc) n=32	*p*-value
Time marker or wire in situ (days; median (IQR))	1 (0–1)	10.5 (5–19)	
Any in situ complications	0	0	
Operative time[a] (minutes; mean ±SD)	53 ± 18	54 ± 14	0.942
Successful retrieval of marker/wire (n,%)	35/35 (100%)	32/32 (100%)	
Intra-operative re-excision (n,%)	11/35 (31%)	8/32 (25%)	0.560
Postoperative complications (n,%)			
SSI	0	1/32 (3%)	
Seroma	1/35 (3%)	2/32 (6%)	
Hematoma	2/35 (6%)	1/32 (3%)	
Specimen weight (g; median (IQR))	39 (30–50.5)	36 (29.0–47.4)	0.744
Specimen volume[b] cc; median (IQR)	42.9 (33.1–64.7)	39.5 (30.5–61.5)	0.605
Margin status[c] (n, %)	n = 34	n = 28	0.021
Negative, minimal margin ≥2 mm	15/34 (44%)	22/28 (79%)	
Close, minimal margin <2 mm	13/34 (38%)	4/28 (14%)	
Positive, focally	6/34 (18%)	1/28 (4%)	
Positive, more than focally	0	1/28 (4%)	
Re-operation[c] (N, %)	2/34 (6%)	1/28 (4%)	

[a]Calculated for lumpectomy+SLNB procedures only, for comparison.
[b]Calculated as ellipsoid: $4/3\pi$ (0.5 × length × 0.5 × width × 0.5 × height).
[c]Benign tumors and complete response after NAC excluded.

group than in a WGL group. Overall, our results suggest that clinical and pathological are comparable.

Interestingly, we found fewer positive or close margins in the MaMaLoc group when compared to WGL; however, the study was not powered to show a difference on this variable. This difference might be biased by underlying differences in tumor characteristics (eg, more lobular carcinoma in WGL group). In contrast to DCIS, in current SSO/ASTRO consensus guidelines on margins in BCS for invasive cancer, there is no distinction between negative and close margins. Nevertheless, these findings do warrant further exploration in an adequately powered study, as in some countries the presence of close margins may result in reoperation or an extra radiation dose, with consequent patient burden and cosmetic deterioration.[36-38]

Strengths of this study include the random comparison of the investigational technology with the standard of care; its adequate powering to hypothesized benefits (surgical preference, rather than clinical outcome) and the collection of a broad range of variables that are potentially related to the localization technology used. Also, the population is representative for an early-stage breast cancer population, there was no loss to follow-up, and protocol compliance was 100%.

Several limitations of this study merit discussion. First, only 35 MaMaLoc markers were supplied to the investigatory team, of which three became unsterile during unpacking and aseptic preparation of the implantation needle. This was a consequence of the specific packaging of these markers within the clinical investigation. Therefore, we were unable to complete inclusion in the investigational group up to the planned 35 patients. However, as all randomized patients received the allocated treatment in both groups, this did not result in bias. Furthermore, post hoc analysis showed that the statistical power was sufficient (>0.9) with the obtained study numbers.

Second, we found that patients reported significantly less pain during implantation using MaMaLoc, even though the needle size is considerably larger. This result is probably biased, as the use of local anesthesia differed between groups. However, this does indicate that it would be interesting to formally assess the value of local anesthesia for WGL as this may lead to improved patient experience.

For future research, we recommend performing an analysis of the logistic and cost benefit of implementing a marker-based technique compared to WGL. We also recommend a larger randomized trial that is powered to detect a difference on one or more of our secondary parameters, such as positive margin rates and resected specimen volumes. This is important as these factors have direct impact on surgical morbidity and cosmetic outcome.

5 | CONCLUSION

Our findings support the hypothesis that MaMaLoc has a higher surgical usability and better patient-reported outcomes than WGL with comparable clinical outcomes. This indicates that MaMaLoc may be

a valuable nonradioactive alternative to replace WGL in the treatment of early-stage breast cancer.

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ENDNOTES

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APPENDIX A

	Strongly disagree	disagree	neutral	agree	Strongly agree
1. I think that I would like to use this localization technique frequently	1	2	3	4	5
2. I found the localization technique unnecessarily complex	1	2	3	4	5
3. I thought the localization technique was easy to use	1	2	3	4	5
4. I think that I would need the support of a technical person to be able to use this localization technique	1	2	3	4	5
5. I found the various functions in this localization technique were well integrated	1	2	3	4	5
6. I thought there was too much inconsistency in this localization technique	1	2	3	4	5
7. I would imagine that most people would learn to use this localization technique very quickly	1	2	3	4	5
8. I found the localization technique very cumbersome to use	1	2	3	4	5
9. I felt very confident using the localization technique	1	2	3	4	5
10. I needed to learn a lot of things before I could get going with this localization technique	1	2	3	4	5

APPENDIX B

	Strongly disagree	disagree	neutral	agree	Strongly agree	N/A
1. This localization technique is intuitive to use						
	1	*2*	*3*	*4*	*5*	
2. The marker or wire was easy to identify						
	1	*2*	*3*	*4*	*5*	
3. This localization technique gives me the freedom to choose the location of skin incision						
	1	*2*	*3*	*4*	*5*	
4. This localization technique gives me the freedom to choose my surgical approach						
	1	*2*	*3*	*4*	*5*	
5. I am confident that this localization technique leads me to the correct location						
	1	*2*	*3*	*4*	*5*	
6. The localization technique allowed me to choose exactly the size of my resection						
	1	*2*	*3*	*4*	*5*	
7. The localization technique influenced the size of my resection						
	1	*2*	*3*	*4*	*5*	
8. I think this localization technique is uncomfortable for the patient						
	1	*2*	*3*	*4*	*5*	

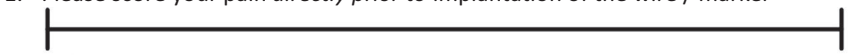
	Definitely MaMaLoc	Probably MaMaLoc	No preference	Probably WGL	Definitely WGL	**N/A**
1.When I compare MaMaLoc with WGL, I would choose in this patient						
	1	*2*	*3*	*4*	*5*	

Retrospective Think Aloud (RTA)

Retrace your steps during the past procedure, focus on the localization technology that was used. Note what characteristics or features struck you? What were positive points and what were negative points. What was inherent to the technology, and can be overcome by using the technology more. Be concise, but complete.

APPENDIX C

1. Please score your pain *directly prior to* implantation of the wire / marker



No pain at all — Worst possible pain

Instruction: Provide the score by drawing a vertical line or cross on the line, between both ends, at the position that reflects your pain as best as possible. Note: fill in before placement of wire / marker.

Date:

2. Please score your pain *during* implantation of the wire / marker

No pain at all — Worst possible pain

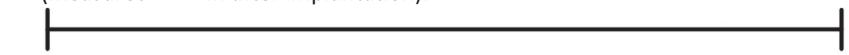
Instruction: Provide the score by drawing a vertical line or cross on the line, between both ends, at the position that reflects your pain as best as possible. Note: fill in after placement of wire / marker.

Date:

3. Please score your satisfaction *with regards to the implantation procedure* (measured after implantation).

1. very dissatisfied	2. dissatisfied	3. not satisfied / not dissatisfied	4. satisfied	5. very satisfied

4. Please score your pain *in the period after the implantation procedure up until now* (measured 12-24h after implantation).



No pain at all — Worst possible pain

Instruction: Provide the score by drawing a vertical line or cross on the line, between both ends, at the position that reflects your pain as best as possible.

Date:

5. Please score your pain *in the period after the implantation procedure up until now* (measured prior to surgery).

No pain at all — Worst possible pain

Instruction: Provide the score by drawing a vertical line or cross on the line, between both ends, at the position that reflects your pain as best as possible.

Date:

6. Please score your overall satisfaction *with regards to the used localization technology* please (measured after surgery)

1. very dissatisfied	2. dissatisfied	3. not satisfied / not dissatisfied	4. satisfied	5. very satisfied

7. To improve our care, we would like to learn more about your experience with the localization technology. Please write down your positive and negative associations and experiences (measured after surgery).

positive	• ..... • ..... • ..... • ..... • .....
negative	• ..... • ..... • ..... • ..... • .....