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Evaluation of a Wireless Localization System for Nonpalpable Breast Lesions — Feasibility and Cost-effectiveness in Everyday Clinical Routine

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Abstract. *Background/Aim: Smaller, earlier-stage breast tumors are being found in breast cancer screening, and neoadjuvant chemotherapy is the gold standard when chemotherapy is indicated. Precise marking and localization of the tumor are thus becoming increasingly important. Wire-free localization techniques are under investigation in order to reduce presurgical radiography, pain, the risk of wire dislocation, and allow scheduling flexibility for patients and surgery departments. Patients and Methods: This single-center observational study from June 2020 to October 2021 included 15 patients with mammographically or sonographically detected nonpalpable breast lesions. Radiofrequency identification (RFID) tags were placed preoperatively under ultrasound or radiologic guidance to localize lesions for planned surgery. All patients underwent breast conservation surgery, including one bilateral and one targeted axillary dissection. Results: Histology identified two benign and 13 malignant lesions, including three ductal carcinomas in situ and 11 invasive breast cancers. Placement, control radiography, and handling of the RFID tag were feasible in everyday routine for different radiologists and surgeons and managed cost-effectively. All of the RFID tags were found in the specimen radiographs. Conclusion: The feasibility and cost-effectiveness of this non-wire localization method were demonstrated in this rather small cohort of patients. Further studies including larger numbers of patients are needed to confirm the method's accuracy.*

Breast cancer (BC) is the most common type of cancer found in women and the most common cause of death in women between the ages of 35 and 55 years. In Germany, approximately 70,000 women are diagnosed with BC annually (1). In addition to surgery, every BC patient requires systemic therapy to some extent. Tumor size, histology, and biomarkers are the most important factors that influence the therapy strategy in BC (2, 3). The inclusion of mammography in screening procedures in order to achieve earlier detection of BC and thereby reduce the mortality rate has been one of the main strategies in recent years, and screening mammography is now included in recent local guidelines in Germany (4, 5).

International BC guidelines recommend preoperative confirmation of suspicious lesions (2). In addition, nonpalpable breast lesions should be marked before surgery (2, 6, 7).

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Most BC guidelines recommend chemotherapy in a neoadjuvant setting, if chemotherapy is indicated (2, 8-10), due to its effectiveness and impact on the long-term survival of BC patients (11, 12). In addition, the effectiveness of these treatments is improving through new drugs. An increase in the rate of pathological complete remissions (pCR) has been achieved with the help of these novel therapies (13). Along with the increase in pCR rates, problems are arising more frequently with the marking and identification of lesions for radiologists, surgeons, and pathologists. Localizing a lesion that has disappeared from view in order to carry out definitive breast surgery is one of the most challenging problems. Several studies have been published on the use of marker clips, demonstrating the feasibility of this method during neoadjuvant treatment and for preoperative localization of breast lesions (14-17). In addition, less radical approaches to axillary breast surgery are now being adopted. Methods of detecting lymph nodes more easily have been investigated and implemented in everyday clinical routine work — for example, with targeted axillary dissection (TAD). Studies have also validated TAD techniques for reducing the radicality of surgical approaches after neoadjuvant chemotherapy, with higher success rates than sentinel lymph-node biopsy (SLNB). Reports in the literature show that clipped lymph-node biopsy can detect sentinel lymph nodes in 95.65% of cases, in comparison with 80.16% with standard sentinel lymph-node dissection. The use of magnetic seeds for localizing axillary lymph nodes with a wireless localization method identified 37 of 38 magnetic seeds (97%) for definitive surgery (18, 19). Local recommendations in Germany also suggest that TAD should be used after neoadjuvant therapy in selected cases (20).

In the breast or axilla, marker clips make it possible to locate lesions using mammography or ultrasound. However, the surgeon requires a second localization process intraoperatively. The most common method is wire-guided localization (WGL). This proven method has some disadvantages, and improvements are therefore needed to reduce the risk of infections, pneumothorax, and pain due to the additional invasive procedure, as well as to reduce the risk of wire dislocation. Another point for improvement is to make the scheduling of the procedure independent of the radiologist's availability for wire placement. A promising method for overcoming these issues is localization using microchipping with radiofrequency identification (RFID) tags (21-25). For this procedure, an RFID tag that can be located with a special probe during surgery is placed in the lesion.

On the basis of our extensive experience with marker systems (14-17), the aims of this study were to evaluate the clipping method with RFID tags and its feasibility in clinical everyday routine work, and to compare the costs of RFID tagging to the standard wire-based method.

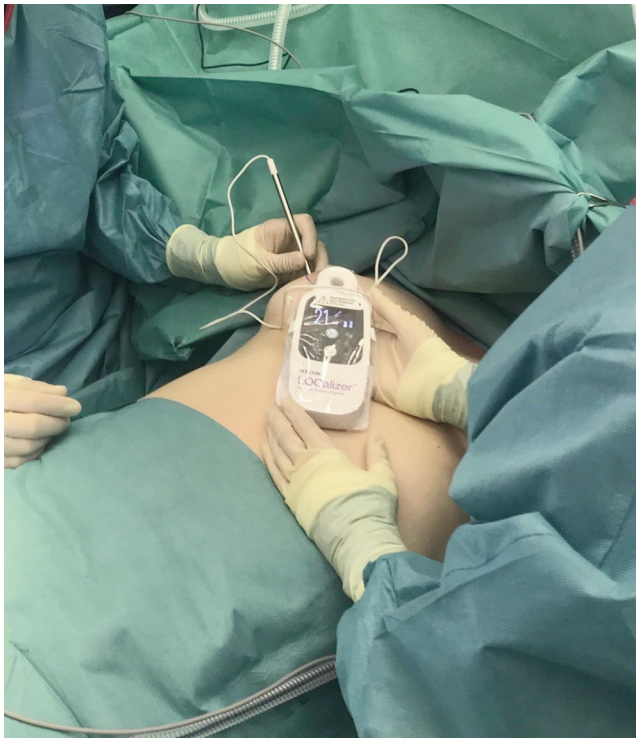

Figure 1. *Intraoperative use of the LOCalizer device.*

Patients and Methods

Study population. Fifteen consecutive patients with suspected or recurrent breast lesions and one axillary lesion, with an indication for preoperative marking of the nonpalpable lesion, were marked with RFID tags as part of clinical routine work. Histological samples were obtained preoperatively using a core needle biopsy or vacuum-assisted biopsy. The patients were examined, marked, and operated on at the University Breast Center for Franconia between June 2020 and October 2021.

Ultrasound-guided RFID marking. The procedures were carried out between zero and 7 days before surgery. The position of the RFID tag was analyzed and displayed to the surgeon using digital full-field mammography with a standard mediolateral oblique and craniocaudal projections, or *via* digital breast tomosynthesis (Selenia Dimensions 3D, Hologic) and ultrasound (2-D, Acuson Antares, 13 MHz, Siemens, Erlangen, Germany) in the operating theater.

The same three experienced radiologists performed intramammary RFID tagging. A single-use marking system (LOCalizer, Hologic Medicor GmbH, Kerpen, Germany) was used for RFID tagging.

The LOCalizer system is a wireless system for precise localization of breast lesions. Tag applicators with lengths of

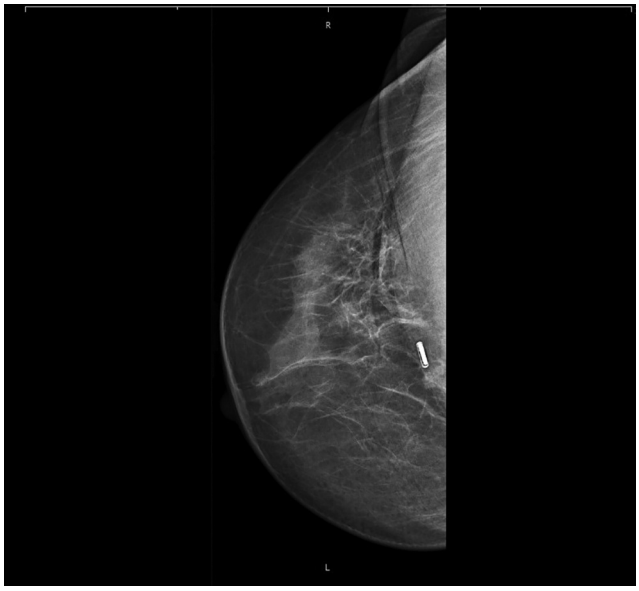

Figure 2. *Mammography for clip localization after ultrasound-guided lesion tagging, craniocaudal projection.*

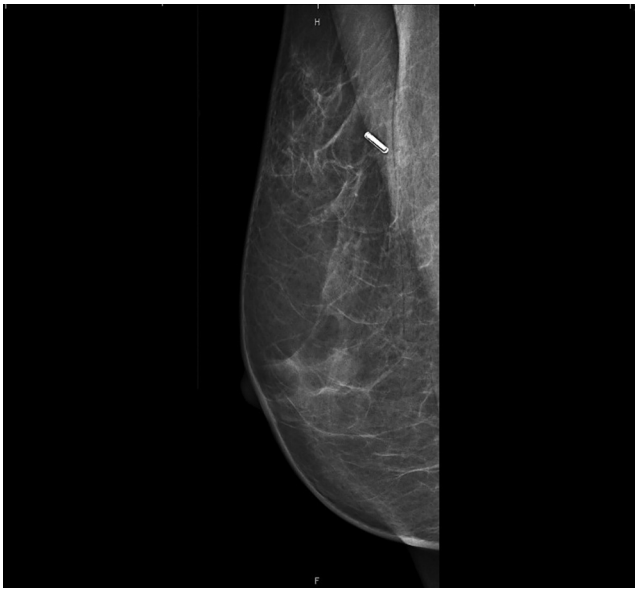

Figure 3. *Mammography for clip localization, mediolateral oblique projection.*

5, 7, and 10 cm are available for marking intramammary lesions. The tag applicator is loaded with a ready-to-use RFID tag. After disinfection and application of local anesthetic, the single-use breast biopsy system (an 11-gauge coaxial cannula) is placed over the focal tumor under ultrasound or radiologic guidance and the clip is placed in the suspicious lesions. The tag is 10.6 mm long and 2 mm in diameter and has a special coating that minimizes dislocation. Each tag has its own identification number, so that each lesion can be separately identified.

Using a hand-held probe, the tag can be located with its unique identification number. The distance between the probe, which looks like a pencil, and the tag is displayed on the hand-held display (Figure 1).

All of the patients underwent surgery, and a radiograph of the breast specimen was taken during surgery to demonstrate removal of the tag and of the suspicious lesion. After surgery, an expert pathologist with experience in breast pathology analyzed each specimen.

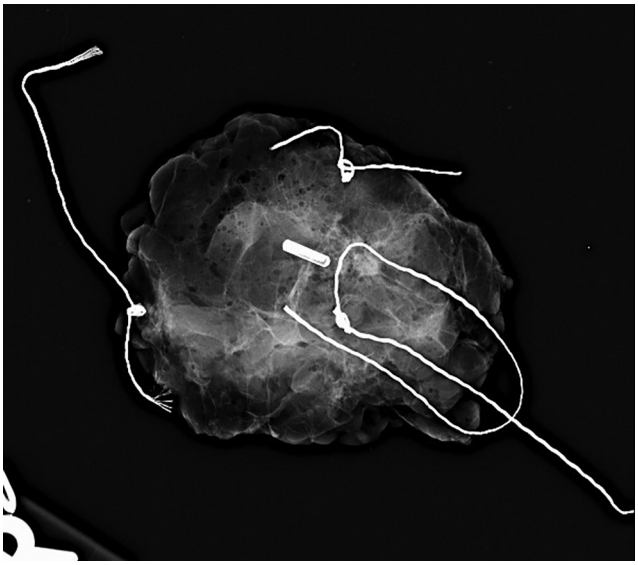

Figure 4. *Specimen radiograph.*

Results

Preoperative deployment of RFID Tag and radiological evaluation of marker position. Sixteen RFID tags were deployed in 15 patients; bilateral tags were placed in one patient. Eleven RFID tags were deployed under ultrasound guidance and five with stereotactic guidance. The patients' mean age was 57.9 years; two were premenopausal and 13 were postmenopausal. The final pathological histology findings were benign in two cases, carcinoma in situ in three cases, and invasive BC in 11 cases. After the clip had been placed in the breast, its location was verified using ultrasound and digital breast tomosynthesis (DBT) (Figure 2 and Figure 3). No dislocation of the clip was observed after removal of the applicator system. A specimen radiograph is shown in Figure 4, with the RFID tag placed in the middle of the lesion. Patient and tumor characteristics are listed in Table I.

Postoperative pathological assessment and exclusion of intraoperative loss of clip. Fourteen patients underwent breast-conserving surgery and one patient received targeted axillary dissection. Intraoperative specimen x-rays showed the RFID tag in all of the specimens, and no clip migration was observed. Pathological assessment was carried out for all specimens. The pathologist reported no difficulties in preparing and evaluating the specimens resulting from the RFID tags. No special actions in relation to the specimens had to be taken into account – *e.g.*, in connection with radioactivity.

Implications for clinical routine. As the marking took place on the day of the operation at the latest, there was no need for wire-guided localization on the day of surgery. It was possible to schedule the operations independently of the marking of the lesion. No loss of time in the operating theater was observed, thanks to localization and easy use of the device (Figure 1).

Table I. *Patient characteristics*.

	RFID (N=16)
Age (mean)	57.9
Menopausal status	
Premenopausal	2
Postmenopausal	13
BMI (mean)	25.7
Tumor histology	
Benign	2
DCIS	3
Invasive carcinoma	11
Operating time, min. (mean)	41.6
Mean tumor size, mm	12
Repeat excision rate (%)	13

BMI: Body mass index; DCIS: ductal carcinoma *in situ*; RFID: radiofrequency identification.

Cost-effectiveness. Costs for patients with placement of radiopaque clips before neoadjuvant chemotherapy were compared with costs for patients with RFID tags (Table II). The cost of RFID tags, including ultrasound and mammography, breast examination, placement of the clip, RFID applicator, and RFID tag is approximately twice as expensive as regular titanium clips. This calculation does not include indirect costs – for example, for scheduling operations only after WGL when this is possible for radiologists. For smaller hospitals, there is more flexibility for planning surgery when a radiologist is on duty on the day of the operation. If the radiology department and the operating theater are in different locations, patients do not have to be taken from one department to the other and back.

Discussion

The aim of this study was to evaluate the clipping method using RFID tags and its feasibility in everyday clinical routine. Currently, up to 80% of breast-conserving operations for nonpalpable breast lesions are wire-guided (26). Techniques for localizing breast lesions are becoming more important, as neoadjuvant treatment regimens are becoming more frequent and larger numbers of smaller lesions are being detected on screening mammography. Many limitations with the wire-guided approach are known, such as migration and wire breakage, patient anxiety and pain, fixed scheduling of the operation procedure, risk of pneumothorax, and very severe cases of wire dislocation (21).

Observations in the present study showed that wireless localization of nonpalpable breast lesions is feasible and safe in clinical routine work, and this has also been reported in other studies (27-29). Published data on the use of LOCalizer tags in Germany include only four patients with benign lesions, in whom the RFID tags were placed on the day of surgery, whereas in the present study the tags were placed up to 7 days in advance and also in malignant lesions (28). With regard to the time of placement of the RFID tags, there is potential for the LOCalizer tags, which can remain in breast tissue for more than 30 days, with no upper limit, as specified in the U.S. Food and Drug Administration (FDA) approval (24, 27, 29). In our experience, use of the LOCalizer system is time-efficient, there are no differences in operating times in comparison with breast-conserving surgery in which the lesion is wire-located, and the system does not create any problems for the histopathological preparation and assessment of the specimen. Additional advantages include improved scheduling flexibility and lack of a wire with the disadvantages mentioned above – especially in patients with large breasts and a high body mass index. In lesions located near the pectoral muscle, in which safe insertion of the wire and the risk for dislocation are greatest, the LOCalizer tags also showed promising results. The potential for removing less nontargeted tissue, with the resulting improved cosmetic results, is beneficial for all patients, particularly those with smaller breast tissue. Because of the tags' size, they can improve access for targeted axillary dissection and be applied in approximately 10 minutes.

The RFID tag can be deployed with ultrasound or stereotactic guidance with a high degree of precision. The dislocation rate is low in comparison with wire-guided marking (30, 31). The size of the study was fairly small, but all of the LOCalizer tags in close proximity to the tumor tissue were visible on specimen radiography, and no clip migration occurred. These results are in line with the literature findings (27, 29).

Table II. *Cost-effectiveness analysis*.

Clip	Clip after diagnosis	Cost (€)	Wire and surgery	Cost (€)
	Mammography 1 side, 2 views	45,0963	Mammography 1 side, 1 view	30,0375
	Counseling	5,552	Mammography 1 side, 2 views	45,0963
	Biopsy of breast or lymph node	4,164	Counseling	2,776
	Examination	5552	Biopsy breast or lymph-node	4,164
	Additional ultrasound, less than 3 organs	5,552	Examination	2,776
	Ultrasound, bilateral breast, and lymph nodes	14,574	Ultrasound breast and lymph-nodes	7,287
	Clip	78,23	Wire	22,55
	Total (€)	158,72	Total (€)	114,69
LOCalizer	Clip after diagnosis		Surgery	
	Mammography 1 side, 2 views	45,0963	Mammography 1 side, 2 views	45,0963
	Counseling	5,552	Counseling	2,776
	Biopsy of breast or lymph node	4,164	Examination	2,776
	Examination	5,552	Probe head	185
	Additional ultrasound, less than 3 organs	5,552		
	Ultrasound, bilateral breast, and lymph nodes	14,574		
	RFID applicator	185		
	Total (€)	265,49	Total (€)	235,65

NACT: Neoadjuvant chemotherapy; RFID: radiofrequency identification.

With regard to cost aspects, the LOCalizer system is more expensive than standard marking methods, but no costs arise for scheduling of patients or for ensuring that a specialized radiologist is present in the hospital on the day of surgery. Other cost considerations such as psychological effects on the patient and potential complications with the wire-based technique are avoided. The time required for surgery and application of the clip are identical to standard marking, and depending on the organization of the department, the two methods are therefore comparable in terms of cost.

The tags can be placed with the assistance of ultrasound, mammography, and magnetic resonance imaging (MRI), and are also advantageous because there are minimal artifacts on MRI. Each RFID tag has a unique identification number, so that identification of each individual lesion is possible in patients with multiple marked lesions. This allows the surgeon to adjust the resection margins relative to the underlying malignancy.

Several other localization techniques have been examined. A Cochrane analysis published in 2015 compared different methods of radioguided occult lesion localization with wire-guided localization. No statistical differences were observed for successful localization of the clip, positive excision margins, or repeat surgery rates (32).

Migration of surgical clips is one of the major limitations of that method. Increasing pCR rates with neoadjuvant chemotherapy are leading to difficulties for radiologists in marking and localizing tumors. There is a need for localization methods that can be applied at the start of neoadjuvant chemotherapy, with little or no migration of the markers over time. These issues were not addressed in the present group of patients, and further trials are needed in which patients have markers placed before neoadjuvant chemotherapy so that potential migration of the LOCalizer tags can be investigated.

In the literature, the radioactive seed localization technique was assessed in 3,879 breast cancer patients. No significant differences between radioactive seed localization and wire-guided localization were observed in relation to surgical margins and repeat surgery rates (33). With the radiofrequency technique used for the LOCalizer system in the present study, there is no radioactivity with its associated problems, no regulatory issues, no radiation exposure for patients and surgeons, and no potential problems with disposal management. Long-term implantation of the LOCalizer tags might therefore be possible.

Another method was investigated by the iBRA-NET localization study, including 2,300 women with nonpalpable breast lesions. Patients underwent wire-guided *vs*. magnetic seed localization, with similar rates of lesion identification, at 99.8% *versus* 99.1% (p=0.048) (34). MAGSEED ferrous-steel surgical tools produce undesirable interference during detection, requiring the use of nonmagnetic instruments, and the results were not convincing for lesions deeper than 4 cm (35). In contrast, the LOCalizer works up to a tissue depth of 6 cm, with standard surgical instruments. The LOCalizer probe is only 8 mm in diameter and can be used for small incisions, and unlike most other technologies, the probe depicts the distance from the tag.

As expected, indocyanine green fluorescence lumpectomy was associated with a significantly higher rate of clear margins (87.5%) in comparison with wire-guided localization (63.3%; p=0.026) (36). In the present study, repeat surgery was necessary in two patients, in one of whom the tumor size had been estimated at 1.5 cm in diameter preoperatively. At the final pathological evaluation, the lesion was 4.6 cm in size, with the LOCalizer tag located inside the tumor on the specimen radiograph. In the other patient, the LOCalizer tag and tumor tissue were also included in the specimen radiograph, but with positive margins, even after subsequent repeat excision. Safe localization of the tumor does not correlate with clear margins and tumor size. The sample of patients was too small, with different surgeons and a lack of a learning curve, for any conclusions to be drawn regarding correlations between marking and the repeat excision rate. Repeat excision rates of 3-17% are reported in the literature, but also with limited numbers of patients (22, 27).

Sample size is one of the major limitations of this study, and there was some recruitment bias, with no patients receiving neoadjuvant chemotherapy.

Prospects. The fact that the LOCalizer system displays the distance between the tag and the probe may be helpful in selecting the correct size for the specimen removed. A low repeat excision rate has been reported in other studies (22). The repeat excision rate was 13% in the present study, which is slightly higher than the rate in our institution in recent years, but in view of the small sample size no general conclusions can be drawn regarding higher repeat excision rates with the LOCalizer.

With targeted axillary dissection and a less radical approach in axillary surgery in recent years, the marking of suspicious but nonpalpable axillary lymph nodes is challenging. Marking on the skin is imprecise and marking using wire is painful and associated with discomfort for the patients. Marking of lymph nodes with clips is well established and feasible but does not make it possible to locate the clip intraoperatively without further devices (*e.g.,* intraoperative ultrasound or x-ray). The option of ultrasound-guided placement of RFID tags may be able to solve this problem, and it should be evaluated in further studies.

Conclusion

LOCalizer RFID tagging is a new method that was successfully applied in 15 patients with both malignant and nonmalignant disease, as an effective localization system for nonpalpable breast lesions. It provides advantages for patient scheduling and flexibility and is therefore cost-effective and should be further evaluated in larger trials including patients treated with neoadjuvant chemotherapy.

Conflicts of Interest

R.E. has received honoraria from Roche, Eisai, Pfizer, BioNTech, Veracyte (PROCURE), Diaceutics, and Novartis, and research funding from Roche, NanoString Technologies, Biocartis, ZytoVision, Novartis, Cepheid, and BioNTech. J.E. has received honoraria from Novartis, Pfizer and Eisai. All of the Authors have declared that they have no conflicts of interest in relation to this study.

Authors' Contributions

F.H.: Conceptualization, formal analysis, investigation, writing – original draft, data curation; R.S-W.: conceptualization, investigation, writing – review & editing; S.J.: conceptualization, investigation, writing – review & editing; R.E.: investigation, writing – review & editing; C.C.H.: investigation, writing – review & editing; C.P.: investigation, writing – review & editing; A.B.: investigation, writing – review & editing; P.P.: conceptualization, formal analysis, investigation, writing – original draft, data curation; J.E.: conceptualization, formal analysis, investigation, writing – original draft, data curation. The publication has been approved by all co-authors.

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