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NOTE

Optimization of an implantable magnetic marker for surgical localization of breast cancer

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Abstract

For small, early-stage or otherwise non-palpable breast tumors, surgeons rely on localization technologies to accurately find and remove the tumor tissue during breast conserving surgery. However, current widely accepted localization technologies either use painful and logistically challenging guidewires, or complex radioactive iodine sources. We have developed an implantable magnetic marker, intended to mark the location of a breast tumor, that can be detected during surgery using a clinical handheld magnetic susceptometry system. Here, we report on the development and optimization of this magnetic marker, focusing on the material, shape and various material assemblies. It was found that the effects of magnetic shape anisotropy may decrease localization precision. This can be circumvented by combining multiple isotropic magnetic elements separated from one another. A final optimized prototype was constructed and compared to a commercially available magnetic marker. Finally, the technology was tested in an *ex vivo* surgical setting on tissue to assess radiological visibility and surgical feasibility. The marker was successfully detected and removed in all *ex vivo* sessions, and the technology was found feasible.

1. Introduction

Breast conserving surgery (BCS) is the cornerstone of curative treatment for patients diagnosed with early stage breast cancer [1]. In BCS, the goal is to remove only the malignant tissue whilst keeping the healthy breast intact. The clinical challenge is often to locate the tumour tissue during surgery, as early stage breast cancer looks and feels very alike healthy tissue. Surgeons require additional guidance during surgery to accurately remove the tissue of interest [2].

Wire guided localization (WGL) has been the standard approach for this since its introduction in the 1970s [3], but it is associated with drawbacks including (1) high patient discomfort [4, 5]; (2) reduced surgical flexibility [2, 4]; (3) logistical challenges [2, 6] and (4) procedural complications [7, 8]. Radioactive seed localization (RSL), in which a gamma detector is used to guide the surgeon towards a radioactive iodine-125 seed that can be implanted up to weeks in advance of surgery, has been proposed to solve the drawbacks of WGL by providing logistical and surgical flexibility. However, the safe use of these tiny (4.5*0.8 mm) radioactive sources is strictly controlled by governmental legislation. From procurement, storage and issuing towards recovery and disposal of these sources, every step needs to be recorded and strictly controlled. The risk when losing a source is large, as an inspection body may retract the clinics' license. Therefore, the adoption of RSL was only as low as 18% in the Netherlands in 2014, and expected lower abroad [9].

Interestingly, research towards the use of magnetism for a variety of medical applications—both diagnostic and therapeutic—has gained considerable traction over the past decades. Indeed, magnetic resonance imaging (MRI) has become one of the key modalities of the radiology department, whilst magnetic particle imaging [10], magnetorelaxometry [11] and susceptibility measurements [12] have all become very active research fields. What these technologies

have in common is that they exploit the specific characteristics of single-domain magnetic nanoparticles. Of these technologies, alternate current (AC) susceptometry has reached clinical maturity first. Indeed, handheld susceptometry systems can be used in combination with an injectable solution of magnetic nanoparticles (Sienna+, Endomag Ltd Cambridge, UK) as a replacement of radioactive technetium-based sentinel lymph node biopsies in breast cancer [13]. The use of these solutions for primary tumour localization is suboptimal as the fluid diffuses within the tissue with time.

The goal of the current research was to develop and optimize a magnetic implantable marker that can be detected using a commercially available clinical handheld susceptometry system. This innovative approach should allow accurate tumour localization of breast cancer, potentially eliminating the need for cumbersome wire guided localization or radioactivity. From the clinician's perspective, a novel implantable marker for surgical localization should at the very least (1) meet the dimensional constraints of conventional needles for breast biopsies (at maximum 14 G); (2) be able to mark small lesions (at maximum 5 mm in length) and (3) function as a point-source—or a signal hotspot for the surgeon to operate towards.

The research starts with experimental bench-top measurements in which a variety of shapes, materials and assemblies are investigated to optimize the marker design. An optimized marker prototype was compared to a commercial magnetic marker that became available during the execution of this work. Finally, the developed technology was tested in an *ex vivo* surgical setting in human breast tissue to assess clinical applicability.

2. General experimental set-up

Throughout all experiments, a commercially available clinical handheld AC susceptometer (Sentimag, Endomag Ltd, Cambridge, UK) was used. This system consists of a base system and a cable-connected detection probe that contains a set of concentric drive and sense coils. The sense coils are arranged in an axial 2nd-order gradiometer configuration [14]. To limit the influence of temperature, the coils are wound around a high-grade ceramic body that has a low coefficient of thermal expansion. A susceptometer measures the magnetic susceptibility of a sampling volume by emitting a small sinusoidal exciting field using the drive coil (typically several mT) that fluctuates with frequency f (in the case of the SentiMag 1 0 KHz). This field causes a time-dependent field in the sampling volume. Following Faraday's law, this field will induce a current in a separate sense coil. Exact detection parameters and coil geometry of the Sentimag system are not known as this entails proprietary commercial information. Coil diameters are estimated

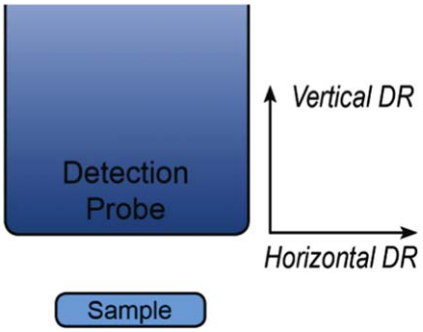

Figure 1. Schematic overview of measurement set-up to obtained horizontal and vertical distance response (DR).

at approximately 16 mm (full probe diameter is 18 mm).

The sampling volume may contain (a combination of) dia-, para- and/or ferromagnetic material, which will create a small negative, small positive or large positive induced magnetization, respectively. As the magnetization of a ferromagnetic material is much higher than either dia- or paramagnetic material, a relatively small volume of ferromagnetic material will govern the behaviour of the entire sampling volume. Therefore, the amplitude of the induced field will be strongly correlated to the amount of ferromagnetic material in the sampling volume, and the distance between the excitation coil and the sample. Dia- or paramagnetic materials may slightly attenuate the signal. To accommodate for these attenuations, the SentiMag offset may be subtracted before measurements. The Sentimag system feeds back the amount of induction in the sense coils to the end-user using a relative count value (range 0–9999) on the display and a sound that increases in pitch when the count increases. It therefore functions as a proximity sensor.

In the bench-top set-up, the SentiMag probe was suspended vertically from a manual XYZ translating table sufficiently far away from any metallic objects (>15 cm from tip). Horizontal distance response (DR) curves were obtained by incrementally moving the probe at a constant vertical distance from left to right over the marker and noting the count value at each increment. Vertical DR curves were obtained by incrementally increasing the distance between sample and probe and noting the count value at each measurement location (figure 1). All experiments were performed twice, and values were averaged. In horizontal DR graphs, the sample was placed in the origin (0, 0), and all measurements were performed along the axis of longitudinal samples. For clarity, vertical DRs are plotted on a log-lin scale. In previous, non-published research we determined the lower limit of reliable detection to be 30 counts, everything under 30 counts is considered not sufficiently reliable in our analyses.

During the experiments, we define the relative sample shape isotropy by dividing the length of its

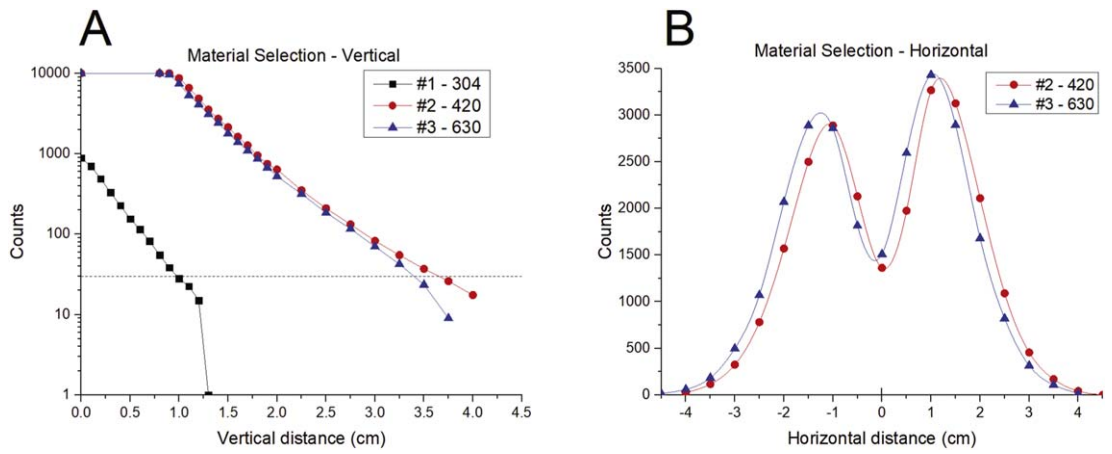

Figure 2. (A): Vertical distance response of samples 1–3 (see table 1). Line through points serves as a guide to the eye. Horizontal dashed line represents the lower limit of reliable detection. (B): Horizontal distance response of samples 2 and 3. Sample 1 was omitted due to inferior performance in vertical direction. Line through points serves as a guide to the eye.

Table 1. Three types of tested Stainless Steels (STS).

Sample	Material	Type	Shape	Size (length × diameter; mm)
1	STS 304	Austenitic	Wire	10 × 1
2	STS 420	Ferritic	Wire	10 × 1
3	STS 630	Martensitic	Wire	10 × 1

shortest axis D by its longest axis L. A value of 1 means the sample is isotropic, a value near 0 means highly anisotropic.

The marker development process is subdivided into two steps, namely (1) material selection and (2) volume, shape and configuration selection. As a final step (3) *ex vivo* testing was performed to assess clinical applicability.

As a rule of thumb, the final marker design was initially constrained to the size of the largest needle used in conventional breast biopsy procedures, which is 14 G or approximately 1.8 mm diameter.

To improve readability, introduction including materials, results and intermediate discussion is provided for each step, as findings from one step led to the substantiation for subsequent steps and actions. The article concludes with a general overview of the findings and implications of the developed technology for the surgical field and future research.

3. Step 1: material selection

3.1. Introduction

For medical applications, stainless steel (STS) is a commonly used material, as it combines good mechanical characteristics and workability with high corrosion resistance and biocompatibility. STSs are subdivided into high-level grades depending on their dominant crystalline structure (i.e. ferritic, martensitic or austenitic). Of these, ferritic and martensitic STSs show ferromagnetic behaviour, whilst austenitic STS is generally known as 'non-magnetic', or having a relative magnetic permeability very close to that of free space.

Of all three STS types, wire samples (10 mm × 1 mm) were tested (table 1). Of these samples, vertical and horizontal DRs were determined.

3.2. Results

Figure 2(A) shows that samples 2 and 3 (ferritic and martensitic) perform equally, sample 1 (austenitic) performs notably worse. The signal decays exponentially with a third power against the vertical distance, which is in line with what one would expect for this type of measurement and device. Figure 2(B) shows the horizontal DRs for the well-performing materials of figure 2(A). Note the prominent bimodal aspect in the curves.

3.3. Discussion

This step shows that the material should be ferromagnetic, and that the specific type of STS is irrelevant for detectability, as they perform equally. Interestingly, the samples create a strong bimodal curve aspect in the horizontal DRs (figure 2(B)). It was hypothesized that this effect was caused by magnetic shape anisotropy, i.e. the tendency of an anisotropic sample to be magnetized preferably along its longitudinal axis [15]. As the detection probe was moved along the longitudinal axis of the sample, the magnetic field is largely perpendicular to this axis when directly above the sample, and relatively parallel when on either end of the sample. This leads to higher magnetization and thus higher signals when beside the marker, and lower

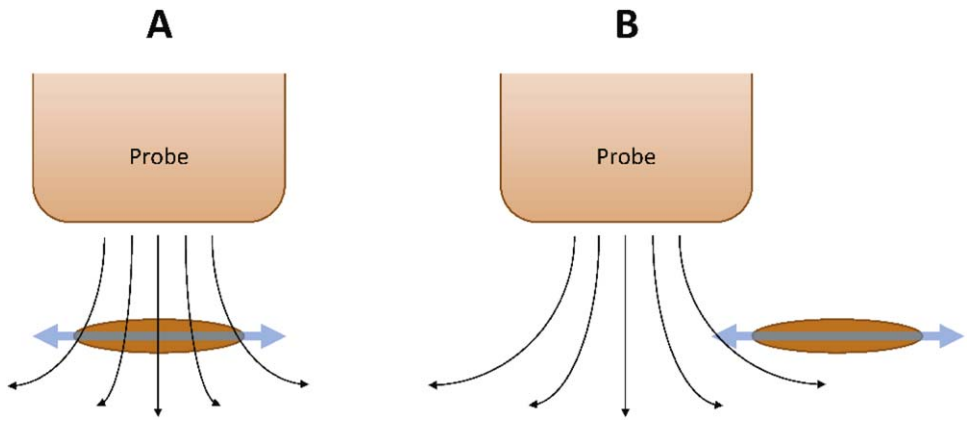

Figure 3. Hypothesized cause of bimodal curve aspect in figure 2(B) due to magnetic shape anisotropy. Blue arrow is the easy axis of magnetization, orange ellipse is a longitudinal sample. In situation A, the detection probe is positioned directly above the sample and a large part of the magnetic field lines are perpendicular to the axis of magnetization. In situation B the probe is next to the sample and the field lines are largely parallel to this easy axis. This leads to relatively higher magnetization and signal than in situation A.

Table 2. Samples to investigate shape (3–5), volume (6–9) and configuration (10 and 11).

Sample	Material	Shape	Schematic shape	Dimensions (length × diameter; mm)	Isotropy (diameter/length)
3	STS 630	Wire	———	10 × 1	0.1
4	STS 630	Wire	–	4 × 1	0.25
5	STS 630	Wire	-	1 × 1	1
6	STS 420	Sphere	●	Ø1.5	1
7	STS 420	Sphere	●	Ø2.0	1
8	STS 420	Sphere	●	Ø2.5	1
9	STS 420	Sphere	●	Ø3.0	1
10	STS 420	2 × Sphere	●●	2x Ø1.5	0.5
11	STS 420	3 × Sphere	●●●	3x Ø1.5	0.33
12	STS[a]	Magseed/wire	—	5 × 1	0.2

[a] Type of STS unknown.

when directly above, see figure 3. A strongly bimodal response curve as shown here is unacceptable for localization purposes, as the signal should have its maximum when directly above the sample, i.e. a standard bell shaped or unimodal curve, centred over the marker. This effect is further investigated in the following step.

4. Step 2: shape, volume and configuration

4.1. Introduction

The extent of the influence of shape anisotropy effects demonstrated in step 1 was further investigated by reducing a wire sample of 10 mm length to 4 mm and 1 mm (increasing isotropy from 0.1, to 0.25 to 1; samples 3–5, table 2). Horizontal DRs were obtained for each of the samples to assess the curve aspect.

The influence of sample volume on detectability was investigated by obtaining vertical DRs of four spherical ferromagnetic stainless steel 420 samples with increasing diameters (1.5, 2.0, 2.5, 3.0 mm, samples 6–9).

Further, it was investigated what would occur if an overall anisotropic sample was constructed by assembling multiple isotropic spherical elements on a single axis whilst touching (samples 10 and 11). Horizontal and vertical DRs were obtained to assess curve shape and the influence of increased total sample volume on vertical detectability, respectively.

As a final step, the optimized marker designed was compared to a magnetic localization marker that became commercially available during the execution of this work (Magseed, Endomag Ltd, Cambridge, UK). This marker has 5 × 1 mm dimensions (isotropy 0.2) and is constructed from medical grade stainless steel of which the specific type is unknown (sample 12).

4.2. Results

Figure 4(A) shows that the bimodal curve aspect is reduced and finally eliminated when sample isotropy increases to 1. The significantly lower curve aspect of sample 5 relative to sample 3 suggests that volume is a relevant contributing factor in the detectability. Figure 4(B) shows that detectability indeed increases when sample volume increases, with maximum detectable distance (were the curve crosses the horizontal limit of reliable detection) increases from

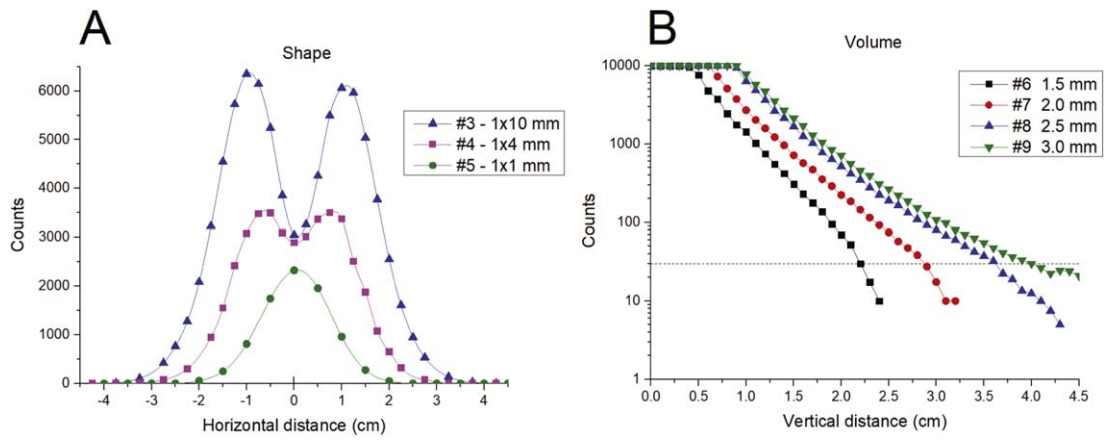

Figure 4. (A): Horizontal distance response of samples 3–5 with increasing isotropy. Line through points serves as a guide to the eye. (B): Vertical distance response of samples 6–9, spheres with increasing diameter. Line through points serves as a guide to the eye. Horizontal dashed line represents the lower limit of reliable detection.

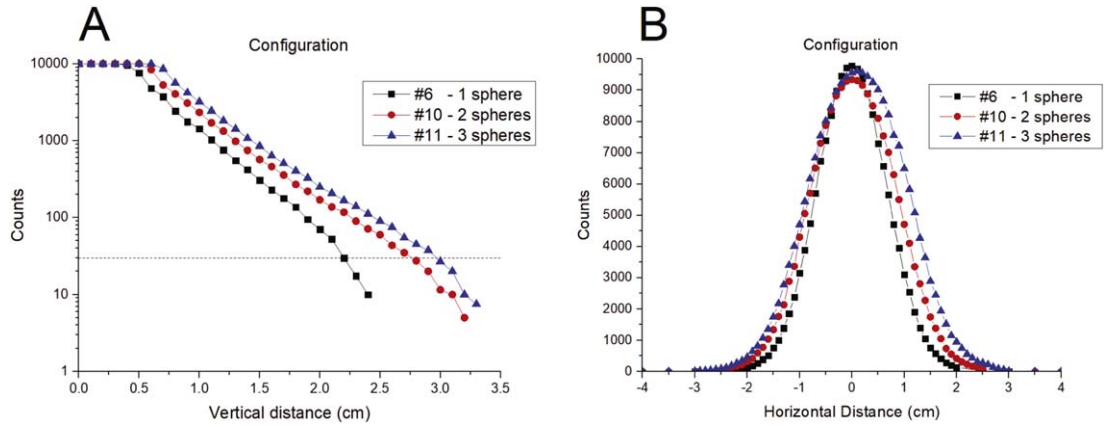

Figure 5. (A): Vertical distance response of samples 6, 10, 11. Assemblies of one, two and three 1.5 mm diameter spheres in a row. Line through points serves as a guide to the eye. Horizontal dashed line represents the lower limit of reliable detection. (B): Horizontal distance response of samples 6, 10, 11. Line through points serves as a guide to the eye.

22 mm, 28 mm, 37 mm to 40 mm for samples 6 through 9, respectively.

For surgical localization purposes, a combination of high detectability with a unimodal curve aspect—i.e. hotspot detection—is essential. The marker design is constrained by the largest needle size clinically applicable for breast, which currently is 14 G (or 1.8 mm diameter). It was attempted to maximize material volume within these constraints by investigating the effects of placing multiple isotropic samples in a row (samples 10 and 11). Figure 5(A) shows that detectability is increased with increasing volume, from 22 mm, 28 mm to 30 mm, which is congruent with figure 4(B). Moreover, figure 5(B) shows that the unimodal aspect essential for localization purposes is maintained, even though the complete sample shape is now anisotropic.

Finally, we compared the performance of our prototype to currently available magnetic markers: the commercially available magnetic marker shows a strong bimodal curve shape, with signal peaks at approximately 1 cm on either side of the marker. In contrast to the commercially available marker, our prototype sample #11 (3 spheres) shows the desired monomodal curve shape, see figure 6.

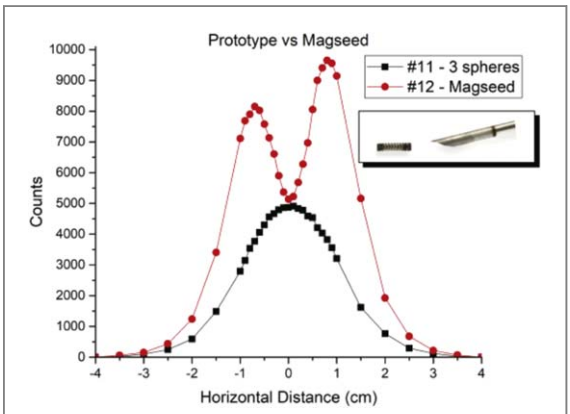

Figure 6. Horizontal distance response of sample #11 versus Magseed, a commercially available magnetic marker. Inset: photograph of Magseed.

4.3. Discussion

Step two confirms that shape anisotropy is the cause of the undesirable bimodal aspect and can be eliminated by using isotropic samples. Second, it shows that detectability is proportional to sample volume, thus sample volume should be maximized. Finally, sample volume can be maximized whilst maintaining a unimodal curve aspect by assembling several isotropic elements in a row.

This behaviour contrasts with an additionally tested commercially available magnetic marker, which shows strong influences from shape anisotropy and therefore high signal peaks detected at approximately 1 cm on either side of the marker, which is undesirable for localization purposes as the end-user will generally navigate towards the high peaks.

5. Step 3: *ex vivo* proof-of-concept

5.1. Introduction

A marker prototype was constructed from three 1.5 mm diameter STS 420 spheres, assembled in a row with no visual space between the spheres (same as sample 11, table 2) and subsequently encased in polymer (4.6 mm × 1.6 mm). In a first session, the marker was implanted at an arbitrary location in a chicken breast, after which imaging from all relevant modalities (x-ray, ultrasound, CT, MRI) was obtained to assess visibility. Subsequently, two experienced breast surgeons were asked to perform surgery to retrieve the marker using the magnetic detector as guidance.

In a second session, two healthy breast tissues from a patient that underwent preventive dual breast removal (due to a genetic disposition) were obtained from the pathology department before slicing. The marker prototype was again implanted at an arbitrary location into the specimen by a researcher. Subsequently, an experienced breast surgeon who did not attend the implantation procedure was invited to perform surgery to retrieve the marker using the magnetic detector as guidance.

After of each procedure, the surgeon was asked to rate the surgical technique of the magnetic procedure on a 5-point Likert scale ranging from 'Far inferior to' to 'Far superior to', relative to WGL.

5.2. Results and discussion

Visibility on the most used imaging modalities for breast cancer (ultrasound, mammographic x-ray and CT-scan) was excellent. On ultrasound the marker was clearly visible with an evident acoustic shadow that helps to identify the marker. On mammographic x-ray, the metal interior of the marker was visible without any artefacts. On CT, a small 6 mm circular metal artefact was visible, with a larger windmill artefact surrounding it.

On MR an imaging artefact was expected as the ferromagnetic material in the marker influences the field homogeneity of the MR system. Indeed, a large 56 mm susceptibility artefact was found, (figure 7).

A total of four surgical marker retrievals were performed (three on chicken, one on human breast tissue) by two experienced breast surgeons. All procedures went smoothly, and all markers were retrieved on first attempt. See figure 8 for a photographic overview of one of the procedures. Surgeons rated the surgical technique of the magnetic technology superior to far superior over WGL (score 4.5).

6. General discussion and conclusion

A clinical need exists to replace the wire guided approach for the intraoperative localization of small or otherwise difficult to locate breast tumours. Although radioactive alternatives solve the biggest drawbacks of wires, their inherent complexity and strict regulation means clinics are hesitant to switch. We have developed and optimized a novel implantable magnetic marker that can be detected by an off the shelf clinical magnetic susceptometer (Sentimag), together forming a non-radioactive localization technology to replace the wire guided approach.

The expected clinical benefits of our proposed solution over the standard of wire guided localization are (1) patient comfort (no wire protruding from the breast; no extra procedure on day of surgery); (2) logistical flexibility (decoupling of radiology and surgery schedules) [16] and (3) technical (flexibility of surgical approach), the surgeon can (re)assess his surgical approach towards the marked tumour in real-time and at any point.

The benefits of using magnetism rather than radioactivity for tumour localization, are manifold. For example, magnetism does not decay over time and is inherently safe for both patient and user. This implies simplicity, magnetic markers may be acquired in bulk and stored until needed, without any special storage or procurement conditions. At the pathology department, a resection specimen with a magnetic marker in place does not require additional steps for safe disposal and eliminates the risk of contamination (as a result of accidentally cutting through a radioactive marker). For each of the involved departments, the workload when using a magnetic technology is expected to be markedly reduced as opposed to a radioactive technology.

Our research shows that it is possible to construct a marker within the constraints of clinically acceptable needle dimensions (14 G), whilst still being able to detect it up to 30 mm. The challenge was to optimize material volume and marker shape. The first improves detectability, whilst the second may influence accuracy. Indeed, it was shown that an anisotropic sample shape (e.g. samples 3, 4 and 12) created a strong bimodal distance response curve in the horizontal direction, which was indicative of magnetic shape anisotropy and may prevent accurate localization. We found that

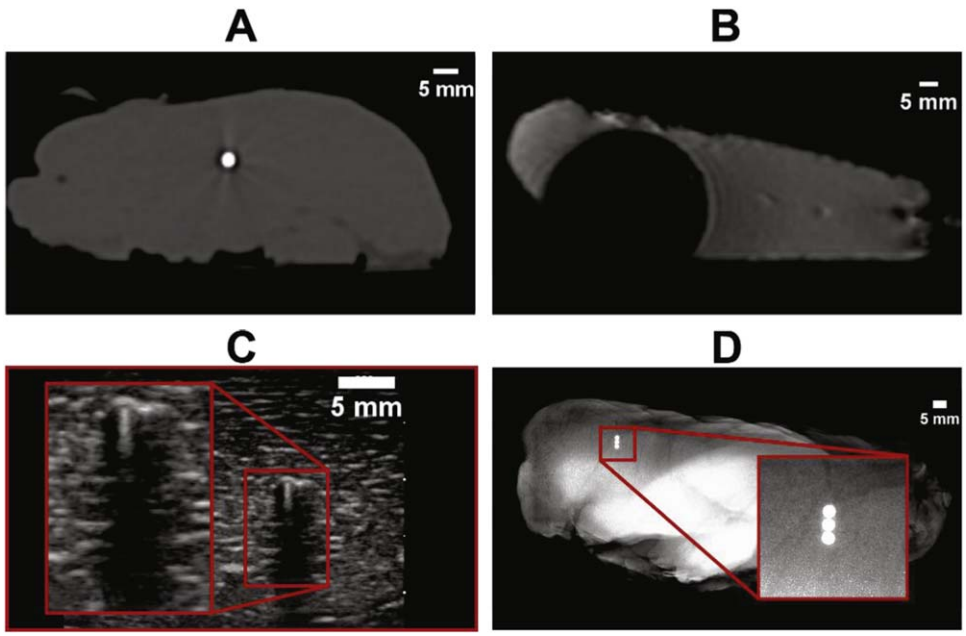

Figure 7. Visibility of marker prototype in a chicken breast on (A) CT. (B) MRI. (C) Ultrasound and (D) x-ray (mammography). Red insets are zoomed details of the marker.

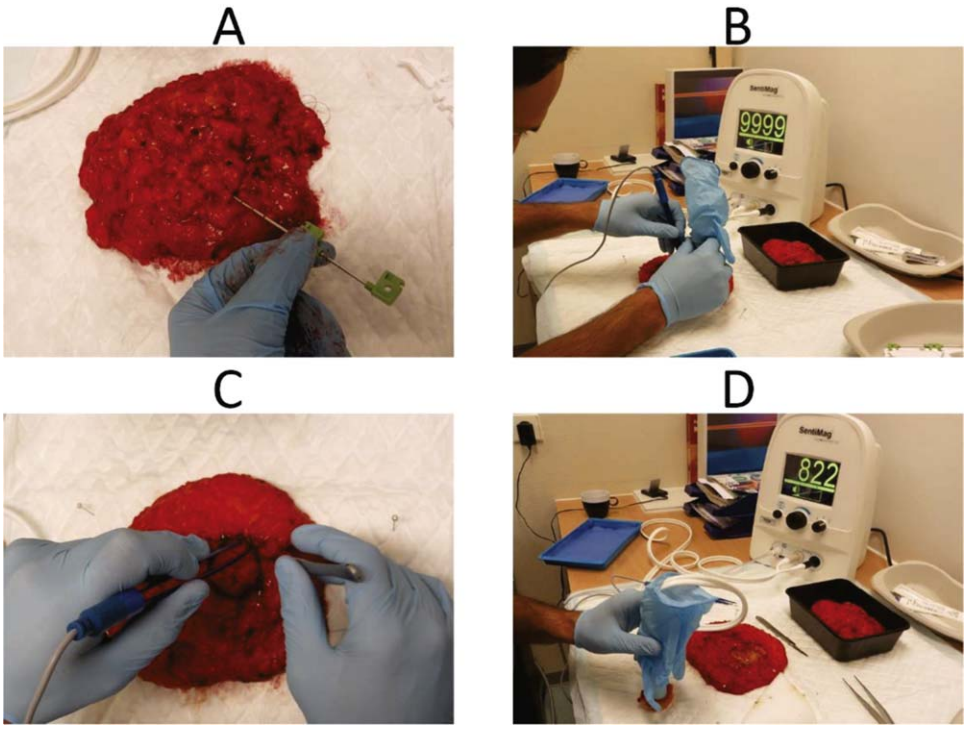

Figure 8. Overview of *ex vivo* proof of concept. (A) injection of marker into specimen. (B) surgical procedure using Sentimag guidance. (C) removal of simulated lump. (D) check if marker present in specimen.

an improved marker, constructed from multiple isotropic elements, prevents shape anisotropy from occurring whilst still having the benefit of improved detectability due to increased marker volume.

Nevertheless, a maximum distance of detection of 30 mm limits the clinical applicability of the technology in the breast. One of the key functionalities of a surgical localization technology is the ability to detect the location of the tumour from the skin onward, so that the surgeon can plan the shortest or most cosmetically optimal route towards the tumour. One can imagine that a centrally located lesion in a large breast may be difficult to bring within the 30 mm from the detection probe from the skin.

Other limitations of the technology are that a fluctuating magnetic field induces Eddy currents in metallic

instruments, which in turn creates a magnetic field which is detected by the susceptometer. This implies that the current system is incompatible with standard metal surgical instruments, and surgeons should switch to polymer tools. Moreover, the large susceptibility artefact with the magnetic marker *in situ* precludes the use of MRI diagnostics with a marker *in situ*, which however can be solved by adjusting the clinical workflow.

Several other parties have worked on non-radioactive marker-based solutions for tumour localization. For example, SAVI scout (Cianna Medical, Aliso Viejo, CA, USA) uses a combination of infrared light and electromagnetic radiation to detect an implanted electromagnetic reflector of 1.2 cm length [17]. LOCalizer (Health Beacons, Inc., Concord, MA, USA) uses a large and a small coil to first transcutaneously and then intraoperatively detect an implanted 12-gauge RFID tag [18]. The benefit of our proposed solution over its non-radioactive alternatives is that it functions by means of a small and passive marker. Our 4.5 mm marker can mark small lesions of interests and even if, hypothetically, the marker was in some way damaged while *in situ*, the ferromagnetic elements would still be detectable as the magnetic material properties would remain unaffected.

In conclusion, we have shown that it is feasible to produce a magnetic marker that is detectable up to 30 mm using a commercially available AC magnetic susceptometer, for the use of tumour localization during surgery. Furthermore, we were able to eliminate the magnetic shape anisotropy effects by assembling isotropic elements in an anisotropic marker shape. Both on animal and human tissue, two surgeons have shown that the entire process of magnetic-based surgical localization using this novel marker is feasible. Limitations of the technology include MR susceptibility artefacts and the necessity to switch to polymer surgical tools during measurements. Future research should focus on clinical proof-of-concept of the technology, especially with regards to the detectable distance, as well as more advanced detection algorithms that reduce or eliminate the influence of surgical tools, and that improve the detection distance.

Declaration of interest

Three authors on this paper (T Ruers, B ten Haken and B Schermers) are inventors on the patent that describes this technology. Two authors are shareholders in a start-up company that aims to bring this technology to commercial fruition (B Schermers and T Ruers).

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