Concept for using magnetic particle imaging for intraoperative margin analysis in breast-conserving surgery

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Breast-conserving surgery (BCS) is a commonly utilized treatment for early stage breast cancers but has relatively high reexcision rates due to post-surgical identification of positive margins. A fast, specific, sensitive, easy-to-use tool for assessing margins intraoperatively could reduce the need for additional surgeries, and while many techniques have been explored, the clinical need is still unmet. We assess the potential of Magnetic Particle Imaging (MPI) for intraoperative margin assessment in BCS, using a passively or actively tumor-targeted iron oxide agent and two hardware devices: a hand-held Magnetic Particle detector for identifying residual tumor in the breast, and a small-bore MPI scanner for quickly imaging the tumor distribution in the excised specimen. Here, we present both hardware systems and demonstrate proof-of-concept detection and imaging of clinically relevant phantoms.

Breast cancer is the most common cancer in women worldwide. Over two million new cases of breast cancer were diagnosed in 2018, constituting 11.6% of all cancers diagnosed that year (men and women), and 24.2% of all cancers in women1. Breast-conserving surgery (BCS, a.k.a. lumpectomy or segmental mastectomy) is the first intervention for the majority (64.5%) of early stage diagnoses, and has been shown to have outcomes similar to mastectomy (complete removal of one or both breasts) when complete tumor resection is achieved3,4. However, incomplete resection correlates with local recurrence5,6, and secondary surgeries are required in 20–66% of initial lumpectomies7–12. Additional surgeries impose risks and challenges including increased costs and complications, as well as cosmetic and emotional burdens on the patient10,13.

Local tumor recurrence, a determining factor for reexcision, correlates strongly with margin status9,14,15, or the proximity of tumor cells to the inked surface (or “margin”) of the excised tissue. The clinical standard for margin assessment is histopathology, and due to the need for formalin fixation, this assessment is done post-operatively. The need for secondary surgery can be reduced with the use of an intraoperative tool that enables the surgeon to iterate tissue removal and margin analysis in real time, enabling greater confidence of clear margins10,16. This concept is illustrated in the flowchart in Fig. 1. To gain regular clinical utility, an intraoperative margin assessment technique must provide sensitive and specific information about the margin status, and be fast and easy to use in the operating room.

The problem of positive margins and reexcisions in BCS has been approached with numerous techniques10,17–23, addressing both macroscopic tumor localization and microscopic margin assessment. These include frozen section, imprint cytology, cavity shave margins, specimen radiography, micro-CT, radiofrequency spectroscopy, and numerous optical methods, to name just a few. However, as summarized by Maloney et al. (2018), “Technologies to determine margin status have been developed to have high sensitivity and selectivity. However, no current modality has matured into a complete solution to the margin problem currently facing BCS”18 due to various limitations, including long analysis times, additional required expertise, and lack of depth penetration.

In this work, we explore a novel approach for margin analysis during BCS: the use of Magnetic Particle Imaging (MPI), in conjunction with an injected superparamagnetic iron oxide nanoparticle (SPIO) tracer. We

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aim to assess MPI's potential to be added to the extensive list of tools investigated for this yet unmet need. The potential for SPIOs in breast cancer is highlighted by recent techniques utilizing magnetic nanoparticles and magnetic detectors (Magtrace/Sienna+ and Sentimag, respectively\(^{24,25}\)) for sentinel lymph node detection and occult lesion localization\(^{20,26}\), and as markers to flag specific locations (Magseed\(^{20,27,28}\)). These technologies use interstitial or intratumoral injections (versus intravenously injected nanoparticles). MPI detection of interstitially injected nanoparticles has also been proposed for use in sentinel lymph localization using a single-sided MPI imager\(^{29,30}\). Together, these demonstrations suggest the potential for magnetic nanoparticles in general and MPI in particular for the related task of margin analysis during breast-conserving surgery. Here, we propose the combined use of two novel MPI devices\(^{31–33}\) for margin assessment in BCS utilizing an intravenously injected SPIO, and demonstrate their feasibility via clinically relevant phantoms.

**Magnetic Particle Imaging background.** MPI is a tracer-based imaging modality first introduced by Gleich and Weizenecker in a seminal Nature paper in 2005\(^{34}\). MPI utilizes a superparamagnetic iron oxide tracer, identifying and spatially mapping its signature nonlinear magnetization response to an applied AC field. In the presence of the applied drive field (also called “transmit” or “Tx” field) at frequency \(f_0\), the SPIO's nonlinear magnetization includes higher order harmonics of the drive frequency (\(n*f_0\), \(n = 3, 5, 7\ldots\)). Both the drive field and SPIO response are picked up via Faraday detection in a receive coil, and identification of these higher order harmonics indicates SPIO presence. The drive field must be filtered to suppress harmonics that may be confused for the SPIO signal and \(f_0\) must be suppressed in the receive signal to avoid the direct Tx feedthrough. For sufficiently high magnetic field strength, the SPIO magnetization saturates such that the SPIO response is not detectable. This saturation effect is exploited to enable spatial encoding, using magnetic gradient fields (field-free point (FFP) or field-free line (FFL)), and additional AC “shift” fields to move the FFP/FFL for image encoding. Numerous acquisition and encoding schemes have been implemented in preclinical MPI to date\(^{29,31–39}\).

MPI is currently undergoing rapid development toward a number of clinical applications, including vascular imaging\(^{40–42}\), cell tracking\(^{43,44}\), oncology\(^{45,46}\), including macrophage activity\(^{74}\), hyperthermia therapy\(^{48}\), traumatic brain imaging\(^{49}\), and neuroimaging for stroke and hemodynamic disorders\(^{50,51}\). Biomedical applications of MPI have recently been reviewed\(^{52–55}\).

MPI and its SPIO tracer have a number of promising features, including zero background signal from tissue and positive contrast (MPI detects only the nonlinear SPIO signal; biological tissue is magnetically linear), high sensitivity (due to the strength of the SPIO magnetic moment, \(22\) million times stronger than the nuclear magnetization detected in high-field MRI), and direct and quantitative tracer detection (in contrast to indirect, qualitative detection as in contrast-enhanced MRI\(^{56}\)). As quasistatic magnetic fields are not attenuated in the
In the human body, there are no inherent depth penetration limitations such as those that limit many optical imaging modalities. MPI has also been demonstrated with fast temporal resolution. Finally, SPIOs are stable, have a long shelf life, and are considered safe injected agents with already approved clinical uses. These features make MPI promising for addressing the needs of intraoperative breast cancer margin assessment. While the technology is currently preclinical, scaling the hardware to human sizes gives rise to numerous technical challenges. We have developed and tested two strategies utilizing small- and medium-sized devices suitable for human clinical intraoperative use.

Tumor SPIO accumulation. As MPI detects injected SPIOs only (not the biological tissue itself), SPIOs must serve as tumor markers. Thus, this application relies on high specificity and high sensitivity accumulation. SPIOs are considered safe tracer agents, have routine clinical uses, and can be optimized for targeting via size and coating characteristics.

SPIOs can accumulate at a tumor via passive mechanisms, tumor-associated macrophage uptake, and/or active mechanisms (use of functional groups or antibodies conjugated to SPIO coating). These phenomena have been widely exploited for targeted tumor therapeutics and imaging. While passive accumulation has been extensively tested in animal models, there is some concern about its reliability for clinical uses in humans. Active targeting mechanisms, a potentially high-specificity approach, is an active area of research in the context of breast cancer.

MPI may be considered a two-key problem, requiring (1) hardware with high sensitivity, spatial/temporal resolution, and clinical use feasibility, and (2) safe nanoparticles with application-relevant properties. In this work, we develop the devices needed to take advantage of SPIOs with sufficiently specific tumor uptake and clearance of background SPIOs via the reticuloendothelial system, given the right timing post-injection. Tumor accumulation rates (%) injected dose (ID)/g tumor tissue vary in the literature, with a lower bound found in a study using PEG-coated nanoparticles in vivo in a xenograft mouse model. Here, total tumor accumulation (calculated as area-under-the-curve), is observed to be 0.3% ID/h/g, which we interpret (after accounting for the 2.5 h half-life) to be an accumulation of 0.12% ID/g. However, it is unclear that this value is ultimately translatable to human clinical application. Active targeting has been shown to enable higher accumulation rates than passive targeting, and therefore 0.12% ID/g represents a reasonable detection goal.

Envisioned clinical workflow. Given sufficiently specific SPIO accumulation and sufficient time for background SPIO clearance, MPI can be applied to both the breast at the excision site and to the excised specimen. We envision an MPI BCS workflow as illustrated in Fig. 2. Prior to surgery, the patient receives an intravenous SPIO injection, and sufficient time is allowed for nanoparticle accumulation and local background vascular clearance (the SPIO agent may still remain in other background organs (liver, spleen), but would sit beyond the

Figure 2. Envisioned MPI workflow during breast-conserving surgery. SPIOs would be injected intravenously prior to surgery with sufficient time for the nanoparticles to accumulate at the tumor and the background signal in the vasculature to be cleared. During surgery, the specimen is removed, and is placed in a small-bore MPI scanner to quickly image the distribution of SPIOs. A hand-held detector would be used at the incision site to detect residual SPIOs still in the breast, indicative of tumor remaining in the breast. Figure created using MS PowerPoint.
hardware’s detection range). During surgery, the specimen is removed, and a hand-held Magnetic Particle (MP) detector can be used at the excision site to identify any residual SPIOs (and thus tumor) in the breast. Simultaneously, the specimen can be inserted into a small-bore MPI scanner to provide a fast image (∼ seconds) of the SPIO distribution in the removed tissue. With information about both the presence of SPIOs (tumor) and its location in the breast, as well as the spatial distribution of SPIOs (tumor) in the specimen, the surgeon can iterate the process, continuing to remove tissue at indicated sites until achieving a high confidence of full tumor removal.

In this work, we develop and test the two MPI devices. The hand-held MP detector is designed to exploit the principles of MPI in its simplest form. It is a compact, single-sided non-imaging device with drive and receive hardware (no spatial encoding), designed to detect residual SPIO not removed with the initial excision. We design, construct, and show proof-of-concept feasibility of such a device to detect SPIO samples embedded in an anthropomorphic breast phantom.

In a separate device, we test the capabilities of a small-bore imager suitable for placement in the surgical suite to enable quick 3D imaging of the SPIOs within an excised specimen.

**Hand-held MP detector**

**Materials and methods.** The MP detector is a single-sided device mounted on a flexible arm, such that it can be held and moved around by the surgeon to and from the excision site, as illustrated in Fig. 2. This enables assessment of the presence of detectable levels of tracer. The application assumes that a limited search space around the surgical margin must be covered and that this region is small enough to be exhaustively covered in a timely fashion.

Single-sided devices have been explored in the field of MPI; for this clinical application, a single-sided, detector-only approach enables a simple, hand-held device. While MPI has no inherent depth attenuation, a single-sided coil has a sensitivity drop-off with distance from the detector, as illustrated in Fig. 3. This feature has the disadvantage that it loses sensitivity for tumors deeper in the breast, but has the advantage of being insensitive to relatively nearby and high SPIO content, such as the heart or liver.

Our device is designed for placement outside the incision; it is a larger device mounted on a moveable arm (similar in concept to x-ray devices common in dentists offices). Other single-sided designs could include smaller, pen-like devices (akin to the Sentimag system, the MarginProbe device, or an OCT probe).

The detector consists of two sets of coaxial, solenoidal Tx and receive (Rx) coils, separated by 6 cm, as shown in Fig. 3. The Tx/Rx coil set closer to the detector’s surface picks up SPIO signal, while the second set toward the back end of the detector has an oppositely wound receive coil and serves to cancel the drive field feedthrough. Both coil pairs are epoxied and water-cooled, and the apparatus is housed in a copper tube to confine the stray fields and reduce susceptibility to nearby conductive surfaces as the detector is moved around. Each coil set is 4 cm long; the Tx coil is 22-turn layers of 16 AWG Litz wire (New England Wire, Lisbon, NH) with an inner diameter of 6.85 cm. The Rx coil, mounted concentrically inside, has two 33-turn layers of 20 AWG Litz wire with diameter of 5.6 cm. The Tx coils in series have a total inductance of L = 22.7 μH.

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The receive chain includes a tuning/notch filter (73 dB attenuation between 3f₀ and f₀), low-noise preamplifier (Ithaco 1201, DL Instruments, Brooktondale, NY), and bandpass filtering 40–99.9 kHz (SR650, Stanford Research Systems, Sunnyvale, CA). Currently only the f₀ frequency is recorded with the NI-DAQ console. The drive field is pulsed in short bursts (48–72 ms), with pauses (300–450 ms) between to enable low duty cycle. The beginning of the received pulse can be discarded or the transmit pulse can be multiplied by a ramp function to mitigate transient effects. In either case, this transition period does not fully contribute to signal detection. Each data point recorded represents the f₀ component of the received signal.

We make the assumption that SPIO can accumulate at the tumor with a rate of 0.12% ID/g tumor tissue (see “Tumor SPIO accumulation” section above) and that background SPIOs will be cleared, such that there is no SPIO signal from healthy tissue. Based on this assumption, a typical SPIO dose of 5 mg/kg Fe, and a 65 kg patient with a 1.35 mm diameter tumor with a density of 1 g/cm³ (that of water), the hand-held device must be capable of detecting 500 ng Fe. Detection of 200 ng Fe is needed to reveal a 1.0 mm diameter volume of residual tumor.

We present three proof-of-concept experiments. First is surface detection of varying concentrations of SPIO samples ( VivoTrax, Magnetic Insight, Alameda, CA) in 18 µL glass bulbs, containing 1 µg down to 100 ng Fe, moved to and away from the detector’s surface. A 0 ng Fe (DI H₂O) control bulb ensures no false detection due to coil loading. Figure 5 shows the experimental setup. The raw acquired data has a baseline drift; to overlay the trials, a low-pass filter tuned to f₀ signal is produced by an NI USB-6363 DAQ console (National Instruments, Austin, TX), amplified by an AE Techron 7548 power amplifier (Elkhart, IN), and filtered by a custom high-power low-pass filter tuned to f₀. The receive chain includes a tuning/notch filter (73 dB attenuation between 3f₀ and f₀), low-noise preamplifier (Ithaco 1201, DL Instruments, Brooktondale, NY), and bandpass filtering 40–99.9 kHz (SR650, Stanford Research Systems, Sunnyvale, CA). Currently only the f₀ frequency is recorded with the NI-DAQ console. The drive field is pulsed in short bursts (48–72 ms), with pauses (300–450 ms) between to enable low duty cycle. The beginning of the received pulse can be discarded or the transmit pulse can be multiplied by a ramp function to mitigate transient effects. In either case, this transition period does not fully contribute to signal detection. Each data point recorded represents the f₀ component of the received signal.

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The second experiment more directly mimicked the clinical setting, testing hand-held use in which the SPIO sample is stationary and the detector is moved to and away from it. Video of the experiment (as well as screen recording of the data control software) was acquired during the experiment. This video is provided in supplementary material S1.

For the third experiment, the SPIO samples (in glass bulbs) are moved to and embedded in the anthropomorphic breast phantom, and detection is demonstrated by holding the detector and moving it to and away from the breast phantom at the known locations of the samples. The samples (each 500 ng VivoTrax) were placed in two locations (one in the lower outer quadrant of the left breast, one in the upper inner quadrant of the right breast), to
vary both the material (gel/rubber vs. hard plastic) and surface curvature of the breast phantom, as these could affect coil loading and positioning. Finally, to verify the detection, the samples are removed and detection tested moving the detector to the same locations. Video and screen recording of data control software was acquired during the experimental procedure. These videos are available in supplementary materials S2 (sample in left

Figure 3. Hand-held MP detector. (a) A schematic of the coils and housing is shown on the far left, with coil A and B both wound on a single former, the center section of which extends to the copper tube to which it is mounted. The Tx windings are illustrated in red (as a cross-section), with water tubes wound around them. An aluminum cap shields the back end of the detector. Note the asymmetry of the coil positioning within the copper tube. Figure created using MS PowerPoint. The middle left photo shows the coils wound in water tubing (the black is tape). The middle right photo shows the Tx coil (coil A is covered in the thermally conductive, MPI-inert Al$_2$O$_3$ epoxy mixture, which had not yet been applied to coil B). The far right photo shows the Rx coil (gradiometer). (b) Finite element simulation (FEMM 4.20) of the Tx coils in copper tube at 25 kHz to show field-shaping effect of tube. Colormap shows $H$ in A/m per 1 A current. (c) Custom simulation of detection sensitivity profile (Tx and Rx coils, no copper tube), using MATLAB (R2018b, https://www.mathworks.com/products/matlab.html). Tx (red coil) simulated with 25 kHz 30 A$_{pk}$ field, SPIO model based on measured spectrometer data of VivoTrax (Magnetic Insight, Alameda, CA) nanoparticles. Colormap normalized to 1 at center surface of detector $(x, y, z) = (0, 0, 0)$. Iso-contour lines are shown with spacing 0.1, with the 0.3 line indicated.
Figure 4. MP detector mounted on moveable arm. Photos at two angles, one with the breast phantom and one without, are shown. The copper tube and aluminum cap are attached to an articulating arm made of anodized aluminum with three joints, enabling a wide range of motion so that the detector can be moved by hand to and from any desired positions. Water tubes and wires are visible and secured to the arm.

Figure 5. Experimental setup for surface detection. A plastic stand holds the glass bulb SPIO samples, and the detector is positioned such that the samples are approximately at the center of the surface/end plane of the coils. The detector’s mounting arm can be tightened so that it stays in place. The holder can be moved up to and away from this position in a repeatable manner. Samples between 1 μg and 100 ng Fe are tested as well as a control bulb filled only with DI H₂O (data shown in Fig. 6).
Results. Figure 6 shows the SPIO signal level with the sample placed at the detector’s surface and distant. The system is sensitive to 100 ng Fe with SNR 1.83 using a pulsed Tx signal of 72 ms and a 450 ms pause time, for a 16% duty cycle. The first quarter of the received pulse is discarded to remove transient effects, for a total 54 ms received pulse every 450 ms, and each data point shows the magnitude of the $3f_0$ frequency component of the received pulse. Preamplifier gain is 500. In post-processing, a two-term exponential magnitude drift is removed in order to overlay the trials. DI water in the same glass bulb and plastic sample holder serves as an experimental control. A plot of the measured signal magnitudes (“avg sig diff”) as a function of SPIO quantity can be found in supplementary figure S4 to illustrate the linearity of MPI signal with iron content.
Figures 8 and 9 show detection of samples embedded in the anthropomorphic breast phantom in two locations (full videos available in supplementary materials S2 and S3, respectively). For the lower outer left breast location, when the sample is removed and the detector moved to that location, small perturbations in the baseline can be seen, indicating some coil loading or parasitic effects due to the proximity of (and/or physical contact with) the breast phantom (this can be seen in the orange shaded regions). For the upper inner right breast location, no baseline perturbations are detectable.

Discussion. The detector is capable of detecting an estimated clinically relevant quantity of SPIO (100 ng Fe VivoTrax). Assuming tumor SPIO accumulation of 0.12% ID/g, the 100 ng Fe sample represents the expected accumulation in a 790 µm diameter tumor. The detector’s feasibility for hand-held intraoperative use is strongly supported by the experiments in which the detector is moved to and away from stationary samples (either in the plastic holder or the anthropomorphic phantom). The detector is held and moved with minimal compromising changes in the baseline signal and with no addition of noise, and it detects a 500 ng Fe sample embedded in different areas of the breast phantom with high sensitivity.

We also note that here, voltage amplitude was used as the metric for tracer detection; a more meaningful metric could be used in a clinical device, such as report of SNR or a statistical metric of expected false-positive confidence level. Overall, the results presented demonstrate that a single-sided hand-held MPI detector has the
Lumpectomy specimen imaging with small-bore scanner

**Materials and methods.** The MPI scanner for intraoperative specimen imaging is envisioned as a compact and portable tabletop or cart-mounted system that can be placed in the operating room and produce fast 3D images of the spatial distribution of SPIOs in the excised tissue. We test a small-bore, mechanically rotated 2D field-free line (FFL) permanent magnet-based imager for this purpose. The imager was previously described\(^3\), and design details and specifications are available open source at https://os-mpi.github.io/\(^3\).

A schematic and photo of the imager are shown in Fig. 10a and b, respectively. Rare earth NdFeB permanent magnets (PMs) produce the FFL along \(y\)’ (primed axes referring to a mechanically-rotating coordinate system) and electromagnet (EM) shift coils (diamond-shaped, circumscribing the PMs) sweep the FFL across the projection axis, \(x\)’. The FFL is produced by permanent magnets (two 2” x 2” x 16” N48), and has a measured gradient strength of 2.83 T/m. The EM shift coils are each 250 turns of 14 AWG magnet wire, water-cooled, and produce a 1.31 mT/A field. A 30 A peak current sweeps the FFL across a \(\sim 3\) cm field of view (FOV).

A copper tube bore is stationary in the \((x, y, z)\) frame and houses the transmit and receive coils. The PM and EM hardware is mechanically rotated about the bore by a motor to acquire 1D projections at multiple angles, using slip rings to enable continuous rotation (rather than having to change rotation directions to avoid twisting wires). The transmit/receive coils and signal chain are similar to that of the MP detector, with a bore diameter of 5 cm. The drive coil is a 12 cm long solenoid with two 41-turn layers of 16 AWG Litz wire (New England Wire). It has \(L = 195\) µH and produces 0.62 mT/A at the center of the imaging FOV (2 cm from end of coil). A gradiometer receive coil is epoxied concentrically inside the drive coil. Its two oppositely wound 20 AWG Litz wire coils (4 cm long, 66 turns each, 4 cm separation) provide first-order drive cancellation. The signal chain utilizes a NI DAQ console and a drive frequency of \(f_0 = 25\) kHz. This signal is amplified by an AE Techron 7548 power amplifier, and filtered by a custom high-power low-pass filter tuned to \(f_0\). On the receive side, a custom tuning/notch filter provides a measured 60 dB attenuation between \(3f_0\) and \(f_0\), followed by further low-noise amplification (Ametek Signal Recovery 5113, Scientific Instruments, Berwyn, PA) and bandpass filtering (SR650, Stanford Research Systems).

A typical image acquisition sweeps the FFL with either a triangular or sinusoidal shift waveform and acquires 27 projections covering 180° with 66 readouts per projection and 150 cycles of the 25 kHz transmit field per readout. The projections are then reconstructed to form a 2D image utilizing a model-based preconditioned conjugate

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**Figure 8.** Breast phantom detection results, detector moved, left breast lower outer quadrant. Detection of a 500 ng Fe SPIO sample embedded in the anthropomorphic breast phantom in the lower outer quadrant of the left breast. The detector is held by hand and moved around during data acquisition to and away from the breast at the sample’s location. Four time points (\(t_1\)–\(t_4\)) are selected to show still frames from a video of the experiment. (See S2 for video.) The SPIO sample (in glass bulb) is removed from the breast phantom at data point 855 (thick green dashed line). The acquisition scheme, receive chain setup, and data analysis are the same as described in the caption of Fig. 7.

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potential for use as a fast intraoperative device, with the sensitivity and stability for detection of small quantities of residual tumor.
gradients minimization; this method uses a numerical model of the FFL smeared by a Gaussian (empirically determined $\sigma = 1.5$ mm), which is swept and rotated according to the measured shift current and rotation angle. This accounts for the sensitivity width as well as imperfections in shift current and angular position, which are not represented in a simple iradon transform. 3D imaging can be enabled by mechanically translating the object (e.g. excised specimen) along the bore ($z$ axis). Figure 10c illustrates the transmit and receive coils positioned inside the copper tube, with the breast specimen positioned inside the first half of the gradiometer receive coil (the $z$ location of the FFL and location of imaging slice).

The imager can produce 2D images in down to 2.9 s; this temporal resolution is not a lower bound, as the system can rotate and image faster than this. However, image speed comes at the expense of SNR and further temporal resolution improvement is unnecessary for this intraoperative application. Spatial resolution in MPI is dependent on SPIO properties and gradient strength; this imager’s spatial resolution has been estimated to be $\sim 2–3$ mm for VivoTrax. The imager is sensitive to 100 ng Fe (VivoTrax) (in a 3 mm bulb) in a 5 s image with SNR = 5.

We developed and 3D printed “lumpectomy specimen” phantoms, in which the healthy tissue of the excised specimen is the 3D printed plastic (no SPIOs), and the “tumor” is a cavity filled with a chosen SPIO concentration relevant for passive accumulation rates. Based on specimen and tumor sizes found in the literature91–94 and the imager’s $\sim 3$ cm field of view, the phantoms are designed with specimen diameter of $\sim 1.6$ cm and tumor diameter $\sim 6.5$ mm, with two 2.5 mm fiducials. The phantom is a 5 mm-thick 2D slice for simplicity and proof-of-concept. The arbitrarily shaped “tumor” is filled with a 0.5 mg/mL Fe solution for a total of 51.2 µg Fe. Assuming a 5 mg/kg dose and 65 kg patient, this corresponds to tumor accumulation of 0.154% ID/g. The fiducials are filled with undiluted VivoTrax and each contains 61.1 µg Fe. A margin is considered positive/close if the tumor is $\leq 1$ mm from the inked surface, and negative if $> 1$ mm from the surface92,93. Three versions of the lumpectomy specimen phantoms are developed: a negative margin in which the tumor is centered and $\geq 3.8$ mm from the margin, and two positive margin phantoms in which the tumor is as close to the edge as feasible with 3D printing ($\sim 0.8–0.9$ mm), one of which has the tumor far from the fiducials and the other close to the fiducials to ensure the fiducial-tumor proximity does not produce artifacts. Photos of the three phantoms are shown in Fig. 11a.

Results. Figure 11b shows MPI images of the three “lumpectomy specimen” phantoms, each acquired in 10.7 s. In Fig. 11c, these are shown overlaid onto the optical images of the phantoms using the fiducial locations. By measuring the distance between the tumor edge and the specimen margin, all three images are classified cor-
Discussion. Imaging of phantoms representative of excised breast specimens is demonstrated with high sensitivity and with 10.7 s imaging times, fast enough for intraoperative application, and fiducial coregistration is utilized to show tumor location and proximity to margins. The differing intensities between the fiducials is most likely due to imperfect fiducial shape/filling/sealing of the 3D printed wells in these phantoms, since the 3D printer does not always print repeatable small cylindrical wells. Also, the lower fiducial in the negative margin phantom appears to have a small air bubble. Even with this MPI scanner with spatial resolution \( \sim 2-3 \text{ mm} \), points closer can still be distinguished given sufficient SNR by locating the centers of their overlapping point spread functions. Ultimately, increased gradient strength will be desired to improve spatial resolution for clinical application.

To be useful in a clinical setting, the MPI must be extended to imaging a full 3D volume. With a 2D FFL scanner like the one used here, this can be done by imaging multiple 2D planes as the sample is moved through the bore by a motorized bed. In this process, out-of-slice imaging artifacts must be addressed by either a 3D model-based reconstruction or further encoding along the bore. These approaches have been demonstrated in x-space or system matrix reconstructions. To assess the degree to which the detected nanoparticles near the surface of the specimen, it is important to have 3D knowledge of the surface location. Since disease-free tissue is free of nanoparticles and thus invisible to MPI, this requires a second co-registered imaging modality. Since only the surface location is needed, this could be readily supplied by a 3D optical surface scanner prior to insertion.
in the MPI. The results in Fig. 11 show this registered with 2D optical images as opposed to 3D. Alternatively, the surface information could be provided by a combined MPI/CT or MPI/MRI scanner.

Conclusion

For the clinical need of improved intraoperative margin assessment in BCS, we propose a two-part MPI solution involving a hand-held MP detector and a small-bore MPI imager, used along with an injected SPIO agent as a tumor marker. MPI offers high sensitivity detection and imaging with fast acquisition times, and can both detect residual SPIO in the excision cavity as well as image its spatial distribution on the removed specimen. With these features, MPI can be used iteratively during surgery to better achieve complete tumor removal and thus a higher likelihood of negative margins. Both proposed hardware systems are designed, constructed and validated in phantoms.
The hand-held detector is demonstrated to have clinically relevant sensitivity (down to 100 ng Fe, representing a 790 µm diameter tumor), as well as stable and reproducible hand-held use for samples embedded in an anthropomorphic breast phantom. This demonstrates its ability to detect small volumes of residual tumor tissue in the breast after initial specimen excision.

A small-bore 2D FFL projection imager is developed with a 5 cm imaging bore, 2.83 T/m gradient field, and 3 s temporal resolution with the ability to image continuously. The imager is sensitive to 100 ng Fe (VivoTrax) (in a 3 mm bulb) in 5 s with SNR of 5, and has spatial resolution ~2–3 mm. We demonstrate imaging of phantoms representative of excised breast specimens, showing tumor location and proximity to margins with high sensitivity and with 10.7 s imaging times, fast enough for intraoperative use. This serves as a proof-of-concept demonstration of MPI’s potential for fast imaging of excised specimens with relevant tracer levels. Combined with a 3D optical surface scan or other co-registered structural imaging modality, small-bore MPI may be able to determine the distance between tumor and specimen surface and thus provide a timely margin assessment to the surgeon. Together with the hand-held detector, this work demonstrates the potential for MPI as a clinically realizable solution to the problem of positive margins in breast-conserving surgery.

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**Author contributions**
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**Competing interests**
The authors declare no competing interests.

**Additional information**

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