Registration of Supine MR Mammography with Breast Ultrasound for Surgical Planning of Breast Conserving Surgery: A Feasibility Study

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Abstract

Purpose

To report the feasibility, accuracy and initial clinical experience of the use of real-time magnetic resonance navigated ultrasound (rtMRnUS) in the surgical planning of breast conserving surgery (BCS) via guide wire insertion.

Materials and Methods

Twenty-nine participants were recruited into this prospective ethics committee approved study. The first four cases were utilised as a training set. Participants underwent a supine contrast enhanced breast MR examination with the arm on the affected side abducted emulating the ultrasound position. Prior to MR examination external fiducials with corresponding ink marks were placed, on the skin of the affected breast. The location of the external fiducials and ink marks acted as co-registration pairs. MR examinations included both functional and morphological images.

A LOGIQ E9 ultrasound system (GE Healthcare, Milwaukee, WI, USA) equipped with a 6-15 MHz transducer was utilised for rtMRnUS. To facilitate point co-registration of the previously acquired MR dataset with the real-time ultrasound, co-registration pairs were identified on both imaging modalities. The following co-registration quality metrics were recorded: root mean square deviation (RMSD), lesion and global accuracies. Post co-registration guide wire insertion was performed.

Results

Co-registration was successfully undertaken in all participants. Results from 25 participants are presented. The median (min, max) RMSD was 3.3mm (0.6mm, 8.8mm). Global accuracy was assessed as very good (8), good (12), moderate (3) and poor (2) while median (min, max) lesion accuracy was recorded at 8.9mm (2.1mm, 33.2mm). Positive margin status was noted from 4 participants following rtMRnUS facilitated guide wire insertion.

Conclusion

The use of rtMRnUS to facilitate guide wire insertion is a feasible technique. Generally, very good or good global registration can be expected. Lesion accuracy results indicate a median difference, in 3D space, of 9mm can be expected between image modalities.

Introduction

Localised breast tumours are typically managed by breast conserving surgery (BCS) combined with adjuvant radiotherapy, which provides comparable survival outcomes to traditional mastectomy [1,2], whilst providing a better cosmetic result. However, if histopathology of the resected specimen reveals tumour extending to the surgical margin, so called positive margin, then further resection is advised until a clear margin is obtained, since margin positivity is an important risk factor for recurrent disease [1]. Re-operation for positive tumour margin status can result in poor cosmetic outcome, increased patient anxiety, delayed adjuvant therapy and increased treatment costs [1,2]. The frequency of positive margins following BCS varies depending on the health care setting, however, in the UK the reoperation rate is around 20% [3].

Ultrasound or stereotactic guided wire insertion is frequently used in the pre-surgical localisation of small breast cancers prior to BCS. However localisation of a lesion using a guide wire will be inaccurate if the full extent of the disease is not identified by the imaging modality used to guide the wire insertion. Given its ease of access and low cost ultrasound is frequently utilised to direct wire insertion, yet the accuracy of ultrasound in delineating breast malignancies is known to be inferior to MRI [4]. Conversely, while MR guided wire insertion might improve accuracy, it has limited availability, requires greater time and at increased cost. Recently, real-time MRI navigated ultrasound (rtMRnUS) has been introduced, that combines the benefits of both ultrasound and MRI. In this technique a previously acquired 3D MR dataset is co-registered to real-time US images. Both modalities are displayed simultaneously and the MR images can be used to navigate real-time US, allowing insertion of the guide wire into the optimum location.

Two papers by Rizzatto [5], Fausto [6] and co-workers explored the feasibility of co-registering MR and US images via an rtMRnUS technique in healthy volunteers and patients. The authors concluded that rtMRnUS is both accurate and reproducible. A number of authors have previously reported a superior detection rate for rtMRnUS than second look or targeted ultrasound in the detection of enhancing lesions previously identified on MR [7-10]. Chang et al. reported that rtMRnUS provided a more accurate estimation of breast tumour longest dimension than ultrasound alone when compared to histopathology results [11].

The aim of this study was to evaluate the feasibility of utilising rtMRnUS in the surgical planning of BCS, via guide wire insertion, and to document initial clinical experience. Both lesion and global registration accuracy were assessed along with the number of failed rtMRnUS co-registrations.

Materials and Methods

Participants

Ethic committee approval was obtained for this prospective study. Potential participants were prospectively approached regarding study participation if following triple assessment (mammography, ultrasound and biopsy) they had a biopsy proven malignancy and were scheduled for BCS. Exclusion criteria included normal contraindications to MRI and/or gadolinium based contrast agents. Following written informed consent, study participants underwent a supine contrast enhanced breast MRI examination prior to rtMRnUS guide wire insertion and subsequent BCS.

MR Imaging and Post Processing

Prior to imaging four MR visible external fiducial markers (vitamin E capsules) were placed in the 12-, 3-, 6-, and 9-o'clock positions relative to the nipple. If the lesion was located at an extreme edge of the breast, such as in the axillary tail, then at least one additional fiducial was placed in that location. The locations of the external fiducials were marked on the skin with indelible ink. The participant was imaged in the supine position with the arm on the affected side abducted, thereby emulating the ultrasound position. A plastic bridge was utilised to support a 32 channel phased array torso receiver coil (NeoCoil LLC, Pewaukee, WI, USA) and ensure that it did not deform the affected breast, but allowed the breast to fall into a natural position.

All MRI imaging was undertaken on a 3.0T MR750 Discovery scanner (GE Healthcare, Milwaukee, WI, USA) in conjunction with a dedicated 32-channel torso coil. Participants underwent a limited breast examination consisting of a 3 plane localiser; axial 3D T1W LAVA-flex dynamic test phase (same imaging parameters as

the dynamic series) to review anatomical coverage and ensure visualisation of external fiducials; axial 3D T1W LAVA-flex acquired dynamically over 19 phases with a 14 second temporal resolution (TR/TE 3.9/1.8ms, flip 12°, slice/gap 4/0mm, matrix 288x160, FOV 38x30cm); and a delayed post contrast high spatial resolution axial 3D T1W LAVA-flex (TR/TE 4.3/1.9ms, flip 12°, slice/gap 1.2/-0.6mm, matrix 320x224, FOV 38x30cm). Total scan acquisition time for all four sequences was under 7 minutes. Gadolinium containing contrast agent was administered at the start of the 3rd phase of the dynamic examination, via a bolus injection (0.05 mmol/kg body weight) by a Spectris Solaris power injector (Medrad, Warrendale, PA, USA) and this was immediately followed by a 20ml saline flush; total injection time 10 seconds for all patients.

Post-acquisition MR images were reviewed on an Advantage Workstation (GE Healthcare, Milwaukee, USA) with post processing software (subtraction, multi-planar reformatting, maximum intensity projections and dynamic curve assessment) to identify the malignant lesion. An additional image series was generated by subtracting a ‘water-only’ pre contrast phase from a ‘water-only’ post contrast dynamic phase, thereby displaying the greatest contrast uptake in the identified malignant lesion.

LAVA-flex sequence results in four different T1W image types – in-phase, out-of-phase, water-only and fat-only. The following series were transferred to the rtMRnUS system: in-phase dynamic test phase, water-only subtraction and water-only delayed post contrast high spatial resolution. The in-phase images provided good T1W anatomical detail while highlighting the location of the fiducials. These images were utilised to co-register the MR data to the real-time ultrasound. The water-only subtraction and delayed post contrast high spatial resolution images were

subsequently used to aid ultrasound operator navigation, based on lesion location and extent.

Real-time MR Navigated Ultrasound

A LOGIQ E9 ultrasound system equipped with a 6-15 MHz broad spectrum linear matrix array transducer (ML6-15) (GE Healthcare, Milwaukee, WI, USA) was employed for rtMRnUS. For the purposes of real-time volume navigation, the LOGIQ E9 is fitted with a fixed electromagnetic transmitter with a defined operating volume and two electromagnetic sensors mounted on the transducer. This arrangement provides a means of determining the transducer position and orientation relative to the transmitted magnetic field.

All rtMRnUS examinations were undertaken by either a Consultant Breast Radiologist or a Consultant Breast Radiographer with a minimum of 5 years experience in breast ultrasound, assisted by researchers trained in the application of the LOGIQ E9 system for rtMRnUS purposes. Once again the participant was imaged in a supine position with the arm on the affected side abducted. Since the breast is an easily deformable organ, minimal transducer pressure was applied throughout the co-registration process.

To facilitate point co-registration of the previously acquired MR dataset with the real-time ultrasound, the centre of the transducer was placed over the central location of the external fiducial, as indicated by the skin ink mark. This skin position was recorded on both the real-time ultrasound image and on the in-phase MR dataset. This procedure was repeated for at least three fiducial points. The choice of which three fiducials to use was based on the location of the tumour. For example, if the lesion was located in an upper central location then the fuducials located at 9-, 12-,

and 3-o'clock were used. However, if the lesion was located in a left upper outer location then the 12- and 3-o'clock fiducials were employed, together with the additional lesion related fiducial.

Once three co-registration pairs were recorded the ultrasound system registered the MR and ultrasound and provided a quality measure (root mean square deviation, RMSD). If more than three co-registration points were identified the ultrasound system utilised the 3 co-registration point pairings that resulted in the lowest RMSD. Once the MR and ultrasound images were registered the LOGIQ E9 system simultaneously reformatted the 3D MR dataset to match the position and orientation of the ultrasound image and applied the resulting registration matrix to the two remaining MR datasets. Since the registration matrix had been applied to all the MR datasets it was possible to switch between MR image types, while performing the real-time ultrasound, without repeating the co-registration process.

Following co-registration the RMSD was recorded. Additionally, both lesion and global co-registration accuracy was assessed. Lesion co-registration accuracy was determined by separately recording the centre of the lesion on both the real-time ultrasound image and on the MR dataset. Once the lesion centre had been recorded on both imaging modalities, the LOGIQ E9 system calculated the difference between the two points in 3D space thereby determining the accuracy. Global co-registration accuracy was determined qualitatively by the performing clinician using a five point scoring system (very poor – registration either does not match or only matches in a very limited area of the breast, poor – registration only matches over a limited portion of the breast, moderate – registration matches well but not globally over the whole breast, good – registration matches well globally over the whole breast, very good – registration matches almost exactly globally over the whole breast).

Once co-registration had been achieved the clinician was free to perform guide wire insertion either under rtMRnUS or purely under ultrasound guidance albeit with the cognitively retained MR information.

Results

Twenty-nine participants were recruited between November 2012 and March 2014. To facilitate familiarisation with the co-registration process the first four cases were utilised as a training set. Consequently, the results of twenty-five participants with a median (min, max) age of 61 (48-72) years are presented. Twenty-eight lesions were identified with a median (min, max) histopathological diameter of 11mm (5mm, 19mm). Further participant and lesion characteristics are presented in Table 1.

Following standard triple assessment all study participants were believed to have a solitary malignancy. Supine breast MR concurred with the results of triple assessment in all but two cases; an additional focus of disease was identified in one case and a further two foci of malignancy discovered in the remaining case.

The median (min, max) interval between MRI and rtMRnUS was 1 day (1 day, 5 days). Co-registration was successfully undertaken in all participants. The median (min, max) RMSD was 3.3mm (0.6mm, 8.8mm). Global accuracy was assessed as very good (8), good (12), moderate (3), poor (2) and very poor (0).

At least one enhancing MR lesion was identified in all participants, however, in one case this appears to have represented a false positive MR finding. MR demonstrated a lesion in the lateral aspect of the breast. However at rtMRnUS no lesion was visible on the ultrasound in the area highlighted by the supine MR examination. Review of the findings at triple assessment indicated a medial lesion. Ultrasound investigation of the medial aspect of the breast identified a lesion which was subsequently proven malignant. Routine ultrasound as part of standard triple assessment identified 25 lesions in 25 participants whereas rtMRnUS revealed 27 lesions in 24 subjects. Consequently, lesion accuracy is reported for 24 participants

since for this metric the lesion must be visible on both modalities. Median (min, max) lesion accuracy was recorded at 8.9mm (2.1mm, 33.2mm) from 25 lesions (lesion accuracy is not presented for 27 lesions since in the case with three MR enhancing areas, lesion accuracy was only recorded for the index lesion).

Representative rtMRnUS images are presented in Fig. 1 and 2.

Following rtMRnUS facilitated guide wire insertion and subsequent BCS, histopathology revealed positive margins in 4/25 (16%) participants, two with DCIS alone and two with both invasive and in-situ disease identified at the margin.

Discussion

This study investigated the feasibility of using supine MR images for rtMRnUS mediated guide wire insertion, to facilitate surgical planning of BCS. Additionally, metrics of co-registration quality such as RMSD, lesion and global registration accuracy were assessed. Finally, initial clinical experience is discussed.

For this study co-registration accuracy as determined by RMSD resulted in a median (min. max.) error of 3.3mm (0.6mm, 8.8mm). Rizzatto [5], Fausto [6] and co-workers reported co-registration accuracy from five healthy volunteers utilizing the same ultrasound system and co-registration methodology as this study. Based on five point-to-probe measurements (three external fiducials, the nipple and an internal mammary artery) a ‘misalignment of about 0.5cm’ [6] was reported. Rizzatto et al. [5] further reported that preliminary clinical experience in 41 patients resulted in good co-registration in ‘almost all’ cases.

Two reports by Nakano et al. [7, 8] reported the co-registration accuracy with reference to a lesion. The experimental set-up by Nakano and co-workers employed both an electromagnetic field and a transducer mounted electromagnetic sensor similar to this work. However, to allow co-registration of the two image modalities only the nipple was utilised as a co-registration reference point. In the first paper, Nakano et al. [7] reported a 7mm difference between the US and MR image with reference to the index lesion. The later study [8] reported a mean 3D positioning error of 12.0mm (SD±7.5mm; range 2 to 40mm) between the US and MR lesion location from 63 tumours. The level of lesion co-registration accuracy was similar in our study to the reports by Nakano et al. [7, 8] with a median (min, max) lesion accuracy of 8.9mm (2.1mm, 33.2mm) from 25 lesions.

When considering the accuracy of co-registration for an organ such as the breast, it is important to realise that any quality metric assigned to that registration may not be appropriate to the whole breast. If one considers a hemisphere as a simplified representation of a breast, the pole of the hemisphere would represent the nipple and external fiducials would be placed in 12-, 3-, 6-, and 9-o'clock positions relative to the nipple. Even if the RMSD following co-registration is very low, it only represents the geometry relative to the co-registration pairs utilised in the registration process. Consequently, the registration quality distant to these co-registration pairs may be significantly poorer than the RMSD indicates. It is for this reason that in our methodology if the index lesion was known to be located at an extreme edge of the breast, such as the axillary tail, then at least one additional fiducial was placed in that location, in the hope that the registration geometry would encompass the area of the breast containing the index lesion. The study by Nakano et al. [8], in which the nipple represented the registration reference point, investigated this problem by comparing the lesion accuracy from proximal tumours (<40mm distance to nipple) against distal lesions (≥40mm distance to nipple). A greater but non-significant difference was noted in lesion positional error for distal (13.7mm SD±8.6mm; range 5 to 39mm) compared to proximal (11.0mm SD±6.8mm; range 2 to 40mm) tumours.

In the current study "global" co-registration accuracy was assessed qualitatively by the performing clinician on a five point scoring system. Co-registration accuracy was assessed by comparing the location of prominent features such as nipple, parenchyma, internal mammary nodes and vasculature on both imaging modalities. In three cases global accuracy was assessed as moderate and poor in a further two cases. However, the median (min, max) RMSD in these five cases was 4.1mm (2.9mm, 5.3mm), which was similar to the whole cohort at 3.3mm (0.6mm, 8.8mm).

Consequently, it seems that while a co-registration quality metric is useful, the operator must consider its validity in relation to the lesion position relative to the co-registration pairs utilised in the registration process.

Our initial clinical experience indicates that transducer pressure and breast size are the main factors that impact on rtMRnUS co-registration accuracy. Transducer pressure will obviously affect not only the co-registration accuracy, but also image quality. During the co-registration process as little transducer pressure as possible is used to ensure the breast maintains a shape similar to that obtained at MR imaging. Following registration if transducer pressure is increased the breast deforms and the registration matrix is invalidated. Consequently, areas highlighted on the two image modalities will not represent the same tissue. The disadvantage of reduced transducer pressure is poorer ultrasound image quality consequent to inferior acoustic coupling. In our clinical experience a combination of light and standard transducer pressures might be required to identify lesions. Initially, light transducer pressure is applied for co-registration purposes. Following registration MR images are used to navigate the ultrasound operator to the location of the MR enhancing lesion via the real-time ultrasound. However, we have observed that occasionally the lesion is not visible on the ultrasound images. If the transducer pressure is increased, the registration matrix will become invalid but the image quality will improve, and the ultrasound operator can interrogate tissue in that area of the breast. Frequently, this will reveal the abnormality. If the transducer pressure is reduced and the breast returns to its normal shape the initial registration matrix will be valid once more.

Unlike Fausto et al. [6] we did not exclude participants based on breast size and although not assessed formally we did note that larger breasts can be more difficult

to co-register. Nevertheless, we were able to perform rtMRnUS in all cases. Primarily, we believe that larger breasts can pose a co-registration challenge due to the greater range of deformation, both in terms of the position the breast naturally falls into when the patient is supine and in response to transducer pressure. By comparison smaller breasts have a smaller range of deformation.

The use of rtMRnUS seems to result in a number of benefits. Chang et al. [11] reported that rtMRnUS provided a more accurate estimation of breast tumour longest dimension than ultrasound alone, when compared to histopathology results. Additionally, increased detection rates have been reported for rtMRnUS compared to second look ultrasound, for the detection of previously highlighted MR enhancing lesions [7-10]. These attributes would seem to make rtMRnUS an ideal tool to ensure guide wire insertion is optimal. However, when undertaking procedures such as biopsy and guide wire insertion under real-time ultrasound control the technique used can impede direct rtMRnUS control. During biopsy and guide wire insertion the breast is compressed by the transducer and the operator's hand to ensure immobilisation of the lesion during the procedure [12]. This immobilisation results in a loss of registration due to deformation, as outlined above. However in our clinical experience rtMRnUS can navigate the ultrasound operator to the target lesion. Once the operator is ready to insert the guide wire, the transducer pressure is increased to immobilise the lesion, while visually tracking the real-time ultrasound location of the identified lesion. The operator then inserts the guide wire with cognitive reference to the MR extent of the lesion.

Arguably, an alternative approach to rtMRnUS would be to insert guide wires solely under MR guidance. However, this not only necessitates dedicated localisation hardware and software, but also much greater access to MR scanner time. Further

not all lesion locations, such as chest wall, are accessible to MR guided techniques [13]. The technique outlined in this work minimises the necessary MR scan time while maximising the diagnostic accuracy. Additionally, guide wires can be inserted in the customary manner, albeit with rtMRnUS co-registration, by the regular staff.

A number of limitations should be considered in relation to this report. Firstly, to facilitate co-registration MR data was acquired in the supine position to match the ultrasound position. The image quality of torso phased array supine breast MR is inferior to that obtained in the prone position with a breast coil. Nevertheless, all but one lesion demonstrated by triple assessment was identified by supine MR and three additional foci were also identified using this technique. Secondly, the small number of participants and single centre nature of this study means that the results might be the subject of bias. Thirdly, due to the study design researchers were aware that participants were scheduled for BCS and therefore must have at least one lesion present, this knowledge might also have introduced bias into the results.

In conclusion this study has demonstrated the accuracy of rtMRnUS following co-registration of breast MR and ultrasound data. Furthermore, we have reported initial clinical experience in the use of rtMRnUS in the surgical planning of BCS via guide wire insertion and demonstrated that it is a feasible technique.

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Table 1

Parameter		Participants
Histological grade	n=28	
Grade I		12
Grade II		9
Grade III		7
Histological type	n=28	
NST		22
Ductal		3
Micropapillary		1
Tubular		1
Mixed lobular / NST		1
Oestrogen receptor	n=28	
Negative		3
Positive		25
Progesterone receptor	n=28	
Negative		6
Positive		22
HER2 receptor	n=28	
Negative		25
Positive		3
DCIS component	n=25	
Low grade		10
Intermediate grade		6
High grade		3
Not detected		6
Axillary Node Status	n=25	
Positive		3
Negative		22
Surgical Margin Status	n=25	
Positive		4
Negative		21
Affected Breast	n=25	
Left		13
Right		12

Figure Legends

Figure 1

52yrs patient with palpable lesion, screening mammography: 9mm indeterminate mass upper central right breast, ultrasound: 10mm mass, biopsy: NST, Grade I, with associated high grade DCIS

Top row left to right: Volume render demonstrating position of external fiducials, source image from dynamic sequence and positive enhancement integral map demonstrating an enhancing lesion superiorly within the right breast (arrow).

Bottom row left to right: Co-registered rtMRnUS images demonstrating both global (nipple) and lesion registration. Green box on MR subtracted image represents US field of view. Green numbers and crosses represent central location of lesion from each modality and are used to calculated lesion accuracy. Co-registration via rtMRnUS resulted in a RMSD of 5.7mm, very good global registration and a lesion accuracy of 2.7mm.

Figure 2

61yrs patient with non-palpable mass, screening mammography: single indeterminate density upper inner quadrant right breast, ultrasound: single lesion, biopsy: Ductal, Grade II, DCIS present

Panel a: Positive enhancement integral map demonstrating an enhancing lesion superiorly within the right breast and delayed post contrast high spatial resolution image (long arrow).

Panel b: Positive enhancement integral map demonstrating a second enhancing lesion superiorly within the right breast and delayed post contrast high spatial resolution image (short arrow).

Panel c and d: Co-registered rtMRnUS ultrasound and subtracted dynamic MR images. Green box on MR image represents US field of view. Green numbers and crosses represent central location of lesion from each modality and are used to calculated lesion accuracy. Co-registered rtMRnUS resulted in a RMSD of 8.8mm, very good global registration and lesion accuracies of 7.9mm and 5.6mm.

Panel e: Ultrasound image taken after rtMRnUS co-registration clearly demonstrated two separate lesions. Histopathology of surgical specimen confirmed presence of two separate malignant lesions: 1 upper inner, 1 upper central, both ductal NST, Grade II with associated high grade DCIS

Figure 1

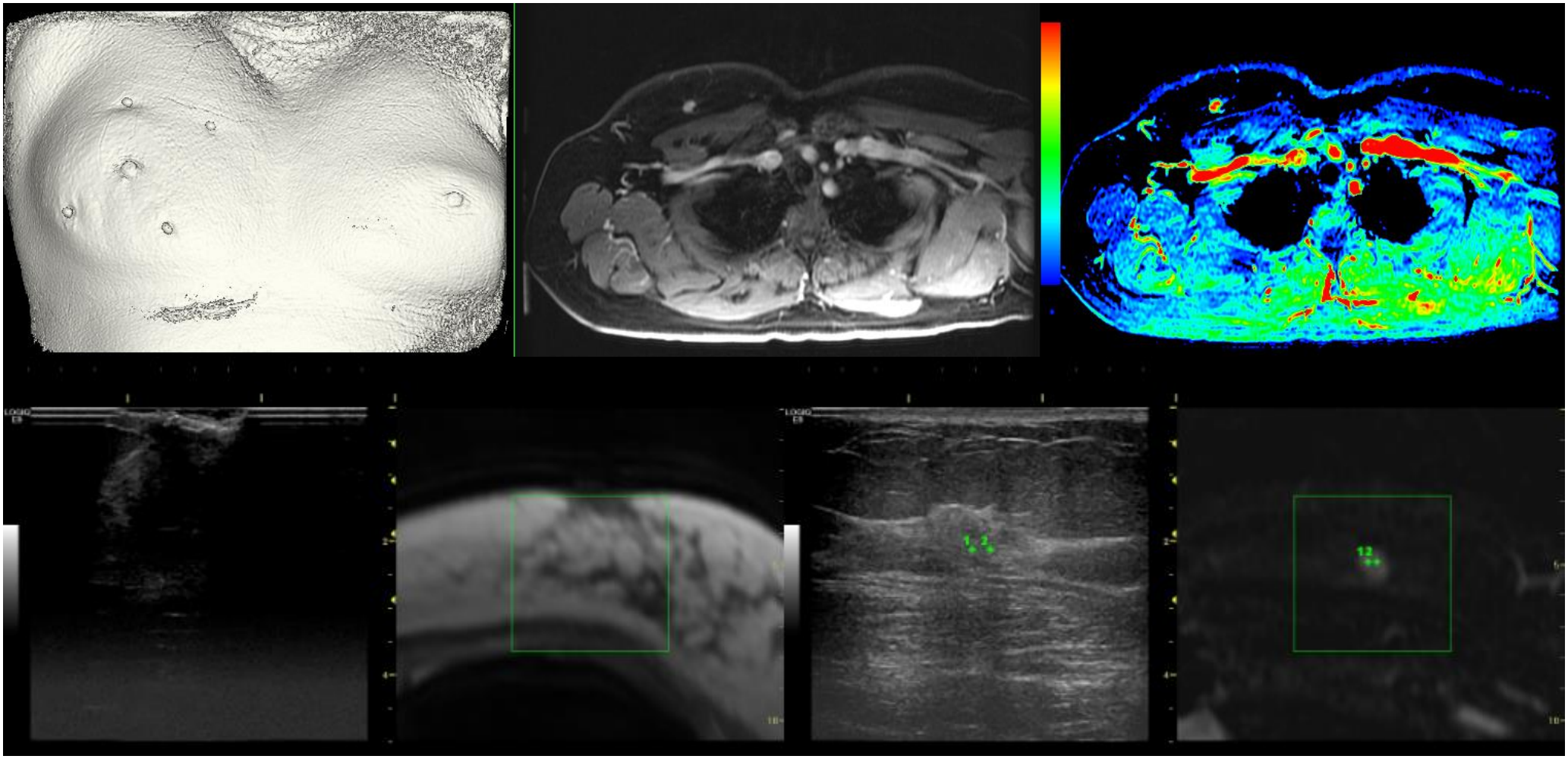

Figure 2