



Research article

MARIA[®] M5: A multicentre clinical study to evaluate the ability of the Micrima radio-wave radar breast imaging system (MARIA[®]) to detect lesions in the symptomatic breast



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ARTICLE INFO

Keywords:

Breast
Breast imaging
Radio-wave imaging
Diagnostic imaging
Breast density

ABSTRACT

The MARIA[®] breast imaging system is a clinical diagnostic tool that uses a hemispherical array of radiowave antennas to generate three-dimensional images of the internal breast. The system utilises the variance of dielectric contrast within the breast volume in order to identify areas of interest for further diagnostic investigation. This multicentre study of 225 patients was conducted at three trial sites and recruited women with both malignant and benign lesions. The MARIA[®] images from the study were read by both clinicians who had access to the patient's clinical information, as well as by 'blind' reviewers who did not. Results from the study show an overall sensitivity of 76% for the system, which was similar across benign and malignant findings, and in denser breasts. The results from this study are outlined here and discussions on ongoing and future work with MARIA[®] are deliberated.

1. Introduction

Breast cancer is one of the most frequently occurring cancers in women and in many countries, it is a leading cause of female death [1,2]. Early diagnosis is demonstrated to be linked to enhanced survival rates [3,4]; indeed, it has been shown that increased tumour size is linked to a reduction in five-year survival rates [5].

X-ray mammography (XRM) has been an accepted form of breast imaging in screening and diagnostics for many years but has its limitations, including patient discomfort, reduced functionality in more 'dense' breasts, and the use of ionising radiation. Alongside XRM, ultrasound (US) is most commonly used in the UK as a 'second look' device as using a hand-held ultrasound probe to image an entire breast is time-consuming and prone to error. Magnetic Resonance Imaging (MRI) is often cited as the 'gold standard', but it is not a practical screening modality in the general population for reasons such as time, costs, overdiagnosis, and the requirement for a specialist facility. As such, it is used routinely only in the surveillance screening of young women at a high risk of breast cancer [6]. Newer technologies exist but

are yet to obtain a firm hold in the day-to-day practice of screening and diagnostics in the UK. A breast imaging device that has a better performance in dense breasts than mammography, without ionising radiation, and without the cost of MRI would be an exciting prospect to breast diagnostics.

Outside of considerations around screening and diagnostics, there is also the issue of monitoring in the general population who are too young for mammographic screening. Self-examination is the only form of monitoring that takes place in this population because the cost-benefit analysis, and the increased breast density of younger women, do not justify further monitoring. A form of imaging that could assess this population, without overdiagnosis, would contribute directly to increasing the number of malignancies diagnosed early; considered to be a primary deciding factor in the long-term survival of cancer patients.

The MARIA[®] system is a novel technology that utilises dielectric value to distinguish between tissue types within the female breast. Radiowave radar-based imaging is well-researched and the unique physiological characteristics of the breast have made it an important research area for radiowave technology including that from the

Abbreviations: BIRAD, breast imaging reporting and data system; CE, confomité européenne; DCIS, ductal carcinoma in situ; MRI, magnetic resonance imaging; US, ultrasound; XRMX-ray, mammography

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<https://doi.org/10.1016/j.ejrad.2019.04.017>

University of Calgary's Tissue Sensing Adaptive Radar (TSAR) system, Umbria Bioengineering Technologies "Mammowave" system, and work from Dartmouth College on a 3D microwave tomography system, amongst others [7–14]. MARIA[®] has completed the most clinical research of any of these devices. It uses the prone patient position that is seen in many of the competitor devices but as the scanning unit is not fully integrated into the bed, it is able to be adjusted and moved more freely for fit before being locked into position. This feature also enables the shells to be emptied of coupling medium and cleaned between patients, a feature that is not present in some other devices. MARIA[®] is a CE-marked device that comprises of a hemispherical radiowave array that collects data of the patients' internal breast tissue, which is then displayed as an image for subsequent analysis by trained personnel. Areas of significant interest within the tissue volume are identified using an intensity scale and MARIA[®] can guide the interpretation of other imaging modalities.

Previous clinical research has taken place with an earlier prototype version of the MARIA[®] system, known as M4. This study, a single-centre project completed in 2013 of 86 participants, achieved 70–80% blind detection of lesions without using prior clinical information [15]. This study, a larger-scale, multicentre study of the commercially-acceptable M5 version of MARIA[®] was designed to build on this research and evaluate the possible position of this technique in the clinical environment, as well as to recruit substantially more patients to test the robustness of the device, the sensitivity of the system, and collect a substantial amount of good-quality data for in-house machine learning. Confirming the diagnostic sensitivity of the device and studying device improvements were key considerations of the research. The inclusion of patients from the age of 18 allowed for the ability of radio-wave imaging to assess lesions in the younger and denser breast to be evaluated. The images that were obtained from the MARIA[®] scans were analysed by radiologists and expert reviewers alongside other information available for the patient (including XRM, US, MRI and clinical notes, as applicable) in order to form an opinion on the success of MARIA[®] at identifying the known lesion within the breast.

As a non-ionising radiation, it is hoped that the MARIA[®] system has the potential to become the imaging method of choice in women under 40 who would only be offered a mammogram where the risk benefit justifies it.

2. Materials and methods

The MARIA[®] system, as shown in Fig. 1, comprises of a hemispherical array which is housed in a scanning unit. This is located under the patient bed, which itself features an aperture through which the patient places her breast when she is laying prone (Fig. 3). The scanning unit is fitted with a ceramic insert which is brought up to meet the breast via controls on the scanning unit, in order to form a close but non-compressing fit. A coupling medium, comprising of beeswax, paraffin oil, aqua and a preservative, and of a uniform dielectric constant is used between the ceramic insert and the breast, and it is possible to fit



Fig. 1. The M5 MARIA[®] system.

additional ceramic inserts within the main insert to allow for different breast sizes.

This study was approved by the NRES Committee Yorkshire & The Humber – South Yorkshire on the 1st April 2015 [REC ref: 15/YH/0084, ClinicalTrials.gov ID: NCT02493595]. Written informed consent was provided by all participants. The study utilised prospective data collection and took place between May 2015 and February 2017. The research group was entirely female, with an age range between 18–80 years and a mean age of 51 years.

The subject group were identified from the symptomatic breast clinic with a palpable lump in at least one breast. The sample was selected based on their eligibility for the study and their own interest in participating in the research. The inclusion criteria stated that participants must have been referred for diagnosis because of a symptom of breast disease; had not had previous treatment or biopsy (due to the potential for that trauma to influence the MARIA[®] image); had a breast size between 32A and 42DD due to size limitations of the system; and, were physically able to lie prone and reasonably still for a period of up to 10 min. Certain females were excluded from the study including those with breast implants, patients with an implanted electronic device, and those who had a recent biopsy as these are currently contraindications in the MARIA[®] instructions for use as untested for their influence on the MARIA[®] scan. In total, 39 exclusions were made from the study (further details in Table 1).

As the study was a feasibility study, a specific sample size calculation was not performed however, following discussion with the research team and the feedback from feasibility conversations, it was anticipated that 300 participants would be scanned in total, with around 200 participants becoming evaluable subjects. In total 264 participants were scanned and there were 225 evaluable subjects. The number of evaluable subjects was deemed enough to provide an evaluation of the experience of the MARIA[®] system within the clinics.

The study took place at three sites in England. The research team at each site consisted of at least one operator who identified, consented and scanned the participants and at least one radiologist, who read the MARIA[®] images with all other clinical information. All study personnel were trained by the company in both the operation of the device and how to interpret the MARIA[®] image.

The scan procedure began with fitting scans that were used to identify air gaps or pools of coupling fluid, which would show up on the fitting image as being of greater intensity. A series of up to 10 fitting scans could be performed by the operator to determine if a good fit had been reached. An example of the fitting scan can be found in Fig. 2 Once the operator found the fit acceptable, the study scans could begin.

The standard MARIA[®] scan for the study comprised of three 22 s scans with the array repositioning itself between each scan, in order to build up the 3D image of the breast volume. This repositioning does not require the patient to move; the participant remains still with her breast supported in the insert which also remains stationary (Fig. 3). The results from the MARIA[®] scan were not used to influence the diagnosis of

Table 1
Reasons for patient exclusion from the evaluable dataset.

Reason for exclusion	Number of exclusions for this reason
Breast identified as normal	13
Breasts too large	9
Patient out of age-range	5
Incomplete data available	4
Non-specific findings	4
Mobility issues meant patient couldn't lie flat	1
Presence of broken skin (skin abscess)	1
Scan image failure	1
Software failure	1
Total	39

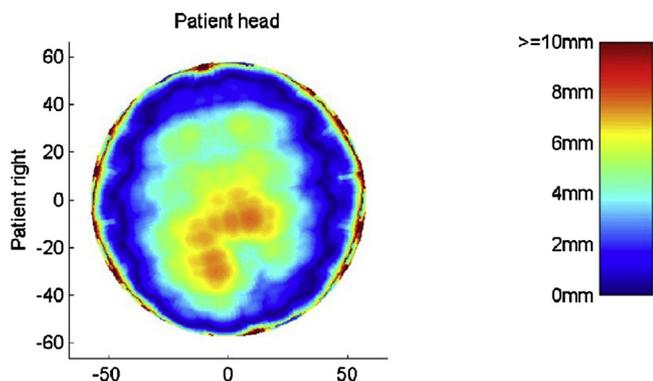


Fig. 2. Generic MARIA[®] M5 fit image, showing the breast volume, with the centre of the breast shown in the centre of the image and an accompanying intensity scale.

the participant.

At the end of the scan period the participant can leave and their direct participation in the study has ceased. Further data collection from the participant’s hospital records took place to ensure that a full profile of their clinical diagnosis was obtained, including obtaining their other imaging and diagnostic information from their visit. Each participant received the standard of care required to form their diagnosis, and the MARIA[®] scan was performed as a standalone research scan only.

In addition to the unblinded reads performed by the radiologist which used all other imaging and clinical data, blind reads were also performed. All readers were trained by the company. At the time of the study, the outcome of a read was described as either a “hit”, a “miss”, or a “probable”. The definition of these was:

Hit: The image is classified as a Hit when there is a good correspondence in the location of an area of high intensity in the MARIA[®] image and the known location of the lesion from the clinical diagnosis. This is defined as MARIA[®] identifying the lesion within 2 cm of its known location (confirmed by histopathology or ultrasound as appropriate).

Probable: The image is classified as Probable when the lesion is found within the imaged breast volume with a spatial displacement compared to the clinical diagnosis. This is defined as MARIA[®] identifying an area of high intensity further than 2 cm from the known location of the lesion as confirmed by histopathology or ultrasound as appropriate.

Miss: A MARIA[®] image is classified as a Miss when it does not identify any areas of high intensity in the target location or identifies an area of high intensity in a different location compared to the clinical notes.

All 73 probable cases were further reviewed, by consensus, to be

able to distribute them to either hit or miss.

Target locations were recorded on a specially-designed recording sheet that utilised the R9 coordinates on a grid, see Fig. 4

There were no statistical end points for the study; instead, the study provided a continuous assessment of MARIA[®] sensitivity. Basic statistics were used to achieve numerical and percentage data on the main areas of interest, including clinical findings, menopausal status, breast density, and age.

3. Results

Due to the nature of the study and the results obtained from it, there were no findings of statistical significance from this study and nor were they anticipated. Initially, results from the MARIA[®] scans were recorded as either ‘hit’, ‘miss’, or ‘probable’. ‘Probable’ cases were further reviewed by consensus between the site and the expert reviewers in-house, in order to be able to allocate them to either the ‘hit’ or ‘miss’ categories. Of the 225 evaluable participants considered here, 170 cases were classified as a ‘hit’ and 55 were classified as a ‘miss’. The smallest recorded lesion size, that was classified as a ‘hit’ with MARIA[®], had a diameter of 5 mm.

Table 2 gives a tabulation of the 225 clinical results considering the pathological characteristics of the finding and shows the findings for both benign and malignant diagnoses.

Note – Data are whole numbers with percentages of the total finding per type in parentheses.

*All percentages rounded to nearest whole number

Certain interrogations were made of the data to ascertain if there were areas that MARIA[®] performed better or worse, in case there was the scope for further analysis. MARIA[®] performed consistently in the detection of both benign and malignant lesions. The sensitivity findings remained broadly consistent when other factors such as menopausal status, BIRAD density, and age were taken into consideration see Table 3.

As seen in Table 3, patients being scanned as part of this research were asked to self-report their menopausal status, based on when they last menstruated. It can be observed that for patients in pre- or perimenopause, MARIA[®] achieved an overall sensitivity of 72.5% (119/160) whereas for post-menopausal patients the device achieved an overall sensitivity of 82.5% (51/64). The dataset for post-menopausal women is smaller which makes this sensitivity value less reliable than for pre- and peri-menopausal women.

Due to the known limitations of mammography in younger women with ‘denser’ breasts, it was of interest to the study to ascertain if MARIA[®] was a successful imaging tool in this population. The study population comprised of 14 women with BIRAD A (6%), 63 women with BIRAD B (28%), 87 women with BIRAD C (39%), and 31 women with BIRAD D (14%) breasts, as recorded from their mammogram. BIRAD density was not recorded for 30 women (13%) as they did not

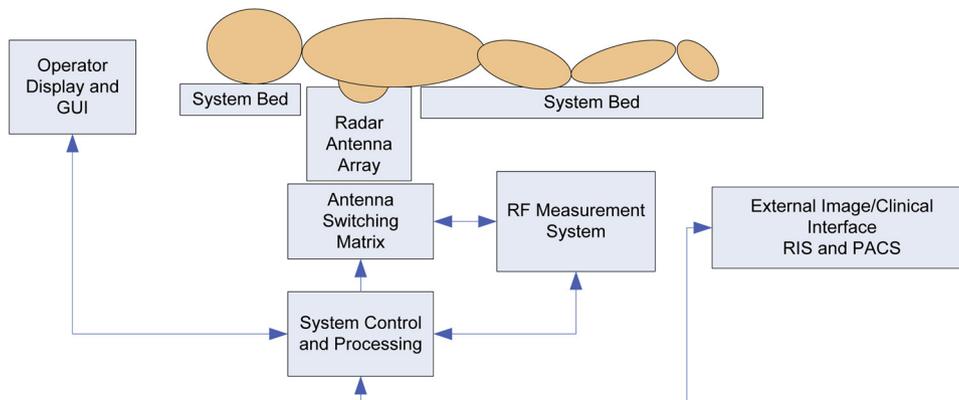


Fig. 3. MARIA[®] System Layout Block Diagram.

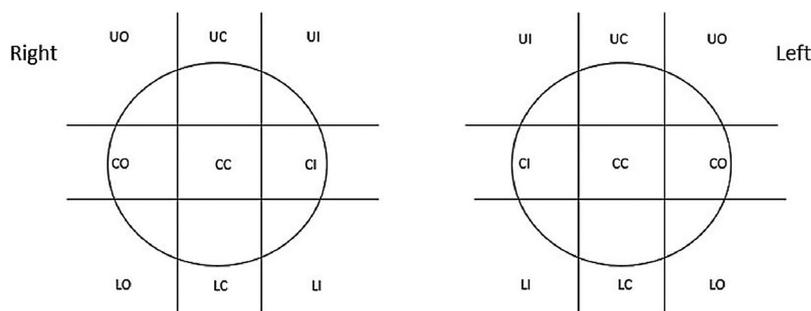


Fig. 4. MARIA[®] image reading using the R9 grid.

Table 2

Clinical result per prediction and type of finding for system performance evaluation.

Finding type	MARIA [®] Read Outcome*		
	'Hit'	'Miss'	Total per finding type
Benign finding	107 (76%)	33 (24%)	140
Malignant finding	63 (74%)	22 (26%)	85
Total per outcome	170 (76%)	55 (35%)	225

have a mammogram as part of their clinical procedures. Of these women without a mammogram, 13 (42%) did not have one performed due to young age. For the purposes of analysis, BIRADs A and B have been combined, as have BIRADs C and D. There was one example in the dataset of a patient with a palpable lump that was not identified on mammography but was identified by MARIA[®], see Fig. 5, as well as eight further cases where the mammogram was not clear.

Due to the presence of a reasonable number of unspecified BIRAD densities it is difficult to use these values to interpret statistical confidence in the specificity of MARIA[®] due to BIRAD density, particularly as these cases represent an often-younger demographic with denser breasts. From the values obtained it appears that increased breast density does not have a negative impact on the ability of MARIA[®] to detect both benign and malignant lesions, however, this would require further data.

The study also saw four complex cases where the standard imaging modalities used at the clinics led to inconclusive results or unclear findings, such as that seen in Fig. 6. Here, MARIA[®] echoed clinical findings that showed multiple findings in the lower half of the breast, echoing the results obtained by ultrasound and MRI. Of these cases, they were all involving participants with dense or very dense breasts.

Women from 18 to 80 were scanned as part of the study. To further analyse the relationship between density and MARIA[®] sensitivity, age was investigated as a variable. Ages of participants, reported as whole numbers of years, were grouped into the following age categories:

Table 3

Findings by type from all evaluable participants, grouped by data analysis questions.

Group type	Malignant finding			Benign finding			Total
	Hit	Miss	Total	Hit	Miss	Total	
All	63 (74%)	22 (26%)	85	107 (76%)	33 (24%)	140	225
Pre-/Peri- menopause**	27 (69%)	12 (31%)	39	92 (76%)	29 (24%)	121	160
Post menopause**	35 (76%)	11 (24%)	46	16 (89%)	2 (11%)	18	64
Lucent (BIRAD 'a' and 'b')	36 (71%)	15 (29%)	51	16 (62%)	10 (38%)	26	77
Dense (BIRAD 'c' and 'd')	26 (79%)	7 (21%)	33	67 (79%)	18 (21%)	85	118
Unknown (BIRAD not recorded)	1 (50%)	1 (50%)	2	25 (89%)	3 (11%)	28	30
Age 18-30***	0	0	0	14 (82%)	3 (18%)	17	17
Age 31-50	21 (66%)	11 (34%)	32	73 (75%)	24 (25%)	97	129
Age 51-80	42 (78%)	12 (22%)	54	21 (84%)	4 (16%)	25	79

*All percentages rounded to nearest whole number.

** Data for only 224 available as one participant's menopausal status was not recorded.

***There were no malignant findings in the 18–30 age range.

- 18–30 (17 women)
- 31–50 (129 women)
- 51–80 (79 women)

Despite some challenging data arising from group sizes, the analysis showed still further similar values of sensitivity for the MARIA[®] system across the age ranges and diagnoses, although with no malignant findings in the 18–30 age range and few malignancies in the 31–50 category, it would be difficult to draw interpretation into this beyond the results presented here.

Analyses were performed by using Microsoft Analysis Toolpak [Version 1810].

4. Discussion

The prospect of a breast imaging modality that does not use ionising radiation or compression to obtain a whole-breast image makes MARIA[®] an interesting prospect in the breast imaging field. The use of ionising radiation, as found in XRM, makes frequent screening problematic, particularly in younger women. The compression required is uncomfortable to patients, with this even being cited as a reason for patient non-compliance in screening programmes [15]. Further, XRM does not have a uniform ability to detect lesions in all breast densities, with the modality finding dense breasts particularly challenging to interpret [16]. Younger patients who fall into the high-risk population are surveillance-screened with MRI; an expensive modality that is often under a lot of time-pressure at site. Other technologies, such as breast tomosynthesis and whole-breast ultrasound exist but are not challenging XRM in terms of patient reach and use in routine screening programmes.

The study had its limitations. Despite the high completeness of the evaluable participant dataset certain fields, such as breast size and menopausal status, were self-reported which leaves them open to error. A further important limitation is that the study did not consider the patient's menstrual cycle and it is currently not known if menstrual

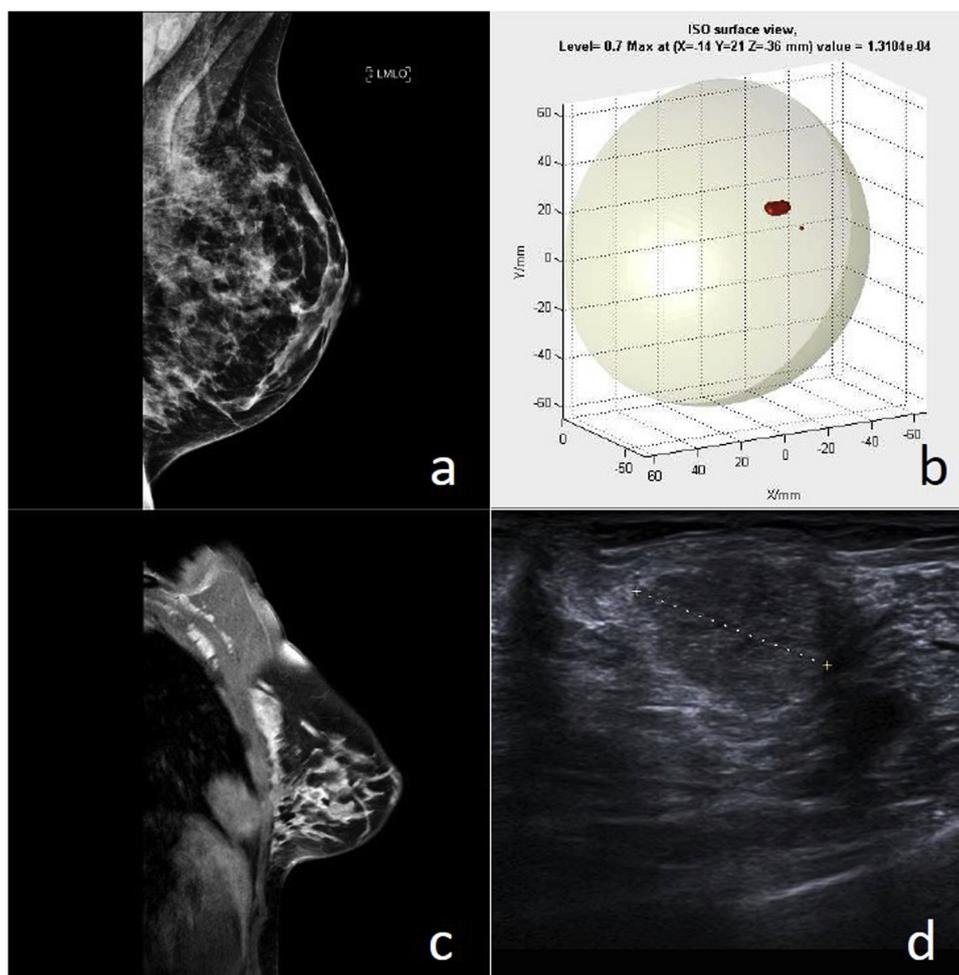


Fig. 5. Patient 035, BIRAD 'd'. Left (a) XRM reported as occult; (b) MARIA[®] showing finding in Upper Outer Quadrant; (c) Gadolinium-enhanced MRI showing 16 mm irregular mass in Upper Outer Quadrant; and, (d) US from image-guided biopsy which confirmed a Grade 2 mucinous carcinoma and DCIS.

cycle influences the MARIA[®] image. It is well documented that menstrual cycle has an impact on XRM, US, MRI, tomosynthesis etc. [17–21] so a difference in image is anticipated for MARIA[®] but until this has been investigated clinically it is not possible to judge the practical implications. For the study, 45% of the evaluable subjects were self-reported as pre-menopausal i.e. still having regular periods, so this is a factor that may be of interest. Information collected at the time of this study on the cancer type and cancer stage, for patients with malignancy, was variable as this was not determined as an outcome measure in the protocol and can therefore not be analysed further. However, current work into the M6 version of MARIA[®] is seeking to collect detailed information on the type and stage of diagnosed breast cancers in order to investigate the performance of MARIA[®] in these populations.

A lot was learned from this study which has gone on to shape the development of MARIA[®] and the design, delivery and analysis of research using the system. The current version of the MARIA[®] system, M6, can scan breasts up to 1 l which is twice the size of the M5 in order to address the large amount of patient exclusions that had to be made due to breast size. The fitting process has also been amended to include the use of clear plastic insert cups that correspond in shape and size to the ceramic inserts used in MARIA[®]. This allows for an accurate fit to be ascertained before the patient lies down on the system and does not rely on self-reported breast measurements, which were found to be highly inaccurate during this study. Recruiting from a busy symptomatic clinic was also a challenge for the study as it was initially difficult to place MARIA[®] in the site workflow; however, by the end of the study all sites had recruited well. Learning from this, all clinical trials now involve

extensive time taken with the site to learn not just how to operate the MARIA[®] system and read the produced images, but also to understand the research protocol and effective trial delivery. Additional technological improvements to MARIA[®], resulting in the M6 version of the device, are currently under investigation.

Statistical interpretation was not able to be performed on the study data, especially as MARIA[®] did not independently indicate the clinical pathway for the patient so a straightforward comparison to other modalities in terms of detection was not feasible. Indeed, the findings from MARIA[®] did not have any influence on the patient's diagnosis or care and were instead only considered alongside other imaging. Despite this, there are trends within the data. The overall detection rate of 76% for both benign and malignant lesions compares favourably to detection rates noted from digital XRM [22]. For dense breasts, MARIA[®]'s sensitivity of 79% in both benign and malignant lesions is also important as this is an area XRM is known to find challenging. Results from studies have reported various values for XRM sensitivity in this population with sensitivity recorded as being as low as 50–60% [16,18,23,24]. However, it must be noted that direct comparison of sensitivities between modalities is difficult due to many studies looking at a population with a combination of normal and pathological findings, rather than a known palpable lesion as investigated in our research.

Whilst patient questionnaires were not completed for this study, patient feedback was reported by the operators to be very good with patients appreciating the comfort of the scanning process. The current investigation of M6 taking place in London is collecting patient feedback via a questionnaire in order to gain valuable insight into patient

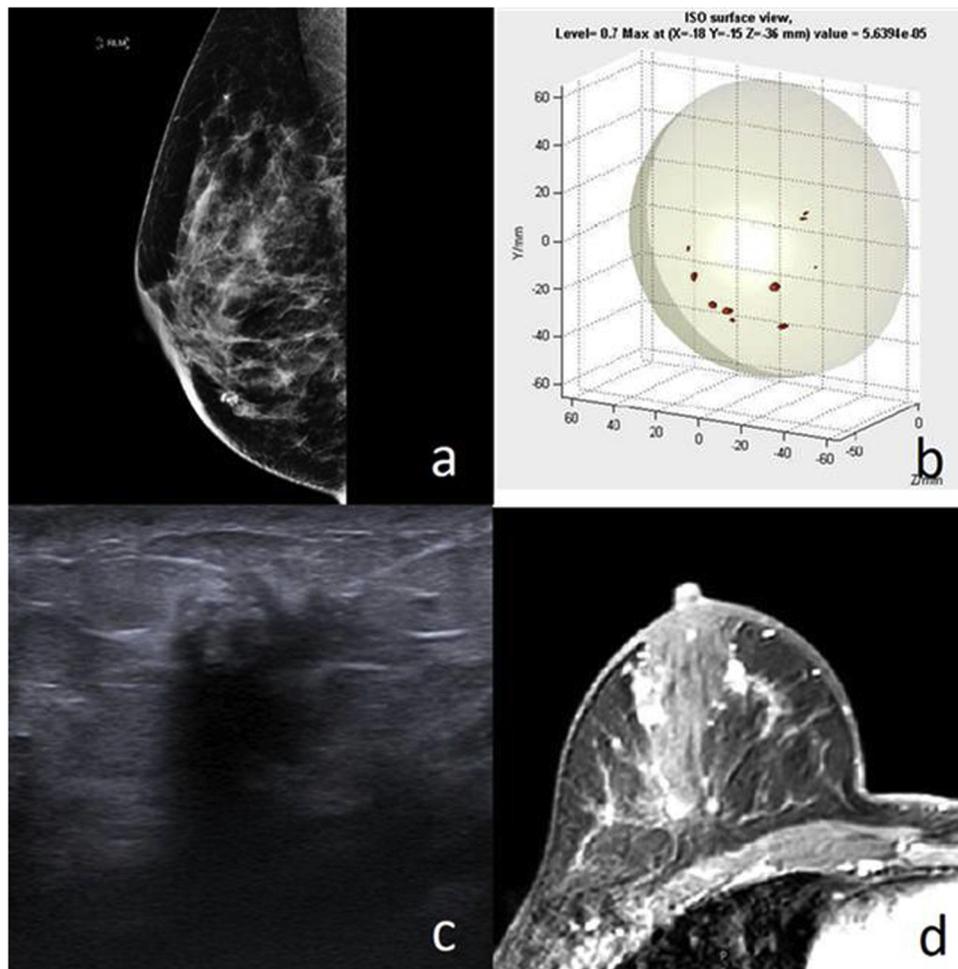


Fig. 6. Patient 028, BIRAD ‘c’, age 38. Left (a) XRM showing ill-defined distortion with coarse calcification; (b) MARIA[®] showing multiple foci throughout lower half of breast; (c) initial US showing only an ill-defined region of concern: and, (d) Gadolinium-enhanced MRI showing more than 10 lesions corresponding to Grade 2 invasive ductal carcinoma with missed patterns of growth accompanied by microcalcifications, high nuclear grade solid and micropapillary DCIS.

experience of the MARIA[®] scan and their thoughts on the scanning procedure in a more formal manner.

5. Conclusions

Further work on MARIA[®] is ongoing and projects are planned to investigate where to place MARIA[®] in the clinical pathway as an adjunct imaging device as well as to investigate MARIA[®] alongside other modalities in a more comparative way. There are promising signs from this research, and the earlier study using the M4 version of the device [7], that MARIA[®] may be useful for patients with lesions that are difficult to identify from XRM.

Further work is also planned in order to address the remaining challenges of MARIA[®], including the high false-positive rate that the system currently has.

This study has shown that MARIA[®] is able to detect both malignant and benign lesions at a similar rate in all breast densities and age groups, where there has been enough data collected to be able to form an opinion. This consistency, especially with regards to breast density, is a positive finding and one that contrasts with the known difficulties of mammography in dense tissue. Using the data collected here from this relatively simple study design has led to the development of the more-complicated, ongoing project researching the M6 version of MARIA[®] which is recruiting patients with known breast cancer as well as those with any symptom of breast disease.

Author declaration

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

Micrima Ltd provided funding for this research to take place to the research sites involved in the research.

Caroline Gillett has been a full-time employee of Micrima Ltd since April 2018.

Richard Sidebottom has been an ad-hoc consultant for Micrima Ltd since December 2017.

We wish to confirm that there are no known conflicts of interest associated with the other authors.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are

acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

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Richard Sidebottom

Helen Massey

Caroline Gillett

Lyn Jones

Funding

This work was funded by Micrima Ltd.

Conflicts of interest

Caroline Gillett is a paid employee of the Micrima Ltd.

Richard Sidebottom is an ad-hoc consultant for Micrima Ltd.

There are no other known conflicts of interest for the other authors.

Acknowledgements

The authors wish to acknowledge the support of Professor Alan Preece and Elizabeth Blake in the construction and review of this publication.

The authors would like to thank the teams at each of the research sites as well as the team at Micrima for ensuring the success of this study. Heartfelt thanks is also extended to all the research participants who undertook the study scan and provided their data for this research.

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