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FULL PAPER

The Wavelia Microwave Breast Imaging system–tumour discriminating features and their clinical usefulness

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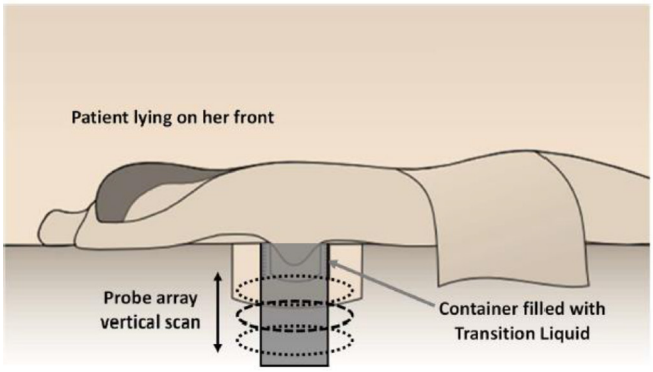
Objective: The Wavelia Microwave Breast Imaging (MBI) system, based on non-ionising imaging technology, has demonstrated exciting potential in the detection and localisation of breast pathology in symptomatic patients. In this study, the ability of the system to accurately estimate the size and likelihood of malignancy of breast lesions is detailed, and its clinical usefulness determined.
Methods: Institutional review board and Health Products Regulatory Authority (HPRA) approval were obtained. Patients were recruited from the symptomatic unit to three groups; breast cancer (Group-1), unaspirated cysts (Group-2) and biopsied benign lesions (Group-3). MBI, radiological and histopathological findings were reviewed. MBI size estimations were compared with the sizes determined by conventional imaging and histopathology. A Quadratic Discriminant Analysis (QDA) classifier was trained in a 3D feature space to discriminate malignant from benign lesions. An independent review was performed by two independent breast radiologists.
Results: 24 patients (11 Group-1, 8 Group-2 and 5 Group-3) underwent MBI. The Wavelia system was more accurate than conventional imaging in size estimation of breast cancers. The QDA accurately separated benign from malignant breast lesions in 88.5% of cases. The addition of MBI and the Wavelia malignancy risk calculation was deemed useful by the two radiologists in 70.6% of cases.
Conclusion: The results from this MBI investigation demonstrate the potential of this novel system in estimating size and malignancy risk of breast lesions. This system holds significant promise as a potential non-invasive, comfortable, and harmless adjunct for breast cancer diagnosis. Further larger studies are under preparation to validate the findings of this study.
Advances in knowledge: This study details the potential of the Wavelia MBI system in delineating size and malignancy risk of benign and malignant breast lesions in a symptomatic cohort. The usefulness of the Wavelia system is assessed in the clinical setting.

INTRODUCTION

While mammography is an effective means of breast cancer diagnosis, inherent shortcomings such as a lower sensitivity in females with dense breasts, uncomfortable breast compression and radiation exposure has resulted in research into alternative methods of breast imaging.[1] Microwave Breast Imaging (MBI) has been highlighted as a potentially viable method for detecting breast abnormalities.[2] MBI has been reported to have a high sensitivity for detecting cancer in denser breasts,[3] with a non-ionising approach to breast cancer diagnosis and tumour response to systemic therapy.[2,4,5]

The Wavelia system is a first generation, non-ionising, low-power electromagnetic wave breast imaging device, developed by MVG Industries (Villejust, France).[6] In a recent publication by this group, the device demonstrated promising results in detecting and localising benign and malignant breast lesions, in the clinical setting.[7] Moreover, a strong safety profile was established, and a favourable patient experience reported. Further larger-scale clinical trials are currently in preparation to further validate the potential of this novel MBI system as a diagnostic adjunct to current practice.

Figure 1. The principle of Wavelia MBI. MBI, Microwave Breast Imaging



Historically, the diagnostic benefit of radiological imaging has been predominantly reliant on the subjective interpretation of imaging data by a radiologist. However, in recent years, there has been intense interest in the area of quantitative, reader-independent imaging markers which have a diagnostic, predictive, and prognostic utility.[8] This has resulted in a surge in the number of scientific publications in this field.[9] Radiomics is an umbrella term for a variety of strategies capable of condensing quantitative, high-dimensional data, imperceptible to the human eye, from medical images.[10] Discriminant analysis, for example, can be used to determine variables that differentiate between two or more naturally occurring groups.[11] Applied to radiological imaging, the discrimination of benign and malignant lesions based on quantitative imaging features such as shape, intensity and texture is increasingly becoming a reality.[12] Shape descriptors have been earlier considered for breast lesion classification with mammography[13,14] and ultrasound.[15] Texture-based features have been earlier considered in radiomics research for cancerous lesions identification on CT, PET and MRI images.[16–18] To date, there are no peer-reviewed reports of the application of discriminant analysis to data derived from microwave breast imaging.

In this study, we report the ability of the Wavelia MBI system to accurately estimate the size of benign and malignant breast disease. Discriminant analysis is then performed to evaluate the malignancy risk of the underlying lesions. The usefulness of these estimations in the clinical setting is then graded by two independent breast radiologists.

METHODS

Ethical approval and trial registration

Ethical approval was sought and granted from the Clinical Research and Ethics Committee, Galway University Hospital, Ireland. The study was subsequently authorised by the Health Products Regulatory Authority (HPRA), Dublin, Ireland. Ethical standards complied with international guidelines including the Declaration of Helsinki and were in accordance with the ethical principles underlying European Union (EU) Directive 93/42/EEC and EN ISO 14155. The study was registered with the U.S. National Library of Medicine (ClinicalTrials.gov NCT03475992).

The Wavelia Microwave Breast Imaging system prototype

The Wavelia MBI system was installed at the host institution for the duration of this study (Sept 2018–Dec 2019).[6] The Wavelia MBI system employs 18 wideband Vivaldi-type antennas arranged in a circle in a horizontal plane outside a cylinder containing coupling fluid, as previously described.[19] With the patient lying in a prone position (Figure 1), each antenna illuminates the imaging domain (*i.e.* coronal section of the breast) individually, while the remaining antennas receive the low-power, non-ionising electromagnetic waves scattered at various angles around the circle, in a multistatic radar system configuration. The probe array moves vertically below the examination table and illuminates the breast at 5 mm intervals, capturing the dielectric contrast for the entirety of the breast. Coronal sections of the breast, of thickness 10 mm (*i.e.* centre of the probe ± 5 mm) are generated using the MBI data at each vertical scan position of the probe array. Overlapping consecutive coronal breast sections, formed per azimuthal sector of illumination (partial images), based on multi static radar detection technology (TR-MUSIC imaging algorithm), are integrated to form the 3D MBI image. The technical principles of this approach and the employed algorithms have been previously detailed.[6,20]

Considering the heterogeneity of breast tissue, the Wavelia MBI prototype creates a series of parametric MBI images under various assumptions on the percentage of fibroglandular tissue (pc_fib) along the path of microwave propagation within the breast (from a given transmitting antenna to the imaging pixel being interrogated and back to a given receiving antenna). Higher pc_fib values indicate denser breast tissue, with higher dielectric constant. Contrarily, a lower pc_fib value indicates a lower breast density, with a lower dielectric contrast. Multiple pc_fib search ranges are assessed independently for each partial image of the breast, in each imaging sector. The unknown dielectric properties of healthy breast tissue are further deduced by assessing the pc_fib parameter, independently in each sub image, while employing two wide search ranges [(10:60)% and (20:50)%] and three narrow search ranges [(10:20)%, (30:40)% and (50:60)%]. Five MBI images ("Raw MBI images") are ultimately formed per patient's breast, one for each pc_fib parameter search range.

Morphological image post-processing is then applied to detect regions of interest (ROIs) persistently present in the set of five 'Raw' MBI images, as previously described.[19] Morphological characteristics of a ROI are assessed, and a ROI detection is validated in a given pc_fib search range if specific morphological and ROI intensity criteria are satisfied (ROI measuring ≥1 cm^3, minimum ROI solidity of 30% and minimum ROI intensity contrast of 5%, against the background tissue). The persistent detection of a ROI in three or greater pc_fib search ranges is considered indicative of an association with a physical object and suggests inclusion of the ROI in the final morphological image. The presence of a ROI in less than three pc_fib search ranges is considered to be associated with imaging artefacts and not reported for clinical data analysis.

Table 1. Inclusion and exclusion criteria set out for the study

Inclusion criteria
1. Symptomatic presentation with a palpable breast lump.
2. Mammography performed at time of presentation (<6 weeks prior to MBI)
3. Capable of comfortably lying in a prone position for 15 min.
4. Subjects with bra size larger than 32B and cup size larger or equal to B.
5. Subjects whose submerged breast would allow a sufficient margin to accommodate the transition liquid around the breast within the cylindrical container. Satisfaction of criteria determined by the clinician at time of initial clinical assessment.
Exclusion criteria
1. Pregnant or breast-feeding.
2. Previous surgery to the breast.
3. Previously received chemotherapy or radiotherapy to the breast.
4. Subjects who have had a breast biopsy within the previous two weeks.
5. Subjects with any active or metallic implant or bearing any nonremovable object.
6. Post-biopsy patients whose breast tissue is not healed sufficiently.
7. Breast cyst aspiration before MBI.
8. Significant co-morbidities.
9. Prior or concurrent malignancy.
10.Under the age of 18 years old.
11.Inflammation and/or erythema of the breast and/or break in the skin.

MBI, Microwave Breast Imaging.

The above-described sectorisation, partial image formation and raw MBI image reconstruction using multiple pc_fib search ranges and the morphological breast lesion detection based on persistence are proprietary patented techniques by MVG Industries.

Patient recruitment process

Patients who presented to the Symptomatic Breast unit with a palpable breast lump were considered for inclusion in the study. Suitable patients were provided with a patient information leaflet, invited to participate in the clinical investigation and written informed consent was obtained. A strict list of inclusion and exclusion criteria was applied, as detailed in Table 1.

Study groups

Three categories of patients were determined for this study, as detailed in Table 2. In the case of Group 1 and Group 3 who underwent core-needle biopsy, MBI was not planned for at least 14 days following biopsy. This minimum time-frame was determined to maximise the opportunity for resolution of residual hematoma at the biopsy site and biopsy tract, without delaying or impacting the overall clinical management of the patient.

Table 2. Grouping of patients for the Wavelia MBI clinical investigation

Group	Details
Group 1	Patients with pre-diagnosed breast cancer (Biopsy ≥14 days before MBI)
Group 2	Patients with breast cyst. No prior biopsy.
Group 3	Patients with pre-diagnosed benign lesion (Biopsy ≥14 days before MBI)

MBI, Microwave Breast Imaging.

Radiological and histological data collection

Full-field digital mammography systems were employed for all mammography studies [Hologic Selenia Dimension (Marlborough, MA) and GE Senographe Essential (Chicago, IL)]. Ultrasonography was undertaken with the patient positioned in the decubitus or supine position employing a high-resolution 12.5 MHz linear array transducer (Philips EPIQ 5W; Amsterdam, Netherlands). For patients included in Group 1 and Group 3, ultrasound-guided core biopsies were obtained with an Achieve™ automatic biopsy device (Merit Medical; Galway, Ireland) or with a TruCore II biopsy gun (Argon Medical; Frisco, TX) 14-gauge automated needle. The radiological database (AGFA IMPAX, Agfa-Gevaert, Mortsel, Belgium) was accessed and all conventional imaging (mammography and ultrasonography) studies were reviewed.

Mammographic/sonographic size, BIRADS category for density and BIRADS category for prediction of malignancy were recorded. The fifth edition of the American College of Radiology (ACR) BI-RADS Atlas was employed.[21] Mammographic breast density was assessed using Volpara® Volumetric Density Measurement (VDM) Software. Sonographic size was recorded. Where available, relevant MRI studies of the breasts were also obtained.

Histological findings from biopsy samples and outcomes of MDM discussion were recorded for Group 1 and Group 3. For Group 1 patients, histopathological reports were collected following surgery. In this group, pathological findings were considered the "gold-standard" reference for tumour size, due to the variability of tumour size measurements between mammography and ultrasound imaging modalities.

All personal or identifying details were removed from patient data, and a trial number assigned, ensuring anonymity. The anonymised data was kept in a secure database designed and maintained by the Clinical Research Facility of the host institution.

MBI lesion sizing

Post-processing of the full cohort of patient datasets, including all persistent and morphologically validated MBI lesion detections, was performed.

The lesion size was estimated by means of fitting an ellipsoid to the ROI associated with the persistent lesion detection, at each of the two wide pc_fib search ranges (W1: pc_fib [10-60]%, W2: pc_fib [20-50]%). The greatest linear dimension of the lesion was defined as the length of the longest axis of the fitted ellipsoid. If the lesion detection were validated in both wide pc_fib search ranges, the maximum of the two estimates of the lesion size (W1 or W2) was used to represent a unique MBI lesion size estimate.

Discriminating benign from malignant lesions

As an output of the morphological post-processing of the Wavelia MBI images, shape-based (*i.e.* solidity) and texture-based (*i.e.* correlation and busyness) features were computed for all the persistent, morphologically validated, lesion detections. These three specific features were identified as mostly appropriate to achieve malignant-to-benign lesion separability in a feature space of low dimensionality with Wavelia MBI. The solidity measures the density or convexity of the lesion, with lower values attributed to it in the case of irregularly shaped lesions or ROI's containing holes. The correlation is a texture feature that measures the linear dependency of grey-level values to their respective voxels. The busyness measures the spatial relationship among three or more pixels neighbourhood, with high values associated with rapid changes of intensity between the pixels.

The three-dimensional lesion feature vector data was further exploited in a 2-class, malignant-to-benign, lesion classification framework. A Quadratic Discriminant Analysis (QDA) classifier was trained in the three-dimensional feature space. For the training of the classifier, the data from Group-1 breast lesion detections in multiple pc_fib search range MBI images was labelled as Class #1, while the data from Group-2 and Group-3 MBI lesion detections was labelled as Class #2. Random non-stratified partition of the full data set in disjoint training and test data sets was performed 10-times to estimate the confusion matrix and loss of the classifier based on the 10-fold cross-validation method.

This classifier type was selected such that its decision hypersurface partitions the 3D feature space in two disjoint continuous manifolds (malignant lesions subspace Versus benign lesions subspace).

Employing this trained classifier, the likelihood for each detection to be associated with 'Class #1 = Malignant lesion' was quantified with a probability of malignancy. This probability detailed:

- If Probability_of_malignancy < 50%: 'Benign' class is predicted.
- If Probability_of_malignancy > 50%: 'Malignant' class is predicted.

If a breast lesion was detected and validated in both wide pc_fib search range MBI images, two classification scores were reported. The maximal probability of malignancy was considered to represent a unique MBI classification score for the lesion.

Assessment of Wavelia MBI results by independent breast radiologists

Following MBI image formation and clinical feature extraction by the MVG group, an independent review was performed by two breast specialist radiologists. The reviewers studied the MBI results independently, such that an inter -reader reliability was determined. The findings of four of patients were used for demonstration and training purposes (training packet), with the remaining patient data sets then provided for an independent radiology review (assessment packet). In both packets, conventional imaging (mammography and ultrasonography) was initially provided, followed by MBI images. Additional information obtained from MBI, was presented following the MBI images. This additional information included:

- Estimated maximal linear dimension of the lesion (mm);
- Lesion features, including solidity, correlation and busyness;
- Lesion classification score (probability of malignancy);
- Number of pc_fib search ranges in which the lesion was persistently detected.

The following questions were posed to both radiologists for each case:

- Is there an obvious abnormality on mammography and ultrasound?
- What is the BIRADS score for the breast/breast lesion?
- Does MBI clearly identify the abnormality?
- Is the MBI lesion size estimate accurate?
- Is the MBI lesion classification score accurate?
- Is the addition of this modality useful in this case?

The histological findings from the core biopsy and subsequent surgery, and the management decisions determined at the MDM, were not provided to the radiologists. These details were not provided in an attempt to simulate as close to real life as possible the initial patient visit to the symptomatic breast unit where MBI has been integrated into the typical diagnostic work-up.

Imaging and data analysis

As this study was a Phase 1, First-In-Human (FiH) clinical investigation undertaken to address early feasibility, the number of subjects included in the study (n = 25) was limited and did not

Table 3. Clinicopathological characteristics of the 24 patients who underwent MBI and were included in data analysis

Breast lesion type and age distribution		
Group	Number (n = 24)	Age (range)
1 – Invasive cancer	11	64.6 (42–83)
2 – Cyst	8	38.3 (35–49)
3 – Fibroadenoma	4	37.5 (36–39)
3 – Complicated cyst	1	47

MBI, Microwave Breast Imaging.

allow for clinically meaningful statistical analysis. MBI image formation and morphological post-processing for persistent breast lesion (ROI) detection and characterisation was performed offsite by the MVG group. Given that this was a FiH investigation, the MBI data processing chain progressively evolved, throughout patient recruitment and its parameterisation was fixed for final data analysis at patient group level. Three interim data reviews were performed to assess and confirm the clinical relevance of the MBI findings based on the available reference clinical data.

RESULTS

Patient demographics

A total of 24 female patients with palpable breast lumps were included in final analysis. A single patient who underwent Wavelia MBI was excluded from the final data and imaging analysis. In this case, the patient presented with a palpable lump that was subsequently determined to be normal underlying breast tissue. Several small cysts were identified in a different breast quadrant, and as a result, the patient was erroneously enrolled in Group two prior to imaging. The mean patient age (range) was 50.5 years (35–83). A further breakdown of age in each patient group is detailed in Table 3. There were 11 cases of invasive carcinoma [six invasive ductal carcinoma (IDC), and five invasive lobular carcinoma (ILC)], eight patients with an underlying breast cyst, four cases of benign breast disease (fibroadenoma) and one case of a complicated cyst. The tumour characteristics of the patients in Group 1 are detailed in Table 4.

Wavelia MBI results

Lesion size

The sizes of all Group 1 breast lesions, as determined by MBI, conventional imaging and final post-surgical histology were assessed and are detailed in Table 5. For MBI, if the lesion detection were validated in both wide pc_fib search ranges, the maximum of the two estimates of the lesion size (W1: pc_fib [10-60]%, W2: pc_fib [20-50]%) was used to represent a unique MBI lesion size estimate. Similarly, for conventional imaging, lesion size was recorded as the maximum size computed with mammography or ultrasonography. Histological size was available on 10 of 11 patients in Group 1. Case 032, a case of ILC, underwent neoadjuvant chemotherapy following diagnosis and had a complete pathological response to treatment, with no residual carcinoma or tumour cellularity identified on subsequent histology. Prior to commencing neoadjuvant chemotherapy, an MRI was performed, where an overall tumour size of 30 mm was recorded.

Table 4. Clinicopathological details of the invasive carcinomas (Group 1)

Tumour characteristics (Group 1)		
Feature	Grouping	Number (n = 11)
Histological type	Ductal	6
	Lobular	5
Tumour grade	I	1
	II	9
	III	1
Nodal status	Positive	3
	Negative	8
BI-RADS lesion classification (At initial triple assessment)	5	6
	4/5	1
	4	1
	3/4	1
	1	1
	0	1

No persistent morphological MBI lesion detection was validated in 2 of 11 cases from Group 1, both IDC. Of note, however, the size of the lesions at histology were 10 mm (Case 013) and 9.5 mm (Case 041). Of the nine remaining cases of invasive cancer where persistent morphological detections were validated, the lesion size determined by MBI was more accurate than conventional imaging in six of the nine cases. This included four of five ILC cases and two of four IDC cases.

Focusing on ILC, MBI successfully detected ILC in case 043. This lesion was occult on both modalities of conventional imaging. Furthermore, the lesion was accurately localised with MBI, and its size estimation was accurate (MBI estimation 62.9 mm; histopathology size 65 mm). In cases 008 and 032, MBI provided a relatively accurate estimation of lesion size (±7 mm), while size was markedly underestimated, by 25 mm and 18 mm respectively, by conventional imaging. The size of ILC was underestimated by both MBI (by 25 mm) and conventional imaging (by 30 mm) for case 004.

While numbers of cases were too few to undertake any meaningful statistical evaluation, a linear correlation was demonstrated between MBI and histological lesion size, as depicted in Figure 2. In this limited number of cases, the histological size demonstrated a more favourable correlation with MBI size (r = 0.704,), when compared to the relationship between histological size and the size as determined by conventional imaging (r = 0.65), Figure 3.

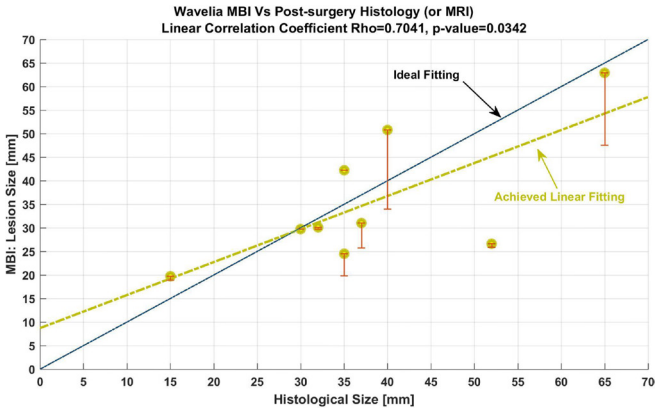
The size of all benign breast lesions, as determined by MBI and conventional imaging is detailed in Table 6. In case 023, where no persistent lesion was discernible, a 12 mm lesion was visualised at

Table 5. Histological, MBI and conventional lesion size of Group 1 cases

Histology subtype		Histology size (mm)	MRI size (mm)	Wavelia MBI			Conventional imaging		
				W1 (mm)	W2 (mm)	Max (mm)	Mx (mm)	Ultrasound (mm)	Max (mm)
Ductal	**002**	40	–	51	34	51	25	15	25
	010	37	–	31	25.7	31	24	22	24
	027	15	–	19.7	18.9	19.7	13	15	15
	029	35	–	24.5	19.8	24.5	23	37	37
	013	10	–	Occult	Occult	Occult	6	5	6
	041	9.5	–	Occult	Occult	Occult	10	10	10
Lobular	**039**	32	–	29.7	30.1	30.1	32	33	33
	004	52	–	26.6	25.9	26.6	22	17	22
	008	35	–	–	42.2	42.2	–	10	10
	032	–	30	–	29.7	29.7	12	12	12
	043	65	–	47.5	62.9	62.9	Occult	Occult	Occult

MBI, Microwave Breast Imaging; Mx, Mammography.
W1 = pc_fib search range (10-60)%, W2 = pc_fib search range (20–50)%.

Figure 2. Correlation between Wavelia MBI and post-surgery histology data, in terms of lesion size: Group 1 patients. MBI, Microwave Breast Imaging.



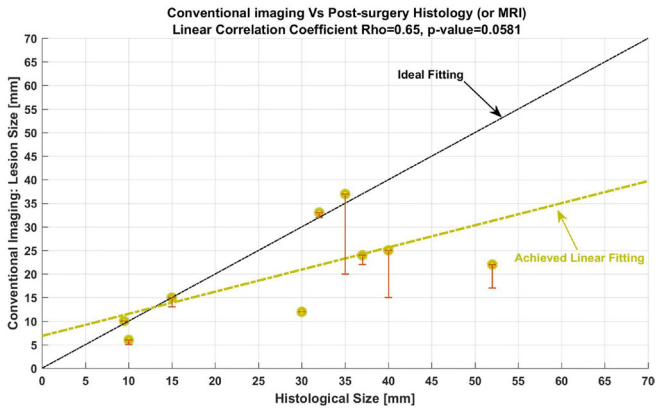
sonography. This was confirmed to be a fibroadenoma following histological analysis.

Discriminating benign from malignant lesions

A Quadratic Discriminant Analysis (QDA) classifier was trained to partition the employed 3D feature space into two disjoint continuous manifolds (malignant and benign lesions subspaces). The decision surface for the trained classifier is illustrated in Figure 4.

Following training, the QDA classifier was able to appropriately classify 88.5% of lesions. 10-fold cross-validation of the classifier indicated correct classification of 77.1% of the malignant lesions (Class #1), and correct classification of 100% of the benign lesions (Class #2), resulting in an estimated overall classification loss of 11.5%. Employing this trained classifier, the probability of malignancy is reported for both wide pc_fib parameter search ranges of all morphologically validated and persistently detected breast lesions in Table 7. The maximal classification score was considered to represent a unique MBI classification score for the lesion.

Figure 3. Correlation between conventional imaging and post-surgery histology data in terms of lesion size: Group 1 patients.



In Group 1, Case 027 was the only patient for whom the probability of malignancy was inferior to 50%, for both wide pc_fib search ranges. In case 029, the probability of malignancy was ambiguous, with classification scores for malignancy of 16.5 and 55.7% calculated for the two-wide pc_fib parameter search ranges. The probability of malignancy was greater to 95% for all the remaining Group 1 lesions. The probability of malignancy was inferior to 15% for all lesions in Group 2. In Group 3, the probability of malignancy for two of four fibroadenomas was ambiguous, with maximum classification scores of 34 and 37.5% recorded. Finally, in Group 3, the probability of malignancy for the complicated cyst was 7.34%, which is somewhat similar to findings for most simple cysts in Group 2.

Outcomes from the independent breast radiologist review

The findings of 17 of the 21 patient datasets with validated MBI lesion detection were provided for independent radiology review, following demonstration and training with the remaining four patient data sets. The outcomes of the reviews are detailed in Table 8.

In Group 1, Case 043, where ILC was occult on conventional imaging, both reviewers agreed that the lesion was a BI-RADS 1 lesion, and that the findings of MBI in this case were particularly useful, especially considering the probability of malignancy provided (100%) in the additional information. In Case 027, a case of IDC, both reviewers agreed that the lesion had a high likelihood of being an invasive carcinoma (BI-RADS 4). In this case, the MBI likelihood of malignancy was recorded as 27.56%. As such, both reviewers agreed that the addition of MBI was not helpful. Similarly, in Case 029, both reviewers indicated that an MBI likelihood of malignancy of 55.68% was unhelpful and added ambiguity to a case which was featured highly suggestive (BI-RADS 5) of invasive carcinoma on conventional imaging. In Case 008, a case of ILC, both reviewers agreed that MBI was overestimating the size of the lesion (42.2 mm), with reference to conventional imaging (10.0 mm on ultrasound). This lesion measured 35 mm on post-surgery histology.

In Group 2, both reviewers agreed that MBI was unhelpful in Case 036. In this case, lesion feature analysis could not be performed due to a small volume of the lesion (less than 1 cm^3). In Case 003, although lesion feature analysis could not be performed, both reviewers felt the addition of MBI was helpful. In the remaining cases of Group 2, there was a slight discrepancy of opinion between the reviewers, with Reviewer 1 indicating the addition of MBI was helpful in all remaining cases. Reviewer 2 indicated that the adjunct of MBI to some cases was unhelpful, however, as many cysts (006, 009 and 012) were sufficiently obvious on ultrasound imaging alone, and that the adjunct of further imaging might only serve to confuse matters.

Finally, in Group 3, both reviewers indicated that the lesion classification score (37.5%) of Case 037, a fibroadenoma, was unhelpful. This lesion was categorised as being a BI-RADS 4 lesion on conventional imaging by both reviewers.

Table 6. MBI and conventional lesion size of Group 2 and 3 cases

Group			Wavelia MBI			Conventional imaging		
			W1 (mm)	W2 (mm)	Max (mm)	Mx (mm)	Ultrasound (mm)	Max (mm)
Group 2	*Simple cyst*	**030**	15.6	12.3	15.6	14	13	14
	Simple cyst	**009**	11.6	16	16	–	16	16
	Simple cyst	**040**	–	16.3	16.3	25	23	25
	Simple cyst	**012**	13	12.9	13	–	13	13
	Simple cyst	**006**	13.5	20.2	20.2	–	9	9
	Simple cyst	**019**	12.7	11.4	12.7	–	10	10
	Simple cyst	**036**	10.8	–	10.8	–	10	10
	Simple cyst	**003**	–	33.8	33.8	–	31	31
Group 3	*Fibroadenoma*	**017**	22.1	13.3	22.1	26	23	26
	Fibroadenoma	**031**	28.6	30.3	30.3	19	19	19
	Fibroadenoma	**037**	18.5	22.4	22.4	–	25	25
	Fibroadenoma	**023**	Occult	Occult	Occult	–	12	12
	Complicated cyst	**033**	14.3	18.4	18.4	17	17	17

MBI, Microwave Breast Imaging; Mx, Mammography.
W1 = pc_fib search range (10–60)%, W2 = pc_fib search range (20–50)%.

Although not specified as a question, reviewer two commented on the inaccurate localisation of MBI for cases 004, 006, 009 and 027. Of these, the location was inaccurate for 004, 009 and 027. In Case 006, however, the MBI location concurred with the report of conventional imaging. It is likely that the localiser on the ultrasound image provided, which was inaccurate, misled the reviewer regarding the true site of the lesion. Reviewer 2 also highlighted concerns on the systematic exclusion of small

Figure 4. Decision surface for the QDA trained classifier; Breast lesion classification in a 3D feature space (solidity/correlation/busyness). 3D, three-dimensional; QDA, Quadratic Discriminant Analysis.

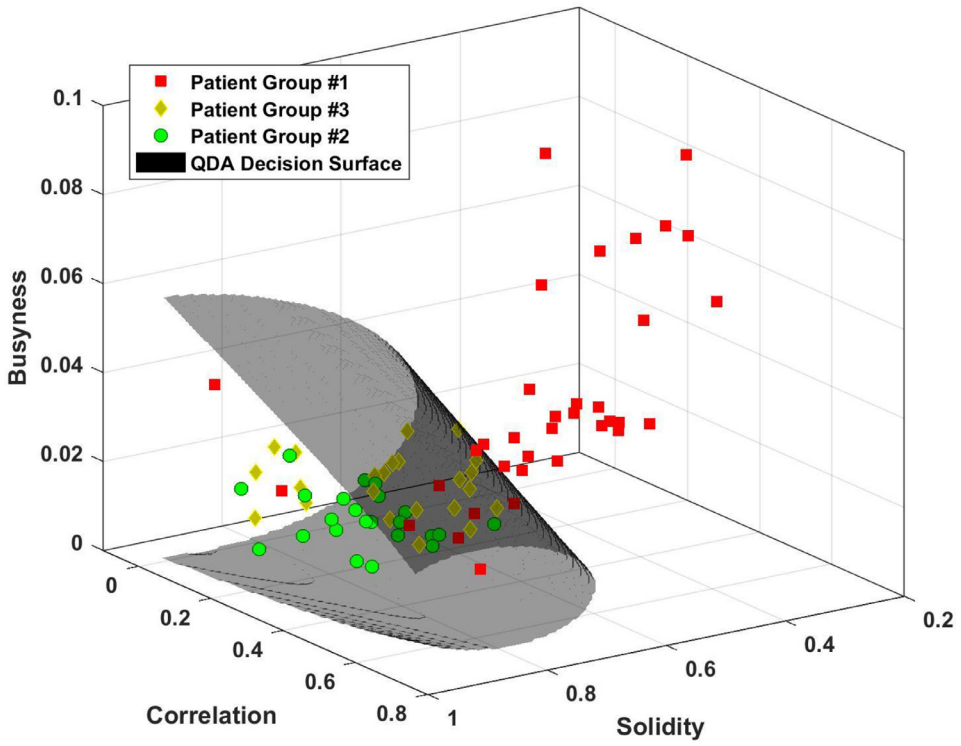


Table 7. Lesion probability of malignancy, as deduced with Wavelia MBI

Group 1		MBI probability of malignancy			Group 2 and Group 3		MBI probability of malignancy		
		W1 (%)	W2 (%)	Max (%)			W1 (%)	W2 (%)	Max (%)
Ductal	**002**	100	99.89	100	Simple cyst	**030**	5.38	10.81	10.81
	010	99.95	97.21	99.95		**009**	10.17	13.44	13.44
	027	21.5	27.56	27.56		**040**	–	7.55	7.55
	029	55.68	16.52	55.68		**012**	2.79	4.02	4.02
	013	Occult	Occult	Occult		**006**	–	7.32	7.32
	041	Occult	Occult	Occult		**019**	1.44	6.71	6.71
Lobular	**039**	99.93	99.88	99.93		**036**	[a]	[a]	[a]
	004	99.42	93.23	99.42		**003**	[a]	[a]	[a]
	008	–	99.75	99.75	Fibroadenoma	**017**	5.54	0.56	5.54
	032	–	100	100		**031**	32.67	34.03	34.03
	043	100	100	100		**037**	13.17	37.5	37.5
						023	Occult	Occult	Occult
					Complicated cyst	**033**	6.11	7.34	7.34

MBI, Microwave Breast Imaging.
[a]In the two patients marked with the asterisks, lesion feature analysis could not be performed due to small lesion size (<1 cm^3, P036), or small breast size being imaged at a single vertical scan position of the Wavelia MBI scanner (A-Cup, P003).

objects (volume ≤1 cm^3) and the concentration of the analysis on a dominant and persistent ROI in the breast.

In summary, the combined results of both reviews indicated that MBI size estimate was accurate in 76.5% of cases, the MBI malignancy risk classification was accurate in 70.6% of cases, and that the addition of MBI was useful in 70.6% of cases.

DISCUSSION

The Wavelia MBI system has demonstrated exciting potential in determining size and discriminating benign from malignant lesions, in this limited cohort. Moreover, the addition of the modality to conventional imaging was deemed clinically useful by independent breast radiologists in the majority of cases. The authors acknowledge, however, that the cohort size is exploratory and serves to be hypothesis generating. It has not been designed or powered to show differences between the two groups at this early stage.

Employing a QDA classifier model, the potential to partition morphologically validated persistent benign and malignant lesions with a decision hypersurface was demonstrated. This was performed using a combination of a 3D shape (solidity) and texture-based features (correlation and busyness). Applying this methodology, a classification loss of 11.5% was computed for the trained QDA classifier, based on 10-fold cross-validation. Previous research by Doshi et al investigated the role of frequency response as an aid for lesion characterisation with the MARIA system (Micrima Limited, Bristol, UK),[22] however, this was early conceptual work, with no further work in this area since published in the literature in the patient setting. The potential application of these classifier models will require further assessment and refinement in future clinical investigations, involving larger patient cohorts.

The Wavelia MBI system demonstrated exciting promise in measuring lesion size with a more favourable linear trend demonstrated between MBI and histological lesion size, than conventional imaging and histological lesion size. Overall, in the small cohort of invasive carcinomas, lesions were underestimated in size by conventional imaging, when compared to MBI. This finding was influenced by the ILC cases, where all but one of the ILC lesions were underestimated by conventional imaging. MBI was able to accurately measure four of five of the ILC lesions. The diagnostic challenges posed by ILC are well catalogued.[23–26] Having previously demonstrated the potential to detect this frequently occult histological subtype,[19] and now demonstrated promise in estimating its size and malignancy risk, the Wavelia system could potentially compliment modern practice and be of most benefit in the detection of these lobular cases.

The independent review of the results of this study by two independent breast radiologists provided invaluable insight into areas which will require improvement, and obstacles the Wavelia MBI system must overcome in future clinical investigations if it is to reach its true clinical potential. Of the patients where an underlying breast lesion was detected with MBI, the system was able to localise 17 of the 21 breast lesions. These inaccuracies were highlighted as a significant concern during the independent review process. MBI is performed on the pendulous breast, with the patient lying prone, which is different to mammography, where the patient is upright, and sonography, where the patient is positioned semi-erect. Correcting for this will be critical for future generations of the Wavelia MBI system.

Table 8. Questions posed to the breast radiologists for each case

		Independent reviewer 1								*Independent reviewer 2*					
		Q1	Q2	Q3	Q4	Q5	Q6			Q1	Q2	Q3	Q4	Q5	Q6
Ductal	**002**	✓	5	✓	✓	✓	✓	Ductal	002	✓	5	✓	✘	✓	✓
	010	Training case							010	Training case					
	027	✓	4	✓	✓	✘	✘		027	✓	4	✓	✓	✘	✘
	029	✓	5	✓	✓	✘	✘		029	✓	5	✓	✓	✘	✘
	013	*	*	*	*	*	*		013	*	*	*	*	*	*
	041	*	*	*	*	*	*		041	*	*	*	*	*	*
Lobular	**039**	✓	5	✓	✓	✓	✓	Lobular	039	✓	5	✓	✓	✓	✓
	004	✓	5	✓	✓	✓	✓		004	✓	5	✓	✘	✓	✘
	008	✓	5	✓	✘	✓	✓		008	✓	5	✓	✘	✓	✓
	032	Training case							032	Training case					
	043	✘	1	✓	✓	✓	✓		043	✘	1	✓	✓	✓	✓
Simple cyst	**030**	✓	2	✓	✓	✓	✓	Simple cyst	030	✓	2	✓	✓	✓	✓
	009	✓	2	✓	✓	✓	✓		009	✓	2	✓	✓	✓	✘
	040	Training case							040	Training case					
	012	✓	2	✓	✓	✓	✓		012	✓	3	✓	✓	✓	✓
	006	✓	3	✓	✓	✓	✓		006	✓	2	✓	✓	✓	✘
	019	✓	2	✓	✓	✓	✓		019	✓	2	✓	✓	✓	✓
	036	✓	2	✓	✘	✘	✘		036	✓	2	✓	✘	✘	✘
	003	✓	2	✓	✘	✘	✓		003	✓	2	✓	✘	✘	✓
Fibroadenoma	**017**	✓	3	✓	✓	✓	✓	Fibroadenoma	017	✓	3	✓	✓	✓	✓
	031	Training case							031	Training case					
	037	✓	4	✓	✓	✘	✓		037	✓	4	✓	✓	✘	✘
	023	*	*	*	*	*	*		023	*	*	*	*	*	*
Complicated cyst	**033**	✓	3	✓	✓	✓	✓	Complicated cyst	033	✓	3	✓	✓	✓	✓

MBI, Microwave Breast Imaging.

(Q1) Is there an obvious abnormality on mammography/ultrasound? (2) What is the BIRADS score? (3) Does MBI clearly identify the abnormality? (4) Is the MBI lesion size estimate accurate? (5) Is the MBI lesion classification score accurate? (6) Is the addition of Wavelia MBI useful in this case? (Asterisks indicate patients that were not included in the review, as no MBI results were reportable)

It is noteworthy that histological outcomes were not provided to the radiologists at the time of the review. It can be argued that if this information had been provided, the true benefit of Wavelia would be more transparent, especially in Case 043, where the underlying invasive carcinoma was occult on conventional modalities, but accurately assessed with MBI.

In this study, the benign-to-malignant discrimination demonstrated early promise. However, both independent reviewers drew attention to multiple cases where the employed feature vector returned an ambiguous classification, or indeed an incorrect classification for a lesion. It was also noted that in the case of simple cysts, which are often completely conspicuous on sonography, the adjunct of further imaging, in this case MBI, would not only be unnecessary, but would result in a waste of resources and may potentially add ambiguity to the case, resulting in an unnecessary diagnostic cascade. As subsequent clinical investigation will involve larger and more diverse patient datasets, benign-to-malignant discrimination will require the potential expansion of further radiomic features and the inclusion of more shape descriptors and texture features to increase the positive and negative predictive values of this adjunct.

As this study was an early-phase investigation limited to a small number of participants, no meaningful statistical analysis could be undertaken. Moreover, only patients presenting with palpable lumps to the symptomatic unit were included. Subsequent investigations, with a broader range of patient demographics,

presentation, breast density and pathology will allow for the true potential of MBI technology to be revealed and its possible role in current diagnostic practice to be determined. The current generation Wavelia system has a number of limitations that were previously described,[7] such as the systems shortcoming in detecting lesions of size less than 10 mm, its limited ability to detect breast lesions immediately anterior to the pectoralis major, and its limited unsuitable for patients with a small or large breast. Future generations will require technical upgrades to allow detection of smaller and non-palpable breast pathologies. Also, the diameter of the container of the scanner will need to be increased to improve scan quality of large breasts and upgraded antennas to improve the imaging of the posterior part of the breast.

CONCLUSION

The results from this Wavelia MBI investigation have demonstrated the potential of this novel system in delineating size and estimating the malignancy risk of breast lesions. This system holds significant promise as a potential non-invasive, comfortable, and harmless adjunct for breast cancer diagnosis. Further larger studies are under preparation to validate the findings of this study.

CONTRIBUTORS

Conceptualization, BMM, SE, AF, LD, MJK; Formal analysis, AF, LD, JDGO, BMM, PM, SE. MJK; Funding acquisition, AF, LD, JDGO; Investigation, BM, PM, SE, CG, AOC, RE, AJL, MJK; Resources, AF, LD, JDGO, MJK; Supervision, AF, LD, MJK; Writing – original draft, BM, PM, MJK; Writing – review & editing, BM, PM, SE, CG, AOC, RE, AJL, MJK.

COMPETING INTERESTS

Authors L Duchesne, A Fasoula and JD Gil Cano are employed by MVG Industries, the company that has funded this study and is currently conducting clinical investigations of Wavelia and have a financial interest in the outcome of those clinical investigations. The remaining authors declare no conflict of interest.

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CONSENT FOR PUBLICATION

Written informed consent obtained from all participants.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was sought and granted from the Clinical Research and Ethics Committee, Galway University Hospital, Ireland. The study was subsequently authorised by the Health Products Regulatory Authority (HPRA), Dublin, Ireland. Ethical standards complied with international guidelines including the Declaration of Helsinki and were in accordance with the ethical principles underlying European Union (EU) Directive 93/42/EEC and EN ISO 14155.

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