

MammoWave Breast Imaging Device: Path to Clinical Validation, Results and Implications in Future Population-based Breast Screening Programs

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Abstract—Microwave imaging for breast cancer detection has attracted growing global attention with a small number of prototypes advancing to the clinical trial stage. This investigation aims to provide an overview of MammoWave, a novel microwave-based imaging system for breast lesion detection and to assess its introduction into the clinical routine and its potential role in future breast screening programs. As a key focus of this work, we will describe in detail the various aspects of the clinical protocol procedure that has enabled us to perform a successful clinical trial. Obtained preliminary results indicate the ability of our device to distinguish breasts with no radiological finding and those with radiological findings, with a sensitivity of 89.6%.

Index Terms—Microwave imaging, Huygens principle, Breast cancer detection, Clinical protocol.

I. INTRODUCTION

Current breast screening programs for early cancer detection have been a topic of worldwide discussion due to some drawbacks of the current gold standard technique, mammography. It is well known that this imaging technique limits its use in population-based screening programs to both a very specific age range, generally from 50 to 69 years old women, and a limited screening frequency, generally biennial [1]. The use of ionizing radiation (X-rays) and the cumulative effect it places on women, have led to many controversies, particularly when dealing with overdiagnosis. Moreover, the discomfort due to breast squishing and the reduction of performance when dealing with dense breasts have motivated many researchers to shift their focus on investigating novel safe techniques that overcome all mentioned limitations [2].

In this context, microwave imaging appears to be an interesting potential alternative to ionizing-based techniques [3-4]. The investigation presented in this paper analyses one of these advancing radar-based microwave systems, named MammoWave (UBT Srl, Italy), uniquely able to function in air with 2 antennas (one transmitting and other receiving the scattered signal from the breast) rotating in the azimuth

plane and operating within the frequency band 1-9 GHz. Unlike mammography, the exam is performed with the patient lying down on an examination table, in a comfortable prone position, without breast compression. The system's acquisition time is approximately 10 minutes per breast [5]. Following MammoWave's feasibility clinical trial, a prospective multicenter international clinical trial has been activated to evaluate the ability of MammoWave in breast lesions detection.

Before starting such clinical trials, a detailed clinical protocol was prepared outlining all aspects of our study. Here, we will present and discuss some of the key aspects of this protocol including its primary and secondary objectives and outputs, the inclusion/exclusion criteria, number of participants and centers involved in the study, and the regulatory path followed.

In more details, to evaluate MammoWave in the framework of this clinical trial, microwave imaging was performed on patients already having conventional exams' radiologist review, which was used as the reference standard. Moreover, to collect participants' output of the novel microwave exam, an on-site questionnaire was provided to each patient, asking about unpleasantness, pain, comfortability, and test duration. Finally, the Net Promoter Score (NPS) was asked to evaluate overall patients' satisfaction about the microwave exam.

The remainder of the paper is organized as follows. A brief description of the device and the algorithm based on Huygens principle is provided in Section II. Various key aspects of the clinical protocol are described in Section III. Section IV presents and discusses our results, while the conclusions are stated in Section V.

II. MAMMOWAVE DEVICE AND ALGORITHM

MammoWave's very first prototype was developed and tested on canonical phantoms in 2015. Since then, the device has gone through optimization cycles until the current clinically ready prototype was constructed. The device can

be seen in Fig. 1(a). It comprises of two antennas, one used for transmitting and the other for receiving the microwave signals. Both antennas always operate in air, at a frequency range of 1-9 GHz, and are positioned on the same vertical height. The two antennas are connected to a 2-port vector network analyzer and are contained by a cylindrical hub internally surrounded by microwave absorbers. This cylindrical hub includes a cup placed inside a hole, which permits the insertion of the patient's breast in a prone position, as depicted in Fig. 1(b).

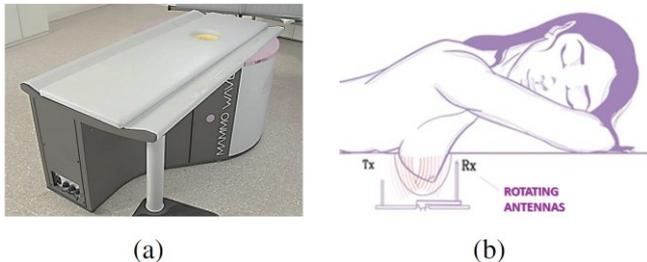


Fig. 1. (a) MammoWave prototype, (b) sketch of its breast scanning configuration showing the hole, cup, and the antenna configuration.

Both antennas rotate around the azimuth in order to collect the S21 signals in a multi-bistatic manner. Specifically, for each transmitter position, the receiver antenna rotates with a step of 4.5° , measuring the signals at 80 receiving positions all around the breast. Besides, 15 transmitting positions, divided into 5 triplet sections centered at 0° , 72° , 144° , 216° , and 288° , respectively, are used in the acquisition configuration.

In terms of the imaging algorithm, we make use of our previously developed Huygens principle-based algorithm [6], which has previously demonstrated promising results for biomedical applications, including breast cancer detection [7-10]. This algorithm has the capability of reconstructing images of a target in a background medium by measuring only the field on the external surface of the object of study. This measured field is then backpropagated inside the breast through the Green's function [6] to reconstruct the internal field. Finally, we construct the intensity image through incoherent summation of the contributions from all the transmitting positions and all the frequency points.

III. CLINICAL PROTOCOL

The sponsored prospective multicenter international clinical trials entitled "Clinical Investigation to Evaluate the Ability of MammoWave in Breast Lesions Detection" has been activated in 2020 (ClinicalTrials.gov Identifier: NCT04253366). Some details of the protocol are provided below.

A. Primary/secondary Output

The primary objective and expected outcome of this protocol is to generate empirical evidence for detection of Breast Lesions (BL), including malignant lesions (BC), by using MammoWave to evaluate its sensitivity (number of

'true positive' results). In addition, we have a key safety objective to evaluate MammoWave's safety and tolerability.

The protocol's secondary objectives are to evaluate:

1. The diagnostic ability (both sensitivity and specificity) of MammoWave in BL detection (against Reference Standard).
2. The ability to localize BL in terms of quadrant (against Reference Standard).
3. Percentage of correct BC diagnosis against Reference Standard.
4. The reproducibility of findings.
5. The sensitivity of MammoWave among different breast densities.
6. The sensitivity of MammoWave versus other diagnostic instruments.
7. Patient satisfaction related to MammoWave use (compared to mammography and/or ultrasound and/or magnetic resonance imaging).

B. Inclusion/Exclusion Criteria

Participants fulfilling all the following inclusion criteria are eligible for the study:

1. Signed informed consent form.
2. Women.
3. Adult ≥ 18 years old.
4. Having a radiologist study output obtained using conventional exams (such as breast specialist visit and mammography and/or ultrasound and/or magnetic resonance imaging) within the last month.
5. Patients willing to comply with study protocol and recommendations.
6. Patients with intact breast skin (i.e., without bleeding lesion, scar).

The presence of any one of the following criteria will lead to exclusion of the participant:

1. Patients who participate in another clinical study.
2. Patients who belong to any vulnerable group.
3. Patients with implanted electronic devices.
4. Patients who have undergone biopsy less than one week before MammoWave scan.
5. Patients with breast implants.
6. Patients with nipple piercings (unless they are removed prior to examination).
7. Participation in other studies in the last month before screening.
8. Pregnancy or breastfeeding.

C. Number of Participants

This study enrolled both patients with BL diagnosis and healthy patients (i.e., no lesion), with a prevalence of BL patients of $\sim 70\%$. Among these 70%, about 40-50% have been BC patients. A minimum total number of 250 patients (175 with BL) was required to verify a sensitivity of at least

70%, with an error of first type $\alpha=0.05$ and a power $(1-\beta) = 80\%$ [11].

D. Centers Involved

Three hospitals in Italy and Spain have taken part in this study. The two Italian hospitals are: Humanitas Research Hospital, Rozzano, Milan; Azienda Ospedaliera Universitaria S. Martino, Genova. In Spain, Hospital Virgen de la Salud in Toledo hosted the clinical trials.

IV. RESULTS AND DISCUSSIONS

All the regulatory path was followed for activating the clinical trials. Specifically, as the device was at a pre CE-marking stage, this included asking for ethical committee and national ministry approvals. In our case the relevant safety procedures were dedicated to class IIa. For enhancing the confidence of scientific community, we decided to perform clinical trials via a dedicated contract research organization (CRO).

The recruitment phase of this sponsored prospective multicenter international clinical trials successfully ended in August 2021. In this paper we show some preliminary results of on-site questionnaires. In more details, we used the first 59 on site questionnaires collected in Hospital Virgen de la Salud, Toledo, from the same set of patients that carried out the microwave scan. The results were the following: 91% of participants gave the minimum class about unpleasantness to the microwave exam; 100% of participants considered that the exam was not painful at all; 65% positively assessed the comfortability of the new exam; and 48% of all participants considered the exam as a little long-lasting.

In addition, we also performed a preliminary investigation to evaluate the ability of MammoWave in breast lesions detection using the data from 89 breasts (from the first 59 patients) collected in Hospital Virgen de la Salud, Toledo. The resulting radiologists review from these exams was used as gold standard for our investigation. Specifically, the radiologists reviewed conventional exams for each patient that agreed to participate in the study, classifying the breasts into two groups: breasts with no radiological findings (NF) and breasts with radiological finding (WF), i.e., with lesions which could be either benign or malignant.

An appropriate combination of MammoWave image features (introduced before the start of this prospective study) leads to a sensitivity of 89.6%, specificity of 77.3% and accuracy of 86.5%. Sensitivity is maintained (86.2%) when considering dense breasts only, while specificity increases to an overall value of 100% and accuracy to 89.5%. Additional sensitivity results for benign and malignant findings, separately, are provided in Table I. It can be seen that when considering all breasts, the sensitivity slightly increases for malignant breasts. On the other hand, when considering dense breast only this slight increase can be observed in breasts with benign findings. These values are in agreement with those obtained using MARIA device (Micrima, UK) and reported in [12, 13], where symptomatic patients only have been recruited.

TABLE I. SENSITIVITY RATES FOR BREASTS UNDER STUDY

	Sensitivity	Sensitivity (dense breasts only)
All WF breasts	60/67 (89.6%)	25/29 (86.2%)
Benign finding ^a	39/44 (88.6%)	21/24 (87.5%)
Malignant finding ^b	21/23 (91.3%)	4/5 (80.0%)

^a. Duct ectasia, cysts, fibroadenoma, benign microcalcifications, architectural distortion (radial scar).

^b. Confirmed carcinoma from nodules and/or architectural distortions.

V. CONCLUSIONS

Microwave-based imaging is a promising technology in breast radiology, avoiding the discomfort and the overuse of ionizing radiation. It could become very relevant in breast cancer screening due to its safe nature for increasing coverage of female population and providing an effective early breast cancer diagnosis. In particular, its accuracy and capability to clearly distinguish benign findings, i.e., cysts, could avoid key issues that mammography cannot solve currently, including re-calls and patient psychological stress, additional unnecessary mammography exams that lead to X-ray overdose and, consequently, higher costs for health systems. In light of the considerations stated above, microwave-based imaging is a safe and cheaper technology that holds great promise in the future of breast cancer diagnosis, as it is comfortable, sensitive, and is not affected by breast density. Its impact and implication can be especially noticeable in population-based screening programs to reduce over-diagnosis, interval cancer and healthcare costs through early-stage detection. In addition, it can make screening programs more inclusive since microwave imaging can be used without any safety restrictions such as age or frequency of use.

MammoWave recently received the CE mark; this also means that more clinical evidence can be acquired following the “post marked” clinical trials, paving the way for the adoption in future population-based breast screening programs.

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