SOLUS | SMART OPTICAL AND ULTRASOUND DIAGNOSTICS OF BREAST CANCER

Project title: Smart Optical and Ultrasound Diagnostics of Breast Cancer

Grant Agreement: 731877

Call identifier: H2020-ICT-2016-1

Topic: ICT-29-2016 Photonics KET 2016

Deliverable 5.3: Report on clinical validation

Leader partner:	OSR
Author(s):	Pietro Panizza (OSR), Elena Venturini (OSR), Giuseppe Di Sciacca (UCL), Simon Arridge (UCL), Giulia Maffeis (POLIMI), Antonio Pifferi (POLIMI), Paola Taroni (POLIMI)
Work Package:	5
Estimated delivery:	Month 60
Actual delivery:	29 December 2021
Type:	Report
Dissemination level:	Public

Table of Contents

Abbreviations

Coll	Collagen
Hb	deoxy-hemoglobin
HbO2	oxy-hemoglobin
HbT	total hemoglobin content
KPI	Key Performance Indicator
LR	Logistic Regression
SVM	Support Vector Machine
US	Ultrasound
SWE	Shear Waves

1. Introduction

The aim of deliverable D5.3 is to analyse the SOLUS system for multimodal imaging from a clinical point of view.

This pertains:

- The system usability on the operator's side
- The examination acceptance on the patient's side
- How the examination can fit in a regular diagnostic path
- The diagnostic potential of the proposed approach.

2. The system usability on the operator's side

Initial mock sessions were designed to train the operators in the use of the SOLUS system, to optimize conditions of use, and to investigate the system usability. They showed that there is no need for absolute darkness, nor to cover the probe with a black cloth (as originally hypothesised to shield the detectors from room light). Low intensity room (white) light allows one to perform an excellent quality exam, without artifacts, with the advantage for the operator who can easily see what they are doing and move around the room, and for the patient who is more relaxed as she can see what is happening.

The lotion used for US and optical matching between probe and patient's skin is a commercial product for US imaging (PolySonic US Lotion from Parker), as previously identified based on laboratory phantoms measurements. It confirmed to work properly, allowing the acquisition of both US images and optical data of high quality.

The examination is easy to perform and takes place exactly as a regular ultrasound examination, with the patient in supine position.

The SOLUS probe is larger than a standard ultrasound probe, but it can be held very well with hands of different sizes. In the case of small breasts, careful positioning of the patient is adopted so that the probe front surface fully adheres to the breast. The probe weighs more than a regular US probe, but once placed on the breast it can be easily kept still in place, and the weight is not such as to cause discomfort to the patient.

3. The examination acceptance on the patient's side

Before the start of any examination, the procedure and the study in general are explained to the patient and written informed consent is obtained. Up to now, the proposed examination has raised no specific concerns in the patients, and all invited patients, once informed, have given their consent to the examination.

On their side, the patients confirmed the operators' impressions:

- The study did not cause any discomfort, it took place like a regular US examination.
- They did not report any problem with the lotion, the weight of the probe or its temperature (the probe is water-cooled for proper operation of the detector and electronics).
- They appreciated the low intensity room light.

4. How the examination can fit in a regular diagnostic path

The SOLUS unit (including the Airexplorer US-SWE system) has the same size as a regular US unit, with a second additional monitor and the probe cooling system integrated into the US unit itself. Therefore, the instrument can be placed in any outpatient room, as a regular US unit (and can replace it).

Before the patient's measurements, about 10 minutes are spent to test the system performance on a breast phantom. The protocol for the validation of the SOLUS system includes 4 measurements on each patient: along the maximum lesion diameter, on the lesion orthogonal to the previous measurement, on the healthy tissue on the same breast, and on the healthy tissue on the contralateral breast. The entire set of measurements lasts about 15 minutes, and the probe needs to be kept still on the target for about 1 minute. Approximately 5 more minutes are needed for the analysis of optical data and the display of the

3D reconstruction results of tissue optical properties and composition. The overall time required by the examination is acceptable. Still some shortening would make it even easier to fit the multimodal examination into the regular diagnostic path. Further use of the system and the results of the clinical validation will show whether all the 4 measurements are strictly needed (e.g., either the orthogonal acquisition on the lesion or the contralateral acquisition may turn out not to contribute significantly to the results).

5. The diagnostic potential of the proposed approach

By the time of writing, data from 16 patients were collected and analyzed to estimate optical properties (absorption and scattering) at 8 wavelengths (635-1060 nm) and derive tissue composition (oxy- and deoxyhemoglobin, water, lipid, and collagen contents) and tissue microstructure (a, b). Examined lesions included 5 malignant cases and 11 benign cases (fibroadenomas), with average size of 1.8 cm. The protocol foresees 4 acquisitions: i) along the main axis of the lesion, ii) orthogonal to the previous one, iii) far from the lesion on the same breast, iv) at a mirror position on the contralateral breast. The procedure is repeated by 3 radiologists.

Optical data were analyzed as described in Deliverable 2.3 – “Identification of algorithms/procedures for DOT reconstruction using US priors” and D4.7 – “Performance assessment of DOT with US priors”. Briefly, soft morphological prior was derived from the US images and exploited to guide the optical reconstructions. Two approached were investigated: i) separate reconstruction of absorption and reduced scattering at each wavelength; ii) spectrally constrained approach that derives directly tissue composition and scattering parameters from the global analysis of time domain data at all wavelengths.

Figure 1 summarizes the absorption properties of benign (green) and malignant (red) lesions at the 8 wavelengths. Even though discretized, it shows an absorption line shape characterized by approximately comparable contributions from lipids at 930 nm and water at 975 nm, as expected from breast tissue averaged over a population including dense as well as adipose breasts. The absolute values of the absorption are also in line with what obtained in a previous clinical study performed with a different diffuse optics instrument [Taroni P., Quarto G., Pifferi A., Abbate F., Balestreri N., Menna S., et al. (2015) Breast Tissue Composition and Its Dependence on Demographic Risk Factors for Breast Cancer: Non-Invasive Assessment by Time Domain Diffuse Optical Spectroscopy. PLoS ONE 10(6): e0128941; doi:10.1371/journal.pone.0128941]. Figure 1 highlights that on average malignant lesions tend to absorb more than benign ones over the entire spectral range of observation.
The relative contrast (lesion vs surrounding healthy tissue) is displayed in Figure 2, suggesting also (on average) a stronger absorption contrast for malignant lesions than for benign ones at all wavelengths.

The relative contrast was calculated also for tissue composition and scattering parameters estimated using the spectrally constrained approach, and the results are shown in Figure 3. Reflecting what obtained for the absorption properties (that depend on composition), the contrast seems more marked for malignant lesions, especially when oxy-hemoglobin (HbO2) and collagen are considered. Perhaps unexpected, positive contrast, stronger for malignant lesions, is observed also on lipid content. Scattering parameters show no clear trend.

All these results need to be evaluated with extreme caution, as they refer to a small number of cases. Still, we made an initial attempt to discriminate between malignant and benign lesions exploiting machine learning classification methods applied to the absorption properties. Specifically, Support Vector Machines (SVMs) and logistic regression (LR) were considered.

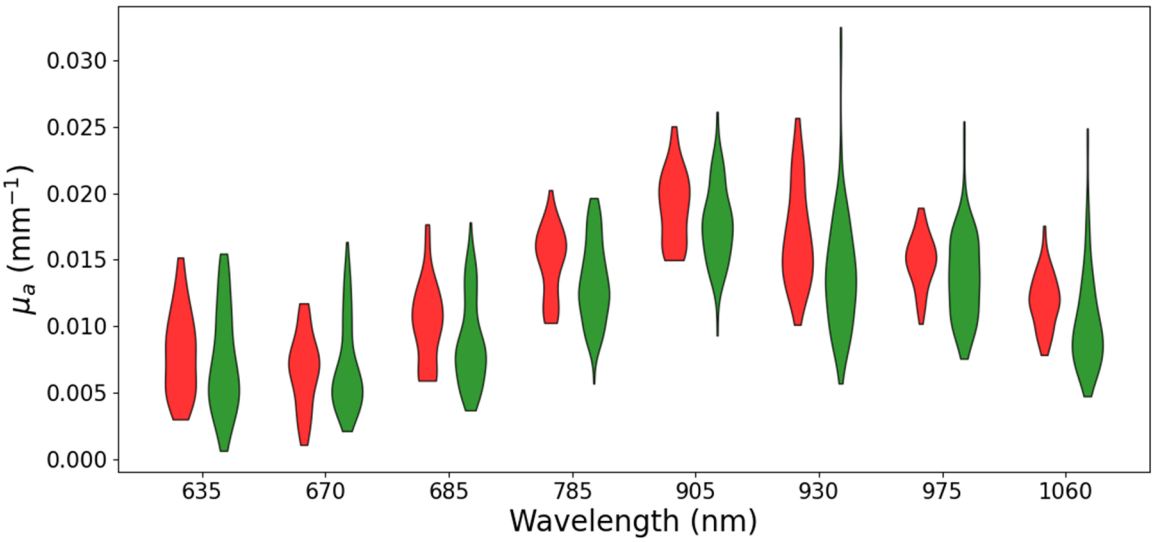

Figure 1 – Violin plot of the absorption properties at the 8 wavelengths. Green (red) refers to benign (malignant) lesions.

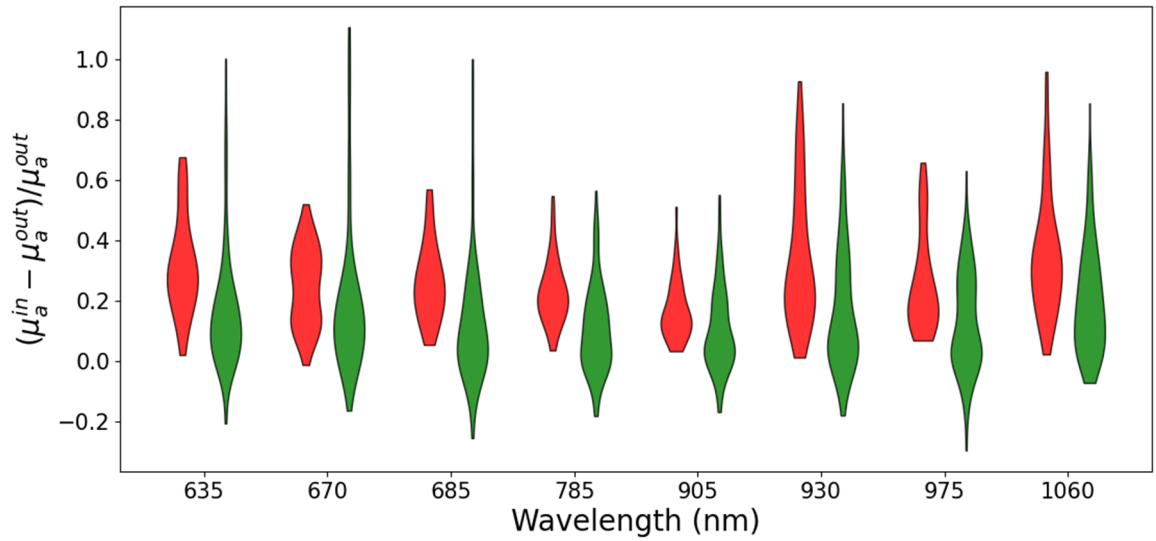

Figure 2 – Violin plot of the relative contrast for the absorption at the 8 wavelengths. Green (red) refers to benign (malignant) lesions.

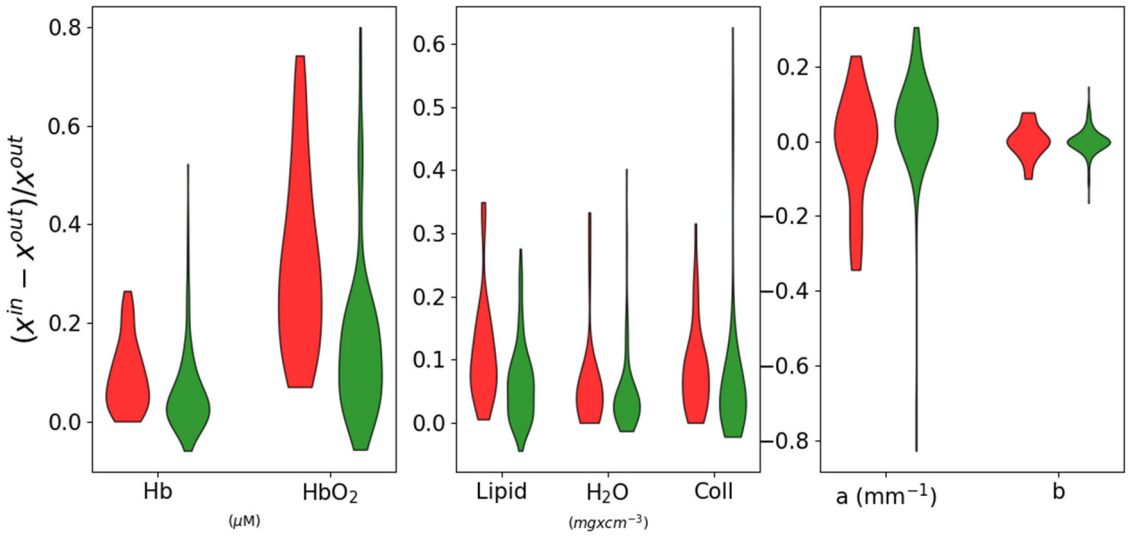

Figure 3 – Violin plots of the relative contrast for the tissue composition and scattering parameters. Green (red) refers to benign (malignant) lesions.

Table 1 – Results of the lesion classification exploiting Support Vector Machines (SVMs) and logistic regression (LR)

	SVM	LR
Sensitivity	0.57	0.54
Specificity	0.91	0.93

Table 1 reports the sensitivity and specificity obtained with the two classifiers in the discrimination between malignant and benign lesions. Sensitivity is very low, while specificity is rather high. As already mentioned, the dataset is limited. Furthermore, data obtained from different views of the same lesion and data collected on the same lesion by different radiologists were considered as independent, while they are not. That might have affected the results, especially favouring specificity against sensitivity. Also, effects of a dataset bias cannot be excluded yet.

KPI8 (sensitivity = 95% for the multimodal examination) and KPI9 (specificity = 90% for the multimodal examination) cannot be addressed, since the number of patients is still too limited. While no increase in sensitivity was expected, we aimed to improve specificity. The figures in Table 1 are promising, but no conclusion whatsoever can be drawn at this stage. Instead, KPI13 (Number of running / completed clinical studies = 1) was accomplished by the clinical validation ongoing at OSR.

The whole analysis procedure, from tomographic reconstruction up to lesion classification is streamlined so that for every new enrolled patient, all figures are updated with minimal operator intervention.

6. Conclusions

In conclusion, both on the operator's and on the patient's side, the SOLUS examination is feasible and shows no significant negative issues. Furthermore, the SOLUS examination can be easily integrated into the daily workflow of a Breast Imaging diagnostic path.

Concerning the diagnostic potential of the SOLUS approach, these initial outcomes, even though obtained from a limited dataset, indicate that the system can estimate the optical properties and composition of breast tissue, and is sensitive to the differences between lesions and healthy tissue and between malignant and benign breast lesions.

The clinical validation is continuing, and the availability of more optical data will allow us to obtain sound and more reliable results. Moreover, optical data will be combined with information provided by B-mode US scanning (on morphology) and Shear Wave Elastography (on stiffness).

More details on the system usability (sections 2-4) can be found in deliverable D5.4 - Final report on usability, while further information on the analysis of clinical data for lesion discrimination are available in D2.5 – Database of lesion properties and composition.

The key commitment of SOLUS (Section 1.3.4. of the Grant Agreement) was to move the new technology from TRL3 (experimental proof-of-concept) to TRL5 (technology validated in the clinical settings). That aim was reached since we were able to use the system in a clinical environment, with good patient compliance and with collection of meaningful datasets (as confirmed by comparison with previous studies). The initial analysis on lesion classification – though promising, considering also the fact that the optical information has still to be added to the US+SWE diagnostic power – is based on too few patients to draw reliable statistical indicators. Transition from TRL5 to TRL6 (technology demonstration in a clinical environment) is out of the scope of SOLUS. In-fact, the relevant call required validation in a clinical setting, but explicitly excluded extensive clinical trials. The TRL5 → TRL6 transition will be addressed in the 2-year prolongation of the clinical study at OSR, already foreseen as an Exploitation phase in the SOLUS Grant Agreement (Figure 4 – Timeline of SOLUS Exploitation) and secured in the Consortium Agreement.

The capability to characterize breast lesions non-invasively and avoid core needle biopsies in case of benign lesions has to be demonstrated by a great number of examinations. If the hypotheses are confirmed, the multimodal SOLUS system can dramatically change the approach to the breast lesions diagnosis, sparing time, money and, last but not least, stress to the patients, who are candidate to undergo breast biopsy.